UiT
THE ARCTIC UNIVERSITY OF NORWAY

Faculty of Health Sciences, Department of Community Medicine

Understanding temporality in human concentrations of organic contaminants

Considering human concentrations over time and through life in perspective of historic production and use

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Therese Haugdahl Nøst

A dissertation for the degree of Philosophiae Doctor – June 2014

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Department of Community Medicine
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Preface

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My rock, my family. I am so lucky to have you keeping me grounded and loved. Thank you for always being there for me.

Contents

Summary

Modern human lifestyle depends on a great number of synthetic chemicals and several are designated as persistent organic pollutants (POPs). When production and use of these persistent and bioaccumulative compounds are constant or intensifying, concentrations increase in the environment and in humans. Harmful health effects of POPs have been demonstrated after exposure to high concentrations. There are also concerns for the background exposure experienced by the general population and especially for foetuses and children. Production and use of many POPs were restricted and banned during the 1970s and 1980s after the demonstration of their harmful effects. Regulatory measures have led to decreasing concentrations in the environment. Diet is the major current exposure pathway to many of the legacy POPs for humans, although concentrations in specific food items are generally low. For newer POPs with recent or current use, the human exposure pathways are more complex.

The overarching aim of this thesis was to enhance our understanding of how human concentrations of POPs have changed in individuals over time and how they relate to the changes in production and use of these compounds. The thesis papers are based on serum or plasma samples from three studies:

- The Tromsø Study, Northern Norway, only men (n=53), with repeated measurements from 1979, 1986, 1994, 2001 and 2007;
- The Northern Norway mother-and-child contaminant cohort study, pregnant women (n=515), with single measurements in 2007-2009;
- The Norwegian Women and Cancer study, postmenopausal women (n=323), with single measurements in 2004.

Samples from the Tromsø Study were analysed for a suite of polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs) and per- and polyfluorinated alkyl substances (PFASs). The two latter studies involved four selected PCBs and measured concentrations were compared with concentrations predicted by mechanistic exposure modelling. The model calculates blood concentrations from emission estimates, environmental fate and human bioaccumulation of PCBs.

The majority of biomonitoring studies of POPs are cross-sectional studies and many have revealed that concentrations of several POPs increase with age. Still, longitudinal serum data from 1979 to 2007 for PCBs, OCPs and PFASs in men from Northern Norway demonstrated that concentrations increased with age only in years before production and use stopped. Concentrations of most PCBs and OCPs decreased from 1979 or 1986 and

likely reflect the decreasing concentrations in the environment during the same period. Concentrations increased for some PFASs from 1979 to 2001, when major productions were phased out, and decreased to 2007. For other PFASs, concentrations increased during the entire study period. Many of the compounds measured were banned before or during the study period and the time trends of POP concentrations display a strong link to production and use of these compounds.

The assessment of age-period-cohort effects in the longitudinal results demonstrated clear periodic trends. Additionally, the indicated birth cohort differences in concentrations of certain POPs likely reflect the significance of a person`s birth year relative to historic emissions of POPs. Further, the cross-sectional observations of increasing POP concentrations with age are conditional observations dependent on past production and use relative to sampling year.

The model simulations for PCB concentrations demonstrated reliable performance to reproduce measured concentrations when comparing predicted and measured median concentrations of PCBs in all three study groups. Person-specific predictions for pregnant and postmenopausal women were in agreement with measurements, although best in the pregnant women. Predicted concentrations from birth until blood sampling for the study subjects demonstrated large differences between individuals in peak concentrations and temporal changes.

The time trends from the longitudinal sample set clearly show that initiatives to stop production and use of POPs have led to decreasing concentrations of the same POPs in humans. The temporal aspects highlighted in this work show that interpretation of human biomonitoring studies should consider the time aspects of the study period and past production and use of POPs. Also, emission-based mechanistic models have potential as useful tools in human biomonitoring and effect studies, as exposure metrics of past concentrations and during sensitive life stages could be obtained.

Sammendrag

I vår moderne hverdag er mennesker omgitt av mangfoldige kjemikalier i våre omgivelser og mange er miljøgifter. Når utslipp og bruk av miljøgifter pågår spres de i miljøet og konsentrasjonene øker i dyr og mennesker fordi de er bioakkumulerende og lite nedbrytbare. Skadelige helseeffekter av disse stoffene er vist i dyr og mennesker som er utsatt for høye konsentrasjoner, men man er bekymret for effekter også i den generelle befolkningen som er utsatt for lave konsentrasjoner over lang tid. Spesielt bekymret er man for eksponering av foster og barn i utvikling. Tidlig i forrige århundre ble mange miljøgifter vist å være farlige og senere forbudt i 1970- og 1980-årene. Som en følge av disse tiltakene har konsentrasjonene av mange stoffer gått ned i miljøet i de siste tiårene. Selv om konsentrasjonene av de gamle miljøgiftene vi får i oss igjennom mat i dag er lave, er det den viktigste eksponeringsveien for disse miljøgiftene. For nyere miljøgifter og stoffer med pågående utslipp og bruk er eksponeringsveiene mer sammensatte.

Det overordnede målet med avhandlingen har vært å øke vår forståelse av endringer i menneskers konsentrasjoner av et utvalg miljøgifter over tid og hvordan de endrer seg i takt med utslipp og bruk. Arbeidet baserer seg på serum- eller plasmaprøver fra tre forskjellige studier:

- Tromsøundersøkelsen, Nord-Norge, kun menn, n=53, repeterte målinger fra 1979, 1986, 1994, 2001 og 2007.
- Studien «Miljøgifter i svangerskapet og i ammeperiode» i Nord-Norge, gravide kvinner (n=515), enkeltmålinger i 2007-2009.
- Kvinner og kreft-studien, Norge, postmenopausale kvinner (n=323), enkeltmålinger i 2004.

Prøvene i Tromsøundersøkelsen ble analysert for en rekke polyklorerte bifenyler (PCBer), klorerte pesticider og perfluorerte organiske forbindelser (PFASer). De to sistnevnte studiene omhandlet fire utvalgte PCBer og blodkonsentrasjoner av disse ble sammenlignet med estimater fra modellsimuleringer som bygger på utslippstall, transport og skjebne i miljøet og menneskets akkumulering.

Mange miljøgiftsstudier har konkludert med at menneskenes konsentrasjoner av mange miljøgifter øker med alderen. Disse studiene har vært tverrsnittsstudier, men i vår langsgående studie, hvor 53 menn i Tromsøundersøkelsen ble fulgt fra 1979 til 2007, økte konsentrasjonene med alder bare når utslipp og bruk var økende eller stabile. Konsentrasjonene av de aller fleste PCBer og klorerte pesticider sank fra 1979 eller 1986. Dette gjenspeiler trolig at konsentrasjonene i omgivelsene også sank i denne perioden.

Konsentrasjoner av noen PFASer økte fra 1979 til 2001 da utslippene ble begrenset før de sank til 2007, mens andre økte i hele studieperioden. Endringene i denne tidsperioden var ulike for de forskjellige miljøgiftene, men de fleste endret seg i takt med estimerte trender for produksjon og bruk.

Endringer i miljøgiftskonsentrasjoner fra 1979 til 2007 var tydelige og i tillegg fant vi generasjonseffekter for noen forbindelser der de eldste personene hadde de høyeste og de yngste hadde de laveste konsentrasjoner for hvert prøveår. Dette kan vise betydningen av fødselsår i forhold til historisk produksjon og bruk av miljøgiftene. Slike effekter kalles alder-periode-kohorte effekter og vil være interessante i overvåkningsstudier som involverer tidsaspekter. Hvordan konsentrasjoner av en miljøgift henger sammen med alder i tverrsnittsstudier er avhengig av når et studie er gjennomført i forhold til utslippshistorikken av den miljøgiften.

Estimerte medianverdier fra modellsimuleringene i alle tre studiegruppene var nøyaktige i forhold til de målte, også for alle prøvetakningsårene i Tromsøundersøkelsen. Konsentrasjoner ble beregnet for hver person i studiene som inkluderte gravide og postmenopausale kvinner. Overensstemmelsen mellom målte og estimerte verdier var god og aller best i de gravide kvinnene. Modellsimuleringene fra fødsel til prøvetakning for alle kvinnene viste stor variasjon i konsentrasjoner tilbake i tid.

Menneskenes konsentrasjoner av en miljøgift over tid kan tydelig relateres til historisk og nåværende produksjon og bruk av den. Tidsaspektene som er belyst i denne avhandlingen viser at tolkning av miljøgiftskonsentrasjoner i mennesker må ta hensyn til studietidspunkt relativt til deres historiske produksjon og bruk. Videre har modellsimuleringer potensiale for å frembringe mål på eksponeringer som ligger tilbake i tid og kan være viktige til bruk i humane overvåkningsstudier og i effektstudier.

List of papers

This thesis is based on three papers, referred to in the text by their roman numerals.

I. Persistent Organic Pollutants in Norwegian Men from 1979 to 2007: Intraindividual changes, age–period–cohort effects, and model predictions.
Nøst TH, Breivik K, Fuskevåg O-M, Nieboer E, Odland JØ, Sandanger TM.
Environmental Health Perspectives. 2013; 121: 1292-1298.

II. Repeated measurements of per- and polyfluoroalkyl substances (PFASs) from 1979 to 2007 in males from Northern Norway: Assessing time trends, compound correlations and relations to age/birth cohort.
Nøst, TH, Vestergren, R, Berg, V, Nieboer, E, Odland, JØ, Sandanger, TM.
Environment International. 2014; 67: 43-53.

III. Person-specific predictions of PCBs in Norwegian Women: Valuable supplements to measurements for understanding of time-variant exposures.
Nøst, TH, Breivik, K, Wania, F, Rylander, C, Odland, JØ, Sandanger, TM.
Manuscript

Abbreviations

AIC - Akaike`s Information Criterion
APC - Age-period-cohort
AMAP - Arctic Monitoring and Assessment Programme
ECF - Electrochemical fluorination
FOSA - Perfluorooctane sulfonamide
GC - Gas chromatography
HCB - Hexachlorobenzene
HCHs - Hexachlorocyclohexanes
LOD - Limit of detection
MISA - the Northern Norway Mother-and-Child Contaminant Cohort
MS - Mass spectrometry
Na^+ - sodium ion
NHANES - National Health and Nutrition Examination Survey
NOWAC - the Norwegian Women and Cancer study
OCPs - Organochlorine pesticides
PCBs - Polychlorinated biphenyls
PFASs - Poly- and perfluorinated alkyl substances
PFBA - Perfluorobutanoic acid
PFCAs - Perfluoroalkyl carboxylic acids
PFDA - Perfluorodecanoic acid
PFHxS - Perfluorohexane sulfonic acid
PFNA - Perfluorononanoic acid
PFOA - Perfluorooctanoic acid
PFOS - Perfluorooctane sulfonic acid
PFPeA - Perfluoropentanoic acid -
PFSAs - Perfluoroalkyl sulphonic acids
PFUnDA - Perfluoroundecanoic acid
POP - Persistent organic pollutant
POSF - Perfluorooctane sulfonyl fluoride
p,p´-DDE - 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene
p,p´-DDT - 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane
QA-QC - quality assurance- quality control
SRM - Standard reference material
UPLC - Ultra-high pressure liquid chromatography

1. Background and context

1.1. Preamble

Humans worldwide are exposed to an array of anthropogenic substances in their everyday life and the production and use of man-made chemicals has increased from the early 20th century. Substances that are considered persistent, bioaccumulative, toxic, and have potential for long-range transport can be classified as persistent organic pollutants (POPs). Today, there are restrictions or full bans on use of several POPs associated with international legislative agreements like the Stockholm Convention. Furthermore, 151 chemicals are designated 'Substances of very high concern' under the European Union regulation of chemicals - REACH (EEA and WHO, 1999). These and other initiatives aim to protect environmental and human health against harmful substances.

Harmful effects of POPs on human health have been apparent after accidental spills or occupational exposures, but the indicated effects in general populations have been diffuse and inconsistent (Longnecker et al., 1997; Stahl et al., 2011; Wigle et al., 2008). Furthermore, causal relationships between exposure to these risk factors and subsequent effects for human health have not yet been well established. There are special concerns for exposure to foetuses and infants with regards to effects and there is a knowledge gap with regards to how concentrations change during a life time. Human biomonitoring of POPs have quantified complex mixtures of concentrations, and several exposure pathways have been identified (AMAP, 1998; Duarte-Davidson and Jones, 1994; EEA and WHO, 1999; Vestergren and Cousins, 2009). There are also likely substances in our blood today that have not yet achieved the attention of researchers.

The research encompassed in this thesis aims to obtain a better understanding of temporal aspects in human biomonitoring of exposures to organic contaminants. The following groups of POPs are included: polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), and poly- and perfluoroalkyl substances (PFASs). The PCBs and OCPs can be referred to as 'legacy POPs' because they were among the first contaminants to be regulated and banned. Conversely, PFASs have been referred to as 'emerging contaminants' in that the production history and research attention towards these are more recent. An overview of the historic production of PCBs, OCPs and PFASs, their emissions, human exposure pathways, toxicokinetic properties, health effects and human biomonitoring is provided below. The terminology for estimated volumes of past emissions differs in the following chapters and is described with the respective mentions.

1.2. The production and use of contaminant classes

1.2.1. Polychlorinated biphenyls (PCBs)

PCBs are industrial chemicals with high thermal stability that were mass produced from the 1930s on for commercial uses, such as paint, plastic and electrical transformer fluids (AMAP, 2004). There are 209 possible congeners of PCBs and many commercial products contained complex mixtures of congeners. The PCBs were extensively used for several decades during the 20th century, and estimates of their historic emissions through use, accidental releases and disposal of PCB-containing products are presented in Figure 1 (Breivik et al., 2002; 2010).

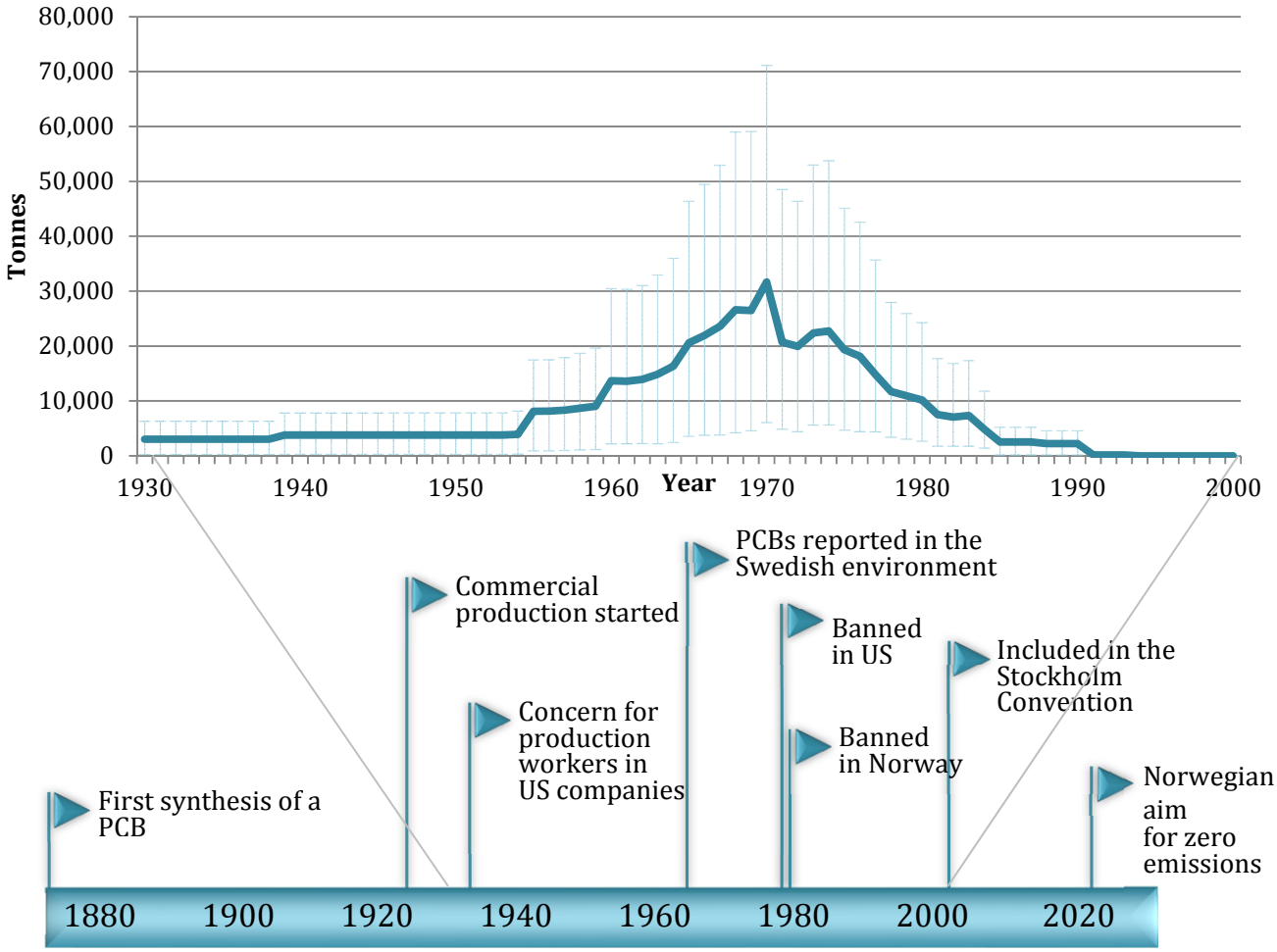

Figure 1. Estimates of global emissions of PCBs (sum of 22 congeners) from 1930 to 2020 (blue line in graph on top, error bars represent the minimum and maximum scenarios) adapted from Breivik et al. (2007) with permission. The time line (bottom) displays important events regarding PCBs between 1880 and 2020 (Harremoës et al., 2001; Norwegian Ministry of the Environment, 2006).

1.2.2. Organochlorine pesticides (OCPs)

The OCP group is comprised of numerous substances of which only a selection is described in this work. The OCPs of interest were chlordanes, 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (*p,p´*-DDT) and its metabolites, hexachlorocyclohexanes (HCHs), hexachlorobenzene (HCB) and toxaphenes. Their chemical structures vary but they have similar toxic properties designed for control of numerous pests and diseases, as illustrated below.

- Chlordane is a mixture of compounds formerly used as a broad-spectrum insecticide and also as herbicide. Major constituents were *cis*- and *trans*-chlordane, heptachlor, *cis*- and *trans*-nonachlor, but the metabolites oxy-chlordane and heptachlor epoxide have also been detected in the environment (ATSDR, 2009).
- DDT has been largely used as pesticides in agricultural crops and in disease control in many parts of the world (ATSDR, 2009). DDT is still employed today as pest control, especially against malaria mosquitoes in countries such as India and South Africa (van den Berg, 2009). The technical mixture of DDT is comprised of two major isomers, namely *p,p'*-DDT (approximately 85%) and *o,p'*-DDT (15%). DDT is converted to the stabile metabolite 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (*p,p'*-DDE) in the environment and humans (Jaga and Dharmani, 2003).
- Technical HCH contains several isomers of HCH of which α-, β- and γ-HCH dominate, while lindane is an insecticide that contains mainly γ-HCH (ATSDR, 2009). HCHs were widely used in agricultural crops. α- and β-HCH are also by-products in the production of lindane.
- HCB is a pesticide which has been frequently used as a fungicide, but equally important emission sources have been industrial manufacturing and HCB as a by-product in the production of chlorine gas and various pesticides (Bailey, 2001).
- Mirex is an insecticide mostly used for the control of fire ants in the US (UNEP, 2002).
- Toxaphenes are a group of around 670 structurally related chemicals (polychlorobornanes and camphenes) that were widely used as insecticides for agricultural use (UNEP, 2002; Voldner and Li, 1993).

The concern for harmful effects on the environment and human health following the production and use of these compounds has resulted in global initiatives to reduce or stop their emissions. Table 1 provides an overview of these measures in Norway and their status

in the Stockholm Convention. The aims for POPs under the Stockholm Convention are to eliminate (Annex A) or restrict (Annex B) their production and use, or to minimize unintentional production (Annex C).

Table 1. Overview of current regulatory measures[a] in Norway and status in the Stockholm Convention for selected OCPs.

OCPs	**Status in Norway**	**Status in the Stockholm Convention**
DDT	Restricted use from 1969 until banned in 1988.	Included in 2001 in Annex B (exemptions for disease vector control).
Toxaphenes	Never used in Norway.	Included in 2001 in Annex A.
Chlordanes	Not marketed since 1970 (AMAP, 2004).	Included in 2001 in Annex A.
HCHs	Lindane was used until 1992.	Included in 2009 in Annex A.
Mirex	Never used in Norway.	Included in 2001 in Annex A.
HCB	Not marketed since 1987.	Included in 2001 in Annex A and C.

[a]Information collected from Norwegian Environmental Agency (Norwegian Environment Agency, 2002) and the Stockholm Convention (UNEP, 2001) unless otherwise indicated.

With regards to global use and emissions of these OCPs, most have been used for several decades in the 20th century, and were banned due to the concern for their harmful effects on the environment. The available information on production and emissions differs between the different OCP groups as summarized below.

- Information on emissions of chlordane is scarce. It was introduced in 1948 and used all over the world until the 1970s (Norwegian Environment Agency, 2002). It was never produced in Europe (UNEP, 2002), and the US production and manufacture was phased out during the 1980s and 1990s (Mattina et al., 1999).
- DDT was the most widely used insecticide worldwide for several decades and estimated peak years in global emissions were the 1960s (Schenker et al., 2008). Emissions of DDT compiled from estimates of production and agricultural use are presented in Figure 2.
- The estimated global emissions of HCHs decreased from 1974 following their restricted or ceased production in many industrialised countries; however, emissions increased again due to escalating use in developing countries until the early 1980s when HCHs were banned in China (Li, 1999).
- HCB was intentionally produced from the 1950s to the early 1980s (Pacyna et al., 2003).
- Mirex was used mainly in US and Canada until 1988 (AMAP, 2004).

- The main period of production of toxaphenes was from 1970 to 1993 (Voldner and Li, 1993). Toxaphene was the most widely used pesticide in the US in 1975 (UNEP, 2001); however there has been little use in Europe and no use in Norway (Norwegian Environment Agency, 2002).

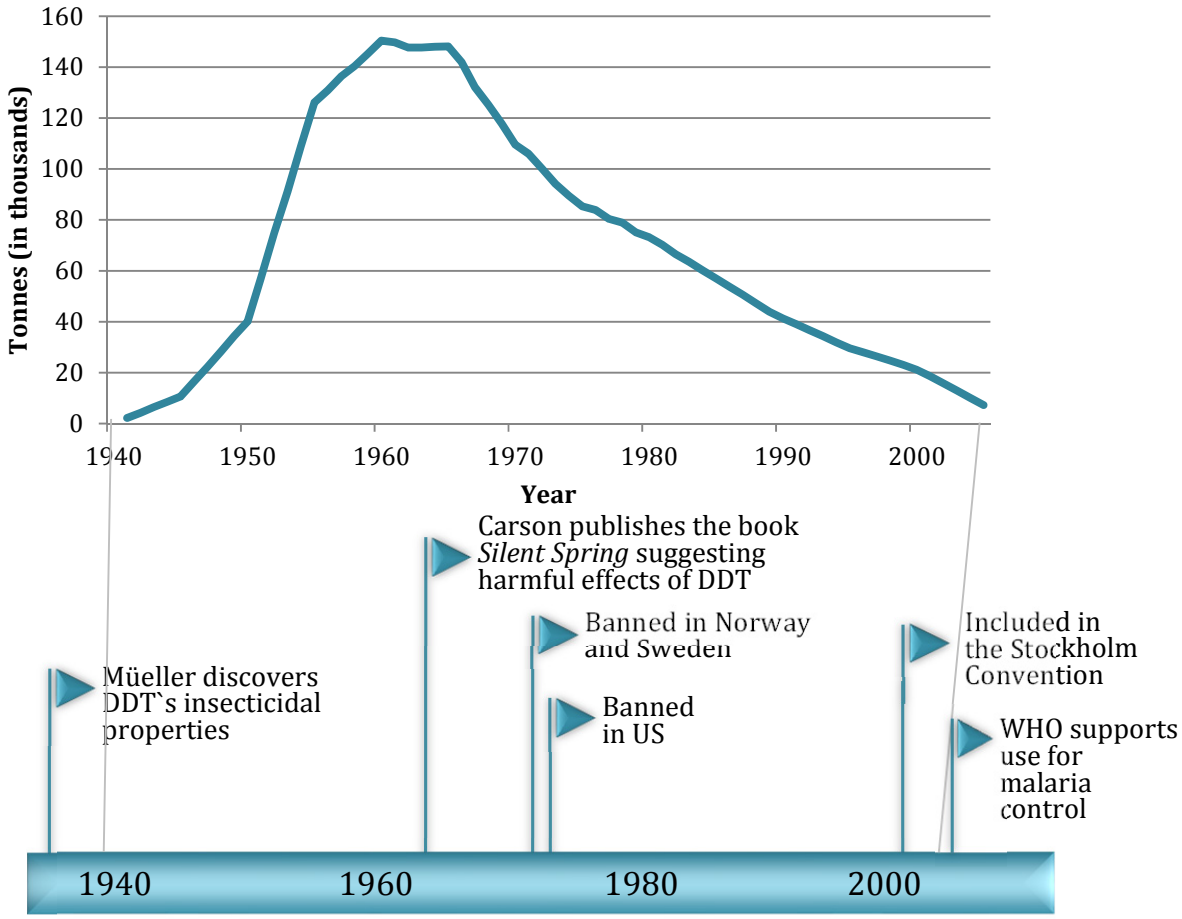

Figure 2. Estimated global emissions of DDT from 1941 to 2005 (blue line in graph on top) adapted from Schenker et al. (2008) with permission. The time line (bottom) displays important events related to DDT in the time frame 1940 to 2001 (Jarman and Ballschmiter, 2012; UNEP, 2001; US EPA, 2012a).

1.2.3. Per- and polyfluoroalkyl substances (PFASs)

PFASs are used in a wide variety of industrial and commercial applications like fire-fighting foams, metal plating and cleaning, and polyurethane production; but also as inks, varnishes, waxes, lubricants and water and oil repellents for leather, paper and textiles (Paul et al., 2009; Prevedouros et al., 2006). Their applications are generally related to their chemical stability and surface tension properties (Paul et al., 2009). Two major PFAS groups are the perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkyl sulphonates (PFSAs), of which perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) have received the most research attention. PFASs were produced by electrochemical fluorination (ECF) since the 1950s and since the 1970s also by telomerisation. The latter resulted in linear isomers and homologs with even-numbered carbon chain-lengths, whereas ECF also produced branched isomers and homologs of varying chain-length (Buck et al., 2011; Lau et al., 2007). The main products of ECF production were perfluorooctane sulfonyl fluoride (POSF) and a PFOA salt which were further used in the manufacture of a variety of fluorochemical products (Buck et al., 2011). Many of these products include precursors of PFOS and PFOA (Buck et al., 2011; Martin et al., 2010). Several PFCAs and their precursors originate from the teleomerisation processes (Buck et al., 2011). The global production estimates of POSF are displayed in Figure 3.

The major manufacturer, 3M, phased out the POSF-production during 2000-2002, and subsequently produced replacements that were shorter-chained and not bioaccumulative (US EPA, 2002). The main emissions of PFOS in Norway were related to the use of fire-fighting foams. In 2005, it was estimated that 57,600 tons had been used in Norway, whereas 21,500 tons of PFOS and related compounds still remained in stored products (Norwegian Environment Agency, 2005). PFOS was banned in Norway in 2007 and by the European Union in 2011, and was included under Annex B (restricted use) in the Stockholm Convention in 2009 (UNEP, 2001). An initiated phase out of PFOA and longer-chained PFCAs aims to eliminate production by 2015 (US EPA, 2006). Production, import, and export of PFOA or PFOA-containing products and textiles will be banned in Norway from June 1st 2014, as well as the trade in such products produced prior to this date (Norwegian Environment Agency, 2013). Still, the production of these compounds has continued in China (Zhang et al., 2012).

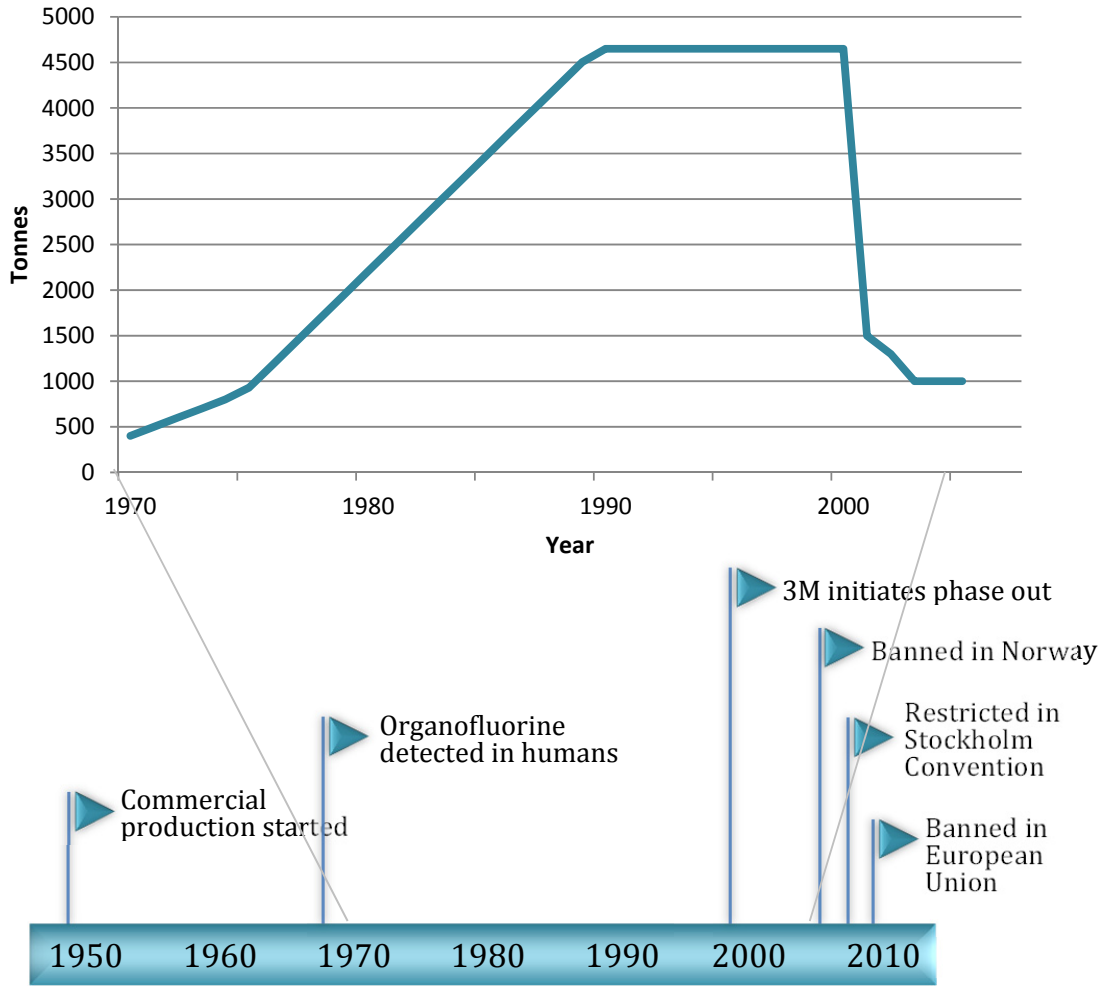

Figure 3. Estimated global production volumes of POSF from 1970 to 2005 (blue line in graph on top) adapted from Paul et al. (2009) with permission. The time line (bottom) displays important events in the time frame 1950 to 2010 for PFOS (Norwegian Ministry of the Environment, 2005; US EPA, 2002).

1.3. Human exposure to PCBs, OCPs and PFASs

1.3.1. From emission sources to humans

Sources of PCBs, OCPs and PFASs to the environment and humans could be the production (intentional or as by-products) and use (in industry, agriculture or as consumer products), or the storage and disposal of materials containing these chemicals. Human exposure pathways relate any abiotic and biotic exposure media to humans such as contaminated air, water, soil and food (Figure 4)(EEA and WHO, 1999; WHO, 2001). Examples of additional exposure sources are elements of the indoor environment (e.g. air and building materials) (Harrad et al., 2006; Shoeib et al., 2011), and consumer products containing POPs (Vestergren and Cousins, 2009). For some individuals, exposure is related to an occupational scenario (EEA and WHO, 1999). Also, exposure pathways differ between foetuses (maternal transfer through the placenta), infants (breastfeeding or other dietary intakes), children (ingestion/inhalation of dust, dietary intake) (Haug et al., 2011; Patandin et al., 1999; UNEP and WHO, 2012; Vestergren et al., 2008), and also across adult ages (Haug et al., 2011; Lorber and Egeghy, 2011). It is likely that the relative importance of various exposure pathways of a POP in persons experiencing background exposure vary across time according to the historic and current production and use of that compound along with the response time of human exposure media to such temporal changes.

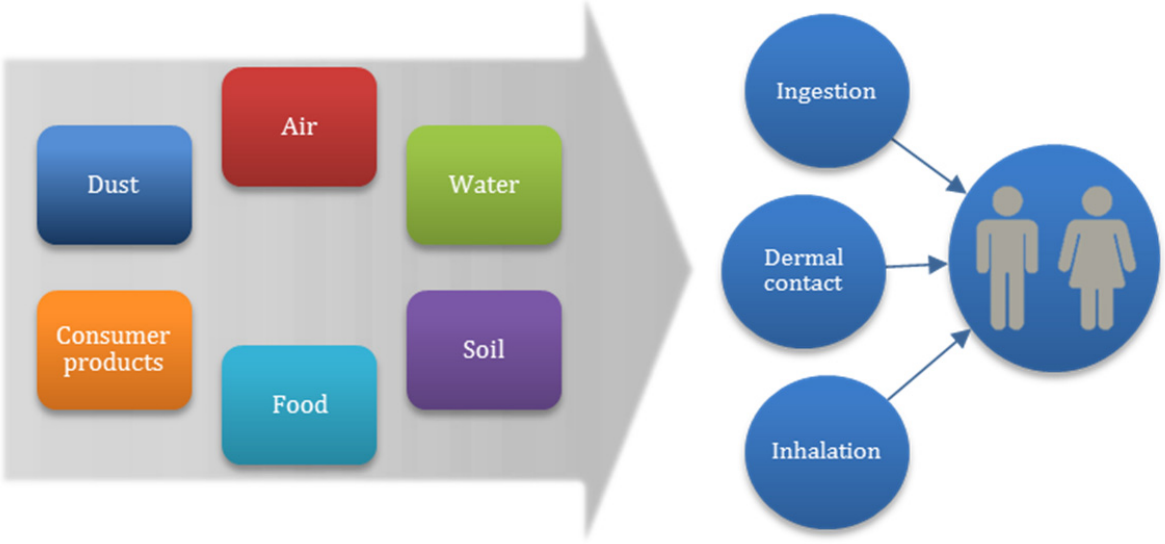

Figure 4. Illustration of the main exposure sources (inside the grey arrow) and intake routes (blue circles) into the human body of environmental contaminants. Adapted from UNEP and WHO (2012) and WHO (2010).

There is no knowledge of any production of PCBs, OCPs or PFASs in Norway, and the use of most compounds has been stopped (see Section 1.2.). Nevertheless, the physicochemical properties of POPs and their metabolites have promoted the geographical distribution by air and ocean currents away from source regions to more remote areas, especially the Arctic (Armitage et al., 2009; Li and Macdonald, 2005; Wania, 2003). Thus, European and global emissions are relevant for environmental concentrations in Norway as long-range transportation has contributed considerably compared to local emissions (Mantseva et al., 2004).

The exposure to legacy POPs for the general population in the Nordic countries has generally been considered to be through food-chain related pathways (Figure 4). Thus, the main route of human exposure is ingestion. Many of the PCBs, OCPs and PFASs accumulate in the environment through food chains (biomagnification) (Haukås et al., 2007; Muir and de Wit, 2010; Woodruff et al., 1994), and diet has been an important predictor of human tissue concentrations of PCBs and OCPs (Caspersen et al., 2013; Darnerud et al., 2006; Odland et al., 2003; Rylander et al., 2012). Also, PFAS concentrations in humans have been greatly influenced by dietary intake in several European countries (Brantsæter et al., 2013; Fromme et al., 2007; Haug et al., 2010a; Haug et al., 2010b; Noorlander et al., 2011; Rylander et al., 2009a; Vestergren et al., 2012).

Additional exposure routes for humans are dermal contact and inhalation. Their relative importance varies dependent on the exposure scenarios and properties of compounds. Diet and ingestion has been considered the main exposure route for legacy POPs. However, human exposure to emerging POPs has additionally been associated with air, drinking water, house dust and contact with consumer products during the years of peak production and use (e.g. of PFASs; Fromme et al., 2009; Haug et al., 2011; Vestergren and Cousins, 2009). Dermal or inhaled uptakes are often relevant routes in high exposure scenarios. For foetuses and infants, respectively, the placenta and breast milk represent the routes of exposure (Norén and Meironyté, 2000; Thomsen et al., 2010; Zhang et al., 2013a).

Humans are typically exposed to an array of compounds through several pathways that result in a composite body burden. The exposure to legacy POPs was constituted by the chemical compounds themselves, as well as their metabolites such as *p,p'*-DDE, *oxy*-chlordane and an array of PCB biotransformation products (e.g. Hovander et al., 2002; Muir and Howard, 2006; Rylander et al., 2012). As has been demonstrated for PFASs, both direct exposure (intentionally produced compounds) and indirect exposure (production

impurities and precursor degradation) are relevant for humans exposure (D'eon and Mabury, 2011; Martin et al., 2010; Prevedouros et al., 2006).

1.3.2. Temporal trends in human exposure media

Ubiquitous presence of POPs has been demonstrated in monitoring of abiotic and biotic environmental compartments worldwide. Surveys of many different media are reported in the literature and there are monitoring programmes in place such as the Arctic Monitoring and Assessment Program (AMAP). Temporal trends differ across different geographic areas, time periods, environmental media and species under study. Overall decreasing concentrations of most PCBs and OCPs in wild-life studies (air and biota) in Northern Europe and in the Arctic followed declining trends in use and emissions during the 1980s and 1990s (Berg et al., 2004; Bignert et al., 1998; Hung et al., 2010; Rigét et al., 2010). By contrast, concentrations of different PFASs have been increasing in the same time period (Butt et al., 2010; Holmström et al., 2005; Holmström et al., 2010; Muir and de Wit, 2010; Roos et al., 2013). In the latter studies, there are few indications of decreasing concentrations of PFOA and PFOS since the phase out of PFOS-related production although a levelling off or slight decrease in PFOS was observed in wild-life in Northern Norway in recent years (Ahrens et al., 2011; Verreault et al., 2007).

Few studies have examined historic trends in estimates of human intakes from diet, indoor environment or consumer products as historic samples are rarely available. Still, estimated dietary intakes in several countries have generally declined since the 1980s for PCBs (Harrison et al., 1998; Llobet et al., 2008; Nakata et al., 2002; Tard et al., 2007) and OCPs (Darnerud et al., 2006; Nakata et al., 2002) and since the late 1990s for PFOS (Johansson et al., 2014; Vestergren et al., 2012). Although scattered studies of other exposure media exist, there is very little information of temporal trends; however, a study comparing PCB concentrations in indoor air in the UK suggested that there was no difference between the survey periods 1997-1998 and 2003-2005 (Harrad et al., 2006).

1.4. POPs within the human body

Toxicokinetics describe the processes of absorption, distribution and metabolism of contaminants within the body and their excretion (US National Research Council, 2006). As mentioned, ingestion is the main route of entry for PCBs and similar POPs (Alcock et al., 2000; Duarte-Davidson and Jones, 1994). Ingestion of drinking water and food is also likely the major exposure route for PFASs (Fromme et al., 2009; Stahl et al., 2011). Once in the blood, all these compounds can be distributed to other tissues in the human body. The PCBs and OCPs are lipophilic compounds that partition into tissues largely dependent on the respective lipid contents (Dewailly et al., 1999; Noren, 1998); however, the PFASs are both lipophobic and hydrophobic, bind to proteins, and partition to blood and liver (Butenhoff et al., 2006; Han et al., 2003; Jones et al., 2003).

The human body can take up chemicals from its environment and due to their persistent properties, many PCBs, OCPs and PFASs can reside in the human body for years once absorbed. When there is a net burden of a chemical in the body after uptake and elimination processes have occurred following an exposure, it is called bioaccumulation (US EPA, 2012b). Metabolism and elimination of many POPs is slow and there is no known mammalian metabolism of PFOS (Stahl et al., 2011). The biotransformation enzyme systems of the liver in particular (e.g. cytochrome P (CYP) enzymes) can modify many compounds striving to create water-soluble compounds that are feasible to excrete from the body (ATSDR, 2009; Hovander et al., 2002; McGraw Sr and Waller, 2006; Rendic and Carlo, 1997; Rylander et al., 2012). Certain PCBs can induce their own metabolism by activating the induction of CYP enzymes (Shimada et al., 2002). Metabolites can also be retained in the human body and frequently reported examples are *p,p'*-DDE (a metabolite of *p,p'*-DDT; Jaga and Dharmani, 2003) and oxychlordane (a metabolite of chlordanes; Barnett and Dorough, 1974). Excretion of POP metabolites occurs largely through urine and feces, but the dominant route varies between chemicals. Excretion of PCB metabolites from the human body is primarily through feces for the higher chlorinated congeners, whereas urine is a major route of excretion for DDT metabolites (ATSDR, 2009; Neal et al., 1946; Schlummer et al., 1998). Renal excretion appears to dominate also for some PFASs in humans (Beesoon et al., 2012; Harada et al., 2005; Zhang et al., 2013b). Also, POPs in women can be excreted through breastmilk and menstruation (Harada et al., 2005; Norén and Meironyté, 2000; Thomsen et al., 2010).

The range of chemical properities within a contaminant class could result in differentiated metabolism; for example, lower chlorinated PCBs are more readily metabolised compared

to the higher chlorinated congeners (Borlakoglu and Wilkins, 1993; Brown, 1994). For DDT, the mother compound appears to be more readily metabolized in human tissues relative to its metabolite (Longnecker et al., 1997). Also, different isomers of a compound can have different retainment in the body as it appears that branched isomers of PFOS are more readily excreted as compared to the linear isomer (Benskin et al., 2009; Zhang et al., 2013b). Also, for certain PFASs, the rate of elimination generally appears to be enhanced with decreasing carbon-chain length and to depend on functional group (Lau et al., 2007; Zhang et al., 2013b).

The concept of a compound`s half-life designates the time it takes for an initial concentration to be reduced by half. There have been many attempts to estimate the half-lives of PCBs, OCPs and PFASs in human tissues. Human half-lives can be estimated as intrinsic half-lives, which reflect the elimination rates (i.e., the biological half-life, or clearance) and on-going exposure is assumed negligible. Another approach calculates appearant half-lives, which incorporate continued uptake and other toxicokinetics factors that are functions of time (Ritter et al., 2011). Elimination half-lives have been often estimated from persons who have experienced high exposure events or periods (Olsen et al., 2007a; Seegal et al., 2010; Shirai and Kissel, 1996). Apparent half-lives are often calculated from the disappearance rate in background exposed individuals and represent the aggregated effect of elimination and continued exposure. Calculation of half-lives corrected for continued intake has also been attempted (Grandjean et al., 2008a). Furthermore, apparent half-lives of lipophilic compounds on an individual basis are influenced by changes such as in body fat (Milbrath et al., 2009; Wolff et al., 2007).

Estimated human half-lives of PCBs range from under one year up to 27.5 years depending on the specific congener; one estimate for the intrinsic elimination half-life of PCB-153 is 14.4 years (Ritter et al., 2011; Shirai and Kissel, 1996 and references therein). For DDT and HCB, examples of estimated half-lives in humans are 7 and 6 years, respectively (Woodruff et al., 1994). For PFOS and PFOA, median (range) half-lives were estimated to be 4.6 (2.4-21.7) years and 3.4 (1.5-9.1) years, respectively (Olsen et al., 2007a) in occupationally exposed individuals. There appears to be considerable variation in half-lives between compounds and individuals, which may reflect methodological uncertainties and inter-individual physiological differences.

1.5. Conduct of human biomonitoring and effect studies

1.5.1. General considerations of human biomonitoring studies of POPs

Describing the exposure of humans to environmental contaminants often considers the concentrations of such compounds in human tissues as indicators of exposure as this demonstrate that the respective compound *via* its emission sources and pathways represents both exposure to and uptake by humans. Indeed, biomarkers of exposure have been defined as "the environmental contaminant, its metabolite, or a product resulting from its interaction with the target tissue" (WHO, 1993). Further, human biomonitoring encompasses effects of and susceptibility to contaminants in humans. Biomarkers of such processes have been defined as "a measurable biochemical, physiological behavioural or other alteration within an organism that, depending upon the magnitude, can be recognized as associated with an established or possible health impairment or disease", and "an indicator of an inherent or acquired ability of an organism to respond to the challenge of exposure to a specific xenobiotic substance", respectively (WHO, 1993).

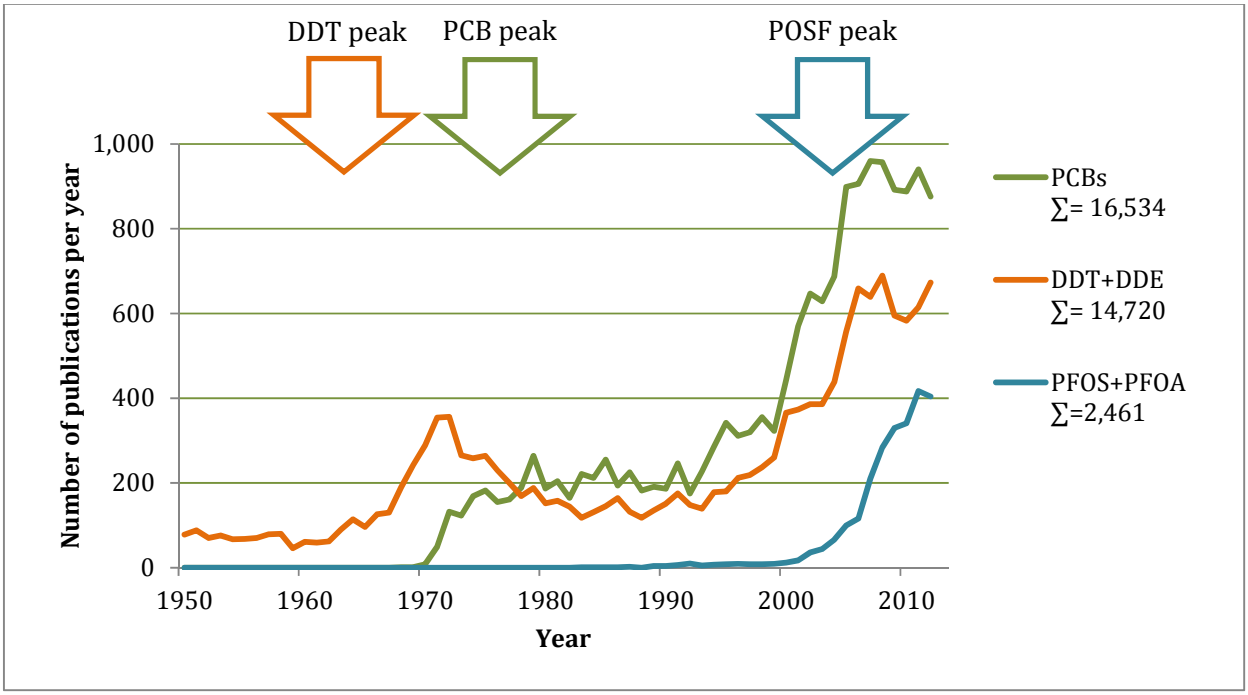

Figure 5. Publication trends with annual numbers of publications indexed by PCBs, DDT and DDE, PFOS and PFOA according to Medline statistics (Corlan, 2004). The approximate peak years in productions of PCBs, DDT and POSF (see Section 1.2.) are indicated.

The description of exposure to human populations through biomonitoring is fragmented and obtained from studies with varying designs, power, and validity and target different study groups and countries. Regular population-based surveys of environmental contaminants are rare, although the US National Health and Nutrition Examination Survey (NHANES) and AMAP are examples of such surveys (Porta et al., 2008). Many studies are cross-sectional and have been conducted in study years after peak exposures have passed for many POPs (Figure 5). Also, the literature on human effects of PFASs is more recent than those for the PCBs and OCPs.

Biomonitoring of the general population is often performed in adult age groups yet selected social, gender or age groups could be targeted (Porta et al., 2008). Due to the transfer of POPs during pregnancy and breastfeeding, surveys of pregnant women and breast milk are considered indicators of exposure to foetuses and infants (Barr et al., 2007; Needham et al., 2008; Norén and Meironyté, 2000). There is a need for better understanding of human exposure to contaminants during its entire life-course and especially during sensitive periods.

The human tissue most frequently assessed for the purpose of human biomonitoring is blood (as whole blood, plasma, or serum), and this facilitates comparisons between studies. Furthermore, reports of concentrations in urine, breast milk, and adipose tissues are common and those of fingernails, hair, faeces and organ tissues also exist (Esteban and Castaño, 2009; Morton et al., 2004; Zhang et al., 2007). Notably, the tissue analysed is of significance for certain compounds, such as the PFAS perfluorooctane sulfonamide (FOSA) which is associated with red blood cells and is present in lower concentrations in plasma/serum.

A wide range of compounds or elements are reported in human biomonitoring studies; however, the most frequently reported are the compounds included in international regulations like the Stockholm Convention. Among 212 chemicals targeted in “Human Exposure to Environmental Chemicals” survey by the US Centers for Disease Control and Prevention, many PCBs, pesticides, and PFASs were included (Crinnion, 2010).

1.5.2. Considerations of exposure in human effect studies

Health effects of POPs are expected to be dependent on the magnitude, duration and frequency of exposure at the site of effect (WHO, 2010). Thus, a good understanding of human exposure relative to the end point under study is imperative (Figure 6). Establishing a causal relationship between exposure to POPs and any subsequent effects are most often not conclusive in epidemiologic studies from the general population. Furthermore, effect studies often include selected POPs and understanding the effects of mixtures still remains a challenge. Although toxic effects of POPs and their mechanisms can be established in animal model studies, they are not easily translated to human health scenarios.

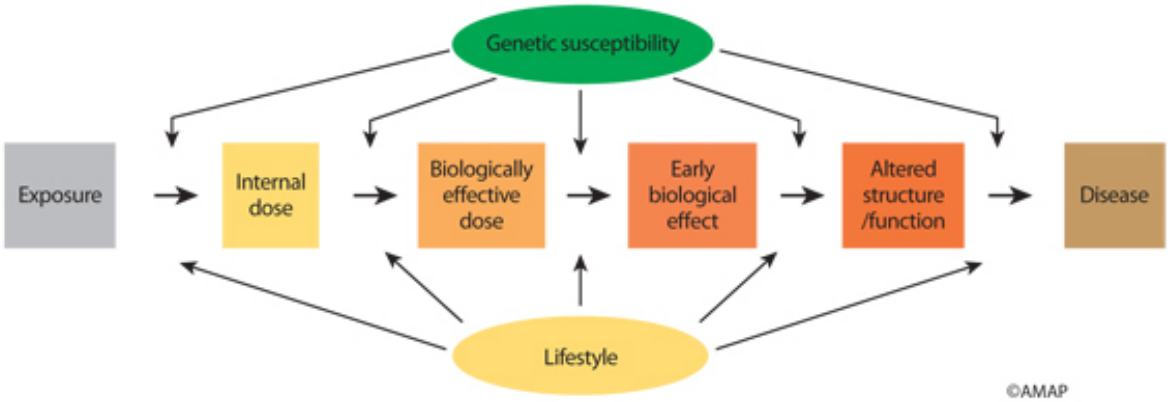

Figure 6. In the pathogenic sequence between exposure and disease, several types of biomarkers of exposure, effect and susceptibility must be understood. Copyright AMAP (2009).

In persons that have experienced high exposures to PCBs after accidental spills, effects like dermal and ocular changes, poor cognitive development in children, and altered thyroid functions were reported (UNEP and WHO, 2012). Use of pesticides has caused lethal poisoning and neurological harmful effects in highly exposed persons (Roos et al., 2013). Reproductive, developmental and carcinogenic (especially hepatic or renal) effects have been suggested following high exposures to PFOS and PFOA (Stahl et al., 2011; Steenland et al., 2010).

Several studies of background exposed populations have indicated concerns for endocrine disruptive effects of many POPs (UNEP and WHO, 2012). Also, metabolic disturbances or diseases following exposure to certain OCPs (Lee and Jacobs, 2006) or PFASs (Stahl et al., 2011; Steenland et al., 2010) have been indicated. Several other immunotoxic, neurotoxic,

hepatotoxic, carcinogenic and detrimental developmental effects have been reported that are compound dependent; however, many studies are inconclusive (Longnecker et al., 1997; Stahl et al., 2011).

There are special concerns for exposures to chemicals for foetuses and children due to elevated body weight-adjusted burdens and immature metabolic pathways while undergoing developmental processes. It is recognized that the timing of exposure relative to sensitive windows of susceptibility is critical for detrimental effects that can become apparent later in life (Boekelheide et al., 2012; Grandjean, 2008b; Wigle et al., 2008). Indeed, prenatal exposure to PCBs has been associated with lowered birth weight (Nieminen et al., 2013) and impaired cognitive function (Jacobson and Jacobson, 2003). Prenatal exposure to PFOA has been associated with adult overweight (Halldorsson et al., 2012) and elevated PFASs concentrations in children with lowered immune response following vaccinations (Grandjean et al., 2012).

1.5.3. Predictors of POP concentrations

Many cross-sectional biomonitoring studies have identified dietary and lifestyle predictors of POP concentrations in human tissues. Concentrations of PCBs and OCPs are frequently reported to associate with age (Hardell et al., 2010; C Rylander et al., 2012; L Rylander et al., 1997; Wolff et al., 2005) or birth year (Bjerregaard et al., 2001; Perry et al., 2005; Wolff et al., 2007). Whereas for concentrations of PFASs, no association (Calafat et al., 2007a, 2007b; Harada et al., 2007; Olsen et al., 2008; Yeung et al., 2006) and inconsistent associations (Haug et al., 2009; Kato et al., 2011) to age have been reported. Parity has been demonstrated to correlate to concentrations of PCBs, OCPs and PFASs among women (e.g. Bräuner et al., 2011; Fei et al., 2007; Hardell et al., 2010; Rylander et al., 1997). Assessments of dietary predictors of POPs in Norway have indicated that consumption of marine food associated positively with concentrations of PCBs and OCPs (Caspersen et al., 2013; Furberg et al., 2002; Rylander et al., 2009b; 2012) and PFASs (Brantsæter et al., 2013; Haug et al., 2010b; Rylander et al., 2009a; 2010). Body mass index (Wolff et al., 2000) and place of residence (Bräuner et al., 2011; Rylander et al., 1997) have also been shown to be predictors of PCB and OCP concentrations.

1.5.4. Temporal trends in human biomonitoring studies

Declining trends of most regulated PCBs and legacy OCPs have been observed in human blood during the last decades in the Northern Hemisphere (Hagmar et al., 2006; Hovinga et al., 1992; Tee et al., 2003; Vo et al., 2008). Further, monitoring studies of human breast milk in Norway have signalled decreasing maternal concentrations of the same compounds (Johansen et al., 1994; Polder et al., 2009). Furthermore, PFOS and PFOA concentrations have generally declined since the early 2000s, whereas variable trends for other PFASs have been observed in several countries (Calafat et al., 2007b; Glynn et al., 2012; Harada et al., 2004; Jin et al., 2007; Kannan et al., 2004; Kato et al., 2011; Olsen et al., 2005; 2012; Schröter-Kermani et al., 2012; Toms et al., 2009), including Norway (Haug et al., 2009).

1.5.5. Age-period-cohort effects in human biomonitoring

Revealing trends of, for example, prevalence and incidence of diseases and risk factors within epidemiology encounters a problem of extreme collinearity where Age + Birth year = Current year. This phenomenon has been known in social sciences as the age-period-cohort (APC) problem and represents three different but highly related time scales (Holford, 1991; O'Brien, 2011; Palmore, 1978) as illustrated in Figure 7. Age effects are changes associated with biological processes or progression through life-course. Periodic effects are environmental or social changes that affect all age groups simultaneously during historic time. Cohort effects, or generational effects, reflect differences due to being born at different times and when a person lived (Glenn, 2003). APC effects can be apparent in disease prevalence and mortality rates over time, such as in prevalence of psoriasis in the Tromsø Study (Danielsen et al., 2013). In cross-sectional studies where persons of different ages are compared, age and birth year cohorts are confounded and portray the same information, whereas in longitudinal studies, age and calendar year (period) are confounded (Glenn, 2003). This is challenging to resolve with statistical approaches, but there have been attempts to estimate the separate effects (Ahacic et al., 2012; Ding et al., 2007; Yang and Land, 2006).

In the context of POPs, increasing age could be expected to associate with physiological changes (changes in bioaccumulation, body composition and metabolism), but also concurrent changes in behaviour, dietary patterns and ingestion rates. Birth cohort membership likely reflect certain exposure histories (including differences in duration and

magnitude of the exposure) and different dietary patterns, whereas periodic changes are characterised by period of use, emissions, post-ban time and population changes in dietary patterns.

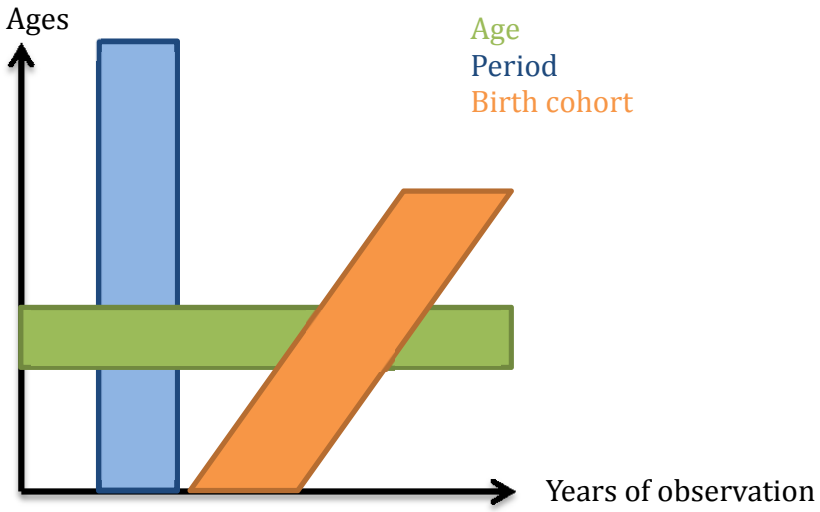

Figure 7. An illustration of the relationship between age, period and cohort as adapted from Cohen and Naumova (2011). Following a a certain age group (green block), or certain birth cohorts (orange block) across years or assessing all age groups at one time point (blue block) will assess time scales differently.

1.5.6. Prediction models in biomonitoring studies

Gaining extensive knowledge on human exposures based on measurements covering different populations, age groups, body tissues, and compounds requires extensive resources such as analytical capability and funding. Consequently, the estimation of human POP concentrations from effective prediction models has potential as non-invasive and valuable tools in human biomonitoring. Mechanistic models are constructed from the available understanding of human exposure to chemicals in historical, active or potential future use. Modelling human bioaccumulation requires estimates of intake rates; however, the empirical basis for and complexity of these mathematical estimations vary. One type of mechanistic models is physiologically-based pharmacokinetic models that describe uptake, accumulation, biotransformation and excretion processes in a body (Krishnan and Andersen, 2001).

Multimedia mechanistic models can express the quantitative understanding of how chemicals are emitted, transported in the environment and accumulated in humans based on physicochemical properties and ecosystem characteristics (MacLeod et al., 2010). Such model frameworks are based on laboratory and field observations reflecting the properties of compounds with regards to partitioning and mass transfer between abiotic and biotic environmental compartments. Furthermore, dynamic models are time-resolved and therefore require time-variant emission estimates. The papers included in the current work employed a dynamic mechanistic model based on estimated historic PCB emissions, transport and bioaccumulation in the environment and the human body (Breivik et al., 2010). CoZMoMAN is a mechanistic model that quantitatively expresses the understanding of transfer of time-variant emissions through environmental and human compartments and estimate concentrations therein. Its estimated PCB concentrations have been demonstrated to perform within the range of those measured in environmental compartments and humans (Breivik et al., 2010; Quinn and Wania, 2012).

Mechanistic models quantitatively express the current knowledge of human exposure and have been suggested as tools for hypothesis testing and interpretation of monitoring data (Cowan-Ellsberry et al., 2009). Certain pharmacokinetic models have been evaluated for human concentrations and shown good ability to predict infant and adult exposures (Sonne et al., 2014; Verner et al., 2009). Several recent studies have assessed the understanding of human POP exposures and impact of regulative and advisory measures by estimating: i) generational differences in prenatal, postnatal and lifetime exposures (Quinn et al., 2011); ii) associations to age in cross-sectional and longitudinal studies (Quinn and Wania, 2012); iii) time trends in Arctic populations with concurrent transitions of dietary habits (Quinn et al., 2012); and iv), impact of dietary advice to pregnant women for pre- and postnatal exposure in children (Binnington et al., 2014).

2. Aims of the thesis

The main objective of this doctoral thesis was to increase the understanding of time trends and life-course characteristics of human concentrations of organic contaminants. The organic contaminants investigated are the PCBs, OCPs and PFASs and this work has focused on Norwegian men and women from the general population. In addition to serum measurements, the potential of a mechanistic model to reproduce measured concentrations and predict life-course concentrations of selected PCBs was investigated.

Specific objectives:

- Evaluate time trends of PCBs, OCPs and PFASs in repeated serum measurements of men from the Tromsø Study, a population-based cohort in Tromsø, Norway (Papers I and II).
- Assess age-period-cohort effects in relation to POPs in the longitudinal sample set (Papers I and II).
- Evaluate the predictive ability of the dynamic mechanistic model CoZMoMAN for median concentrations and time trends of selected PCBs in men from Northern Norway (Paper I).
- Evaluate the predictive ability of CoZMoMAN on an individual level for measurements of selected PCBs in pregnant and postmenopausal women from Norway (Paper III).
- Explore the potential of predicted concentrations with regards to estimations of individual exposures in the past and especially during developmental life stages (Paper III).

3. Materials and methods

3.1. Study populations

The work included in this thesis was based on three established cohorts in Norway, of which two were conducted in Northern Norway.

3.1.1. The Tromsø Study (Papers I and II)

The Tromsø Study is a population-based study which includes participants from the municipality of Tromsø, which is the largest city in Northern Norway (Figure 8). The municipality has approximately 70,000 inhabitants and is situated ~400 km north of the Arctic Circle. The Tromsø Study was initiated in 1972 to examine the causes for the high incidences of cardiovascular diseases in Northern Norway, and included males only. Since then five more surveys have been completed and the research hypotheses included have been expanded to encompass several other aspects of human health (Jacobsen et al., 2012). The invited age groups and number of people have varied across the surveys. The overall participation rate has decreased somewhat since the first surveys; in the survey conducted in 1979, the participation rates were 74% and 82% for invited men and women, respectively, whereas those of the survey in 2007-2008 were 63 and 68, respectively (www.tromsostudy.com).

Subjects from the surveys in 1979, 1986-1987, 1994-1995, 2001, and 2007-2008 comprised the basis for Papers I and II. 60 men were randomly selected from a number of 1,438 eligible men for which blood samples from at least three surveys were available thereby allowing a longitudinal design of repeated measurements. Information on birth year was extracted from questionnaires (Appendix I), and median age was 43, 50, 58, 65, and 71 at the five sampling points.

3.1.2. The Northern Norway Mother-and-Child Contaminant Cohort and the Norwegian Women and Cancer study (Paper III)

The Northern Norway mother-and-child cohort (MISA) study was established to address exposure of environmental contaminants experienced by women during pregnancy and postpartum and also by their new-born (Veyhe et al., 2012). The longitudinal cohort

consists of 515 women in Northern Norway (Figure 8), aged 18-43 years, who were enrolled during early pregnancy (mean gestation week 21; range 4-32). The recruitment period was from May 2007 to June 2009, and 515 of the 2,700 invited women enrolled (20%). The women answered a comprehensive questionnaire (Appendix II) on personal information and food frequency consumption, as well as donating a blood sample upon enrolment in early pregnancy. Additionally, blood samples were donated three days and six weeks postpartum. Only the samples from the sampling during early pregnancy were included in this work.

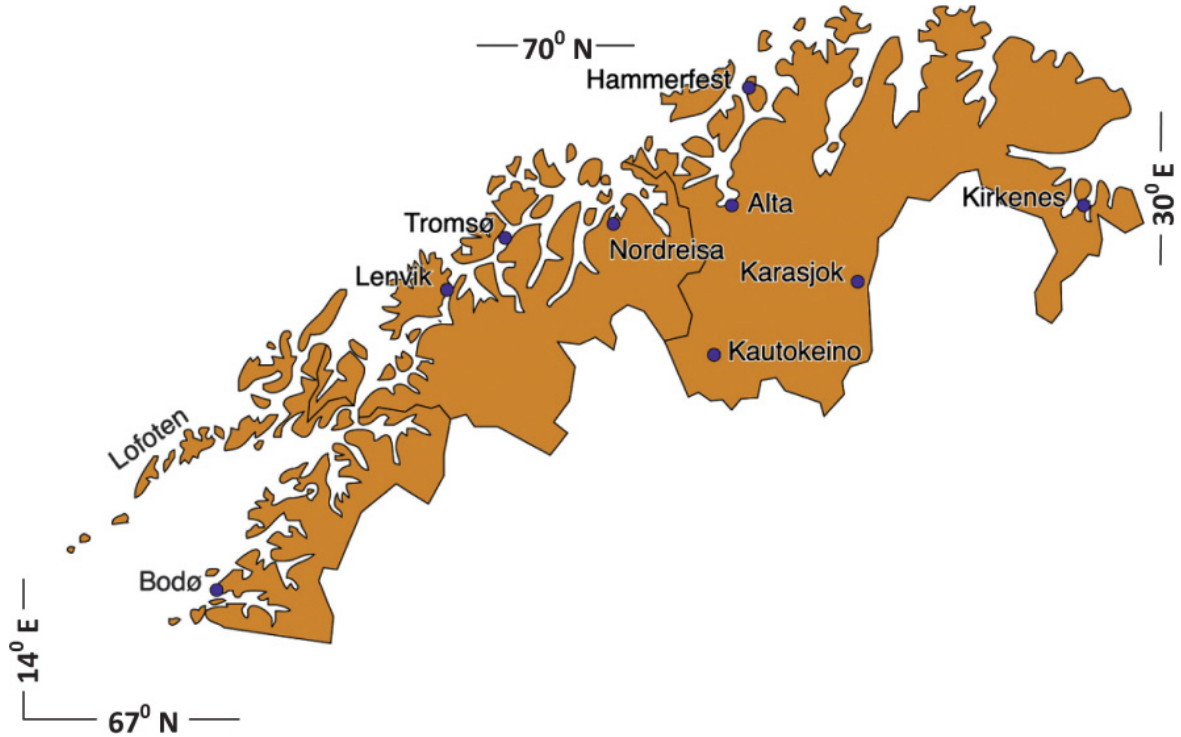

Figure 8. Map of the Northern Norway study area for the MISA cohort (reproduced from Veyhe et al., 2012 with permission). The Tromsø Study is conducted in Tromsø (see Section 3.1.1.).

The Norwegian women and cancer study (NOWAC) is a prospective cohort aiming to explore risk factors for breast cancer. The cohort consists of more than 170,000 women from the general Norwegian population aged 30–70 years (Lund et al., 2008). Questionnaires were filled out by all participants and around 50,000 donated blood samples (Dumeaux et al., 2008). A randomly selected subset of postmenopausal women as classified by sex hormone status (age 48-62, participation rate 89%) (Waaseth et al., 2008)

were included in this work. Blood samples were donated in 2004 and the women answered questions regarding personal information and food intake frequencies (Appendix III). Contaminant concentrations in sera of 311 NOWAC women were previously published (Rylander et al., 2012).

3.2. Sampling procedures and storage

Blood samples were donated in all three cohorts, and plasma or serum was the targeted matrix for the contaminant analyses.

The blood sampling protocol of the Tromsø Study at all surveys involved the routine methods and equipment in use at the time. All samples were collected from an antecubital vein and taken non-fasting. According to Blix et al. (2013), serum at the last three surveys was prepared by centrifugation after a 1 hour coagulation period at room temperature. All samples were stored at the University of Tromsø at -70 °C until analyses.

The women in the MISA study were requested to fast overnight if possible, or at least eat a light, non-fatty breakfast 2 hours before the blood sampling or earlier (Hansen et al., 2010). Blood was drawn from the antecubital vein and collected in BD Vacutainers (SST II Plus Advance 10/8.5 ml). Vacutainers were transported to the University of Tromsø where serum was transferred to glass vials pre-rinsed with *n*-hexane and acetone, and stored at -20 °C until analyses.

The blood samples obtained in the NOWAC cohort was collected in citrate buffer Vacuette Coagulation Tubes (Waaseth et al., 2008). Samples were sent by mail overnight to the University of Tromsø, centrifuged at 3,000 rpm for 15 minutes, and plasma was stored at -70 °C until analyses.

3.3. Analytical methods

3.3.1. Determinations of lipids

Triglycerides, phospholipids, free cholesterol, and total cholesterol were determined enzymatically in all included samples from the Tromsø, MISA cohort and NOWAC studies. Further, summed lipid concentrations were calculated according to the equation proposed by Akins et al. (1989).

3.3.2. Determinations of serum sodium

Sample evaporation during long-term storage (maximum 32 years) in the Tromsø study samples used in Papers I and II could have caused spuriously high POP concentrations. The extent of evaporation was assessed by measuring the concentrations of sodium ion (Na^+) in the sera, as its concentration is strictly regulated in human blood. Determinations were conducted at the University Hospital of North Norway using an ion-selective electrode method. Only 3% of samples (3 samples from 1979) were adjusted due to high Na^+ concentrations (>165 mmol/L) by the ratio $[Na^+]_{mean}/[Na^+]_{sample}$ as suggested by Krieger et al. (1994).

Sodium determinations were not performed in samples from the MISA or the NOWAC study, as these samples had only been stored for a few years.

3.3.3. Analyses of PCBs and OCPs

Analyses of lipophilic POPs were conducted for Papers I and III, and the analytical details are presented therein. The analysed compounds in the Tromsø study samples (Paper I) were PCBs and OCPs [chlordanes, HCHs, HCB, DDT and its metabolites, and toxaphenes] and selected PCBs were analysed for the MISA cohort (Paper III). Extraction of the MISA samples was performed by methods already established in the laboratory, while the extraction of the Tromsø study samples was similar although slightly modified due to low sample volumes. Briefly, a number of internal standards were added to serum before extraction by dichloromethane or *n*-hexane in solvent-solvent extraction for the Tromsø study samples, and solid phase extraction for the MISA samples. All extracts were cleaned

up using Florisil columns. Recovery standard was added to allow for calculation of recovery percentages of internal standards. The separation and detection of these compounds were performed by gas chromatography and mass spectrometry (GC-MS and GC-MS/MS, Agilent and Waters). Quantification was conducted with the Masslynx software.

The analyses of the NOWAC samples were described by Rylander et al. (2012), and the analyses were performed in the same laboratory and the methods closely resembled those of the MISA samples (Paper III).

3.3.4. Analyses of PFASs

Analyses of PFASs were performed for Paper II, and analytical details and lists of analysed compounds are presented there. The extraction procedures were modified from Powley et al. (2005) and described in Hanssen et al. (2013). Briefly, these extractions included addition of internal standards to serum, extraction by methanol, cleaning the extract with acidified charcoal and addition of recovery standard. The separation and detection of these ionic PFASs were performed by ultra-high pressure liquid chromatography triple quadropole mass-spectrometry (UPLC-MS/MS, Thermo Scientific). Quantification was conducted with the LC Quan software.

3.4. Mechanistic modelling

CoZMoMAN is a mechanistic non-steady-state environmental fate and human food-chain bioaccumulation model. On the basis of historic time-variant emission estimates (displayed in Figure 1), environmental fates and human food-chain bioaccumulation of PCBs can be mechanistically simulated by CoZMoMAN (Breivik et al., 2010). The model includes a marine and a terrestrial human food-chain and a graphic presentation of the CoZMoMAN model is presented in Figure 9. The original model domain includes Sweden and parts of South-eastern Norway and estimations of dietary habits were based the food consumption of the Swedish population (Czub and McLachlan, 2004).

The PCB congeners simulated in this work were PCBs 118, 138, 153, and 180. The required input information for CoZMoMAN was birth year, year of sampling, daily intakes of dairy products, meat and fish. For women, their age at child birth(s) and the duration of breastfeeding for each child also had to be specified. Calculations of point estimates of concentrations as well as life-course concentration profiles and temporal trends for a certain period were conducted. Further, the model evaluation included group level (Paper I) and individualised (Paper III) parameterisation of input information. In Papers I and III, estimates of PCB concentrations from CoZMoMAN was confronted with PCB measurements in order to evaluate its performance.

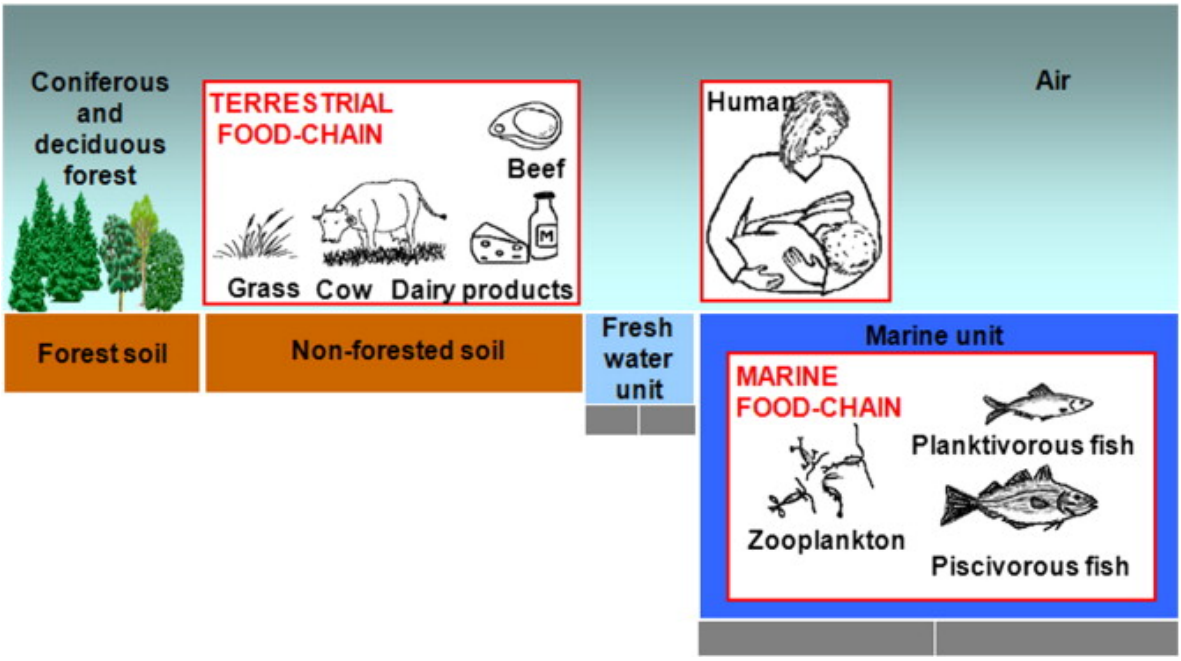

Figure 9. Graphical presentation of the structure of the CoZMoMAN model (reproduced from Breivik et al., 2010 with permission).

3.5. Statistical analyses

The statistical approaches in all three papers were performed in the freely available, open-source software R (R Development Core Team, available at http://www.cran.r-project.org). Approaches to censored values and the confounded APC effects are discussed below, but the details on the different methods are described in each respective paper. Most contaminant concentrations were non-normally distributed and accordingly, non-parametric methods were generally preferred.

3.5.1. Censored environmental data

Managing results of environmental contaminants in the general population often involves handling concentrations that are below a limit of detection (LOD). The LODs were determined from the analytical instruments for each sample individually (instrumental LOD), or for each sample extraction batch from the concentration in blank samples (method detection limit). The approach chosen differed between contaminant classes and has been described in each paper. Concentrations below this threshold must be considered unknown but cannot be disregarded. In Papers I-III, statistical methods for censored data were employed for calculating summary statistics for compounds that were detected in <80% of samples as described by Helsel (2005). Furthermore, statistical analyses focused on the fully-detected and dominating compounds to avoid uncertainty in estimates.

3.5.2. The age-period-cohort conundrum and mixed models

Papers I and II aimed to describe temporal changes in POP concentrations in humans and the disentangling of confounded time dimensions using an APC approach. The extreme confounding of the three time factors age, birth cohort and period is a challenge in studies of time trends, and there have been attempts to reveal the separate effects (Ahacic et al., 2012; Ding et al., 2007; Yang and Land, 2006). This problem has not been addressed statistically in previous studies of POPs in humans. The chosen statistical methods of Paper I and II included mixed models that allowed for assessing longitudinal trends nested in each person as the measurement unit over time. The statistical calculations of fixed and random factors in the models facilitate the separation of the confounded factors (Ding et al., 2007). As these approaches are still being debated, the full (all three factors included) and the

reduced models (including only one or two factors) were presented in the thesis papers to allow for comparison by the readers of the model choices. Also, a graphical approach (Ahacic et al., 2012) was presented and is assumed to be conceptually easier to understand.

3.6. Ethical considerations

This work included handling of blood samples and personal information obtained in three different cohorts, and the inherent management of these cohorts assured the systematic framework for ethically evaluated handling of samples, personal information and analytical results.

Participation was voluntary and signed informed consents were obtained from all participants. In subjects from the Tromsø Study, the surveys in 1979 and 1986-1987 were conducted before this procedure was required and common practice. Indeed, the first guidelines regarding ethical conduct in medical research were published in 1993 (Skavlid, 2010). An appearance to join the study was then regarded as consent to join, and the subjects did sign informed consents in the later surveys.

All use of information and samples in the three papers of this work has approvals from the Regional Committee for Medical and Health Research Ethics and the Norwegian Data Inspectorate (Lund et al., 2008; Veyhe et al., 2012). Information on the study participants was obtained from the cohort data bases at the University of Tromsø and such access met all internal security and confidentiality requirements. The identification of all samples and of questionnaire information was depersonalized.

Other more non-invasive sampling methods might have been employed, but the alternatives like urine do not reflect the internal exposure to environmental contaminants as well as blood. Blood samples were handled according to established routines at the laboratory, including their destruction before disposal.

Results are not to be reported back to the participants and the storage of the results will be according to requirements of the cohort procedures. Results have been or are intended to be published in peer-reviewed journals. None of the co-authors of the three papers had conflicts of interest.

4. Results - Summary of papers

Paper I

Time trends of PCBs and OCPs during 1979-2007 in men from the Tromsø Study

This study investigated periodic trends in concentrations of 24 PCBs and 17 OCPs (including metabolites) in five repeated serum measurements of 53 men from Tromsø, Northern Norway during 1979-2007. APC effects were assessed by graphical and mixed model analyses. Additionally, emission-based mechanistic modelling of 4 PCBs for this time period was performed.

Results demonstrated substantial intraindividual declines in serum concentrations of most legacy POPs from 1979 to 2007. The median decreases in summed serum POP concentrations in 1986, 1994, 2001, and 2007 relative to 1979 were –22%, –52%, –54%, and –68%, respectively. Although the periodic trends were evident for most compounds, the magnitude of the decrease differed between them. The compounds dominating legacy POP burdens were *p,p'*-DDE; PCBs 153, 138/163, 180; and HCB. Many compounds correlated strongly to PCB-153. In addition to the periodic trends for PCB-153, birth cohort patterns were indicated. Predicted PCB-153 concentrations were consistent with measured concentrations in the five sampling years.

Paper II

Time trends of PFASs during 1979-2007 in men from the Tromsø Study

This study investigated periodic trends in concentrations of 10 PFASs in the same sample set as in Paper I. Also, the approach taken to assess APC effects was the same as in Paper I.

The concentration changes of PFASs in the repeated measurements from 1979 to 2007 demonstrated divergent time trends between the different PFASs. The median concentrations of PFOS and PFOA increased five-fold from 1979 to 2001 and decreased by 26% and 23%, respectively, from 2001 to 2007. Perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA) displayed increasing trends throughout the entire study period. Although PFOS comprised

dominating and stable proportions of PFAS burdens during these years, the contributions from PFOA and perfluorohexane sulfonic acid (PFHxS) were considerable. APC evaluation demonstrated that periodic trends prevailed for concentrations of PFOA, PFUnDA, and PFOS, and weaker associations with birth cohort were indicated for PFUnDA.

Paper III

Person-specific predictions of PCB concentrations in two female cohorts

This study investigated the capability of the dynamic mechanistic model, CoZMoMAN, to reproduce measured concentrations of 4 PCBs in serum from 553 pregnant and postmenopausal women. Linear regression models of dietary and lifestyle variables supported the assessment of person-specific concentrations and predictors.

CoZMoMAN could accurately reproduce medians and ranges of measured concentrations in the two study groups. Agreement between predictions and measurements for PCB-153 was good overall as evaluated by Spearman rank correlations and Weighted Cohen`s Kappa, but less accurately so within each study group and for postmenopausal women compared to pregnant women. Statistical approaches identified personal characteristics as predictors for concentration of PCB-153 that were not explicitly addressed in CoZMoMAN. Person-specific predictions for blood concentrations from birth until time of sampling revealed considerable variation between the study subjects, particularly in the timing of peak concentrations. Indeed, NOWAC women experienced increasing concentrations up to adulthood whereas MISA women experienced peak exposures at birth.

5. Discussion

5.1. Considerations of methodological aspects

5.1.1. Study design, population and validity

The design of the Tromsø Study has enabled a longitudinal examination of POP trends including repeated measurements (Papers I and II) which are rare in human biomonitoring studies of POPs. Participation rates throughout the Tromsø Study surveys may be considered high as proposed by Jacobsen et al. (2012). The conclusions made for the Northern Norwegian men in Paper I and II can likely be representative for this age group and gender in Northern Norway (internal validity). Although individual dietary information was inadequate, the intake of marine food in Northern Norway and in particular in elderly men is generally high (Alexander et al., 2006; Norwegian Directorate of Health, 2010; Johansson and Solvoll, 1999). The POP concentrations are likely influenced by the dietary patterns of study subjects which could imply that results could be similar in groups with similar dependence on marine food. The concentration levels and temporal changes are likely not generalizable to other age groups or women because of their reported lower POP concentrations (Furberg et al., 2002; Sandanger et al., 2006) and differences in dietary habits (Alexander et al., 2006; Johansson and Solvoll, 1999). Our results highlight considerable individual differences in temporal trends among the study subjects. Still, the qualitative observations that temporal changes in human concentrations relate to changes in human exposure media and altered production and use, is likely generalizable to other populations. Also, the significance of APC effects and life-course aspects for POP studies is generalizable to other populations and to other POPs and chemicals.

The two cross-sectional sample sets of female subjects for whom person-specific predictions were obtained (Paper III) originated from two established cohort studies. External validity was deemed acceptable in both NOWAC and MISA (Lund et al., 2003; Veyhe et al., 2012). The internal validity in MISA was considered acceptable by Veyhe et al. (2012) although the participation rate among invited women was low. The participation rate in the NOWAC cohort has been designated as high by Lund et al. (2003). Information on dietary habits in the two female cohorts was extracted from questionnaires. The questionnaires of the MISA study were based on those of NOWAC and further expanded for questions on fish intake (Veyhe et al., 2012). The food freqency questions were converted into daily intake in grams per day using a standardized measurement table (Blaker's

Norwegian Weight and Measurement Table) (Veyhe et al., 2012). The external validity of questionnaires and food intakes in NOWAC has been validated by a test-retest, a 24hr recall study and a biochemical marine food markers study (Hjartåker et al., 2007; Hjartåker et al., 1997; Parr et al., 2006). The pregnant women are likely representative for other pregnant women in Norway with similar dietary habits with regards to marine food. The postmenopausal women are from the general Norwegian population and concentration ranges in the included study subjects are likely representative for Norwegian postmenopausal women. It is likely that predictive ability of the CoZMoMAN model is good for these women due to that their exposure pathways are similar to those assumed by the model. The qualitative observations of individual variation in past and current POP concentrations are of significance also for other study populations.

5.1.2. Sample integrity

The storage from 1979 to 2011 for samples in the Tromsø study (Papers I and II) implicates 30 years of potential for desiccation or degradation of the samples. Any sample desiccation or lipid degradation would lead to incorrect concentrations of POPs and possibly interpretations of time trends when expressed as wet weight or lipid weight, respectively. Sodium (Na^+) concentrations in plasma are physiologically controlled within a narrow range and have been shown to be stable in plasma during 100 freeze and thaw cycles (Paltiel et al., 2008). This makes it a suitable indicator of sample volume changes. In the Tromsø study, lipid and POP concentrations of samples with Na^+ concentrations above a specified threshold were adjusted by a factor proportional to the enhanced Na^+ as described by Krieger et al. (1994). Studies targeting effects of long-term storage on lipid concentrations have demonstrated decreasing concentrations of some lipid classes (e.g. cholesterol) and increases of others (e.g. triglycerides) although results have not been consistent (Devanapalli et al., 2002; Shih et al., 2000; Zivkovic et al., 2009). Cholesterol and triglycerides had previously been determined in the samples from the Tromsø study and a reanalysis of lipids served to indicate lipid degradation. After adjusting reanalysed results for desiccation, the past and current measurements deviated <10% and correlations between the two measurements increased (Figure 10). These results indicated the extent of lipid degradation to be small; however, lipid concentrations in 1994 were higher relative to samples from the other sampling years without any apparent explanation.

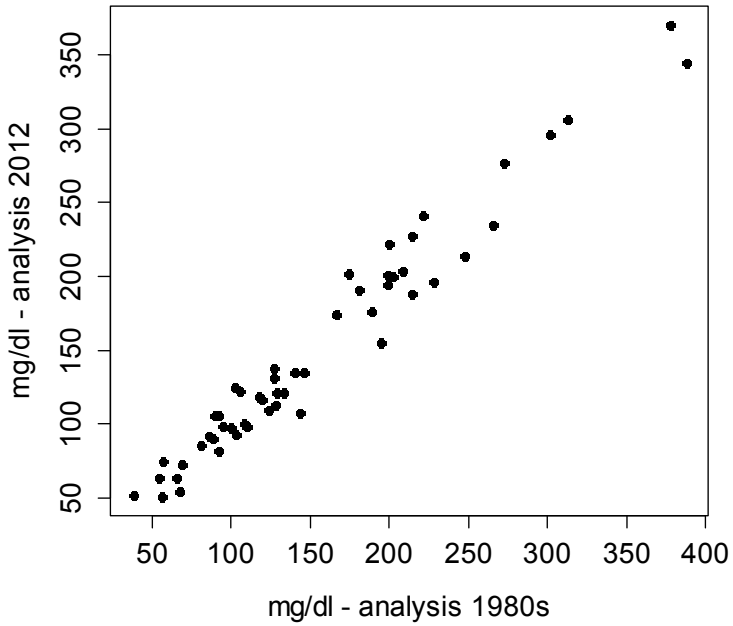

Figure 10. Concentrations of triglycerides measured in serum samples from 1979 during the 1980s and again in 2012. The relationship between measured concentrations is expressed by $\beta=0.95$, $R^2=0.96$, $p<0.0001$.

Effects of long-term storage on concentrations of PCBs, OCPs and PFASs were assumed negliable due to the the persistent properties of these compounds. Accordingly, PCBs and OCPs in human liver samples were stable during storage at -25°C for seven years (Wise and Koster, 1995) and small differences were demonstrated in PFOS and PFOA concentrations after five years of storage (Olsen et al., 2007b). Clearly, these findings indicate that any temporal changes of POP concentrations are not related to deterioration of sample integrity.

5.1.3. Chemical analyses

The use of serum/blood for determination of POPs (Papers I-III) is regarded as a good representation of circulating concentrations of POPs. Generally, concentrations of POPs reside in the plasma or serum and are thus considered to represent that in whole blood (Ehresman et al., 2007; Needham et al., 2007; US National Research Council, 2006). However, FOSA partition extensively to the blood cell fraction and thus serum FOSA concentrations are underestimated compared to those in whole blood (Hanssen et al., 2013; Kärrman et al., 2006).

A wide range of PCBs, legacy OCPs and PFASs (Papers I and II) was targeted and concentrations of 51 compounds were determined in all samples. Another 16 PFASs were screened for in a subset of samples, yet their detection frequency was low. Additional analyses were not possible due to the limited sample volume and availability of pertinent instrumental methods. The expansion of the currently targeted contaminant classes with, for example, isomer-specific PFOS measurements would have offered valuable information.

The chemical analyses of PCBs, OCPs and PFASs employed are well established, although slight modifications were required due to the low sample volume. The analytical protocols included the following systematic quality assurance-quality control (QA-QC) procedures to ensure the precision and accuracy of concentrations.

- Evaluation of analyses of standard reference materials (SRMs) where agreement between the measured value and a certified value ensured the accuracy of analyses. The repeated analysis of SRMs throughout sample processing evaluated the precision of the results. Note that certified concentrations are not available for all compounds.
- Analyses of blank samples served to assess potential laboratory contamination and to determine a threshold to avoid false positive detections of low concentrations.
- The laboratory at the Norwegian Institute for Air Reseach routinely participates in the international AMAP Ring Test for Persistent Organic Pollutants in Human Serum and has performed well (within ± 20% of assigned values).
- A high number of internal standards representing POPs with properties ranging those of the analytes was added to ensure that the method is adequate for compounds with different properties. Further, quantification based on the internal standard method corrects for any loss of sample during sample extraction. One sample batch of the PCBs and OCPs extraction had low recovery, yet there was no association with concentrations.
- Quantified results of PCBs and OCPs were rejected when the isotopic mass ratios deviated by > 20% from those in quantification standards. For PFASs, the presence of two masses were regarded qualitatively to confirm the compound specificity.

QA-QC measures indicated good quality for reported concentrations which, together with the good sample integrity, confirm that good internal validity was achieved. Still, challenges involving single components were encountered during quantification of results and were addressed in Paper I and II.

5.1.4. Statistical methods and sample size considerations

Many human biomonitoring studies that include the analysis of POPs are challanged with the limited number of samples. Sample size calculations for mixed models for the rate of change for PCB-153 (with the package 'longpower' in R, for the simplest models presented in paper I) indicated that with statistical power of 80%, a 30% change over the five repeated measurements could be detected with 48 persons, 40% with 27, and 50% with 17. The change in median concentrations from 1979 to 2007 on was 53% and indicated that the mixed model analysis for PCB-153 was based on sufficient sample size. The power of the calculations of all separate effects in extended models were likely not as strong. Thus, the discussion of absolute effect sizes between models were minimized. For a 10% change in the mixed models for PFOS, PFOA and PFUnDA the number of persons sufficient to provide a power of 80% in the simple models were 5, 7, and 3, respectively. Thus, the sample size included has sufficient power to detect the time trends observed.

Statistical approaches to APC effects (Papers I and II) have been much discussed in the literature (Ding et al., 2007; Holford, 1991; Holford, 2006; O'Brien, 2014; Robertson et al., 1999; Tu et al., 2011; Yang and Land, 2006), yet no consensus has been reached about the best strategy (Glenn 2003). For the purposes in Papers I and II, mixed model analyses were chosen. This allowed consideration of both age and birth cohort patterns, while also allowing for person-specific random variation in the five repeated measurements. Currently, p-values cannot be estimated in these models, and confidence intervals were obtained from *post hoc* model testing. Potential interactions between the time factors could not be considered in the mixed models, and our ability to examine APC effects was limited by the low number of subjects. The methodology chosen for APC effects (Papers I and II) aimed to highlight the conceptual understanding of the three time scales in POP concentrations. Although this topic involves dealing with extreme confounding and since the sample set only included 53 subjects, the strength of our study was the repeated measurements.

Regression models were employed to identify predictors of PCB concentrations in Norwegian women (Paper III) as supplemental approaches to the mechanistic modelling. Studies employing multivariate approaches have established the same predictors and this enhances the reliability of our findings.

Environmental measurement data often involve a challenge with values that are below a threshold for which concentrations are considered certain (Helsel, 2005). Different

strategies can be chosen when assessing concentrations of a compound when a varying fraction of the data is censored. Summary statistics for compounds with detection frequencies between 20% and 80% were calculated for each sampling year according to Helsel (2005). In Paper I, summed concentrations were calculated from lipid-adjusted concentrations of compounds with >60% detection and individual concentration estimates were used for values below LOD rather than employing a replacement strategy (e.g. LOD/$\sqrt{2}$; Anda et al. (2007)).

5.2. Temporal trends during 1979 and 2007 in Norwegian men

5.2.1. Summary of time trends for PCBs, OCPs and PFASs

The observed longitudinal trends of PCBs, OCPs and PFASs from 1979 to 2007 in serum from Northern Norway males are summarized in Figure 11. Concentrations are presented on a wet weight basis to be able to present all POPs combined. Clearly, the magnitude of the circulating burden of these compounds has changed during the 28 year period. The concentrations of PCBs and OCPs have generally decreased, and those of PFASs have first increased and then decreased. In the most recent samples, the circulating organochlorine concentrations appear minor compared to those of organofluorines.

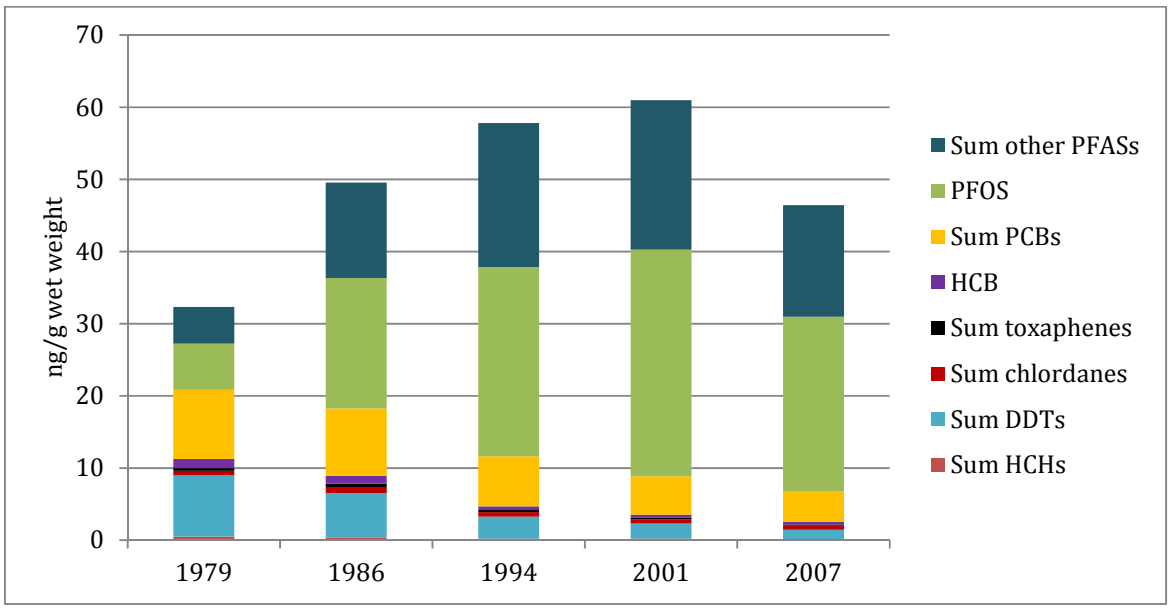

Figure 11. Wet weight concentrations of PCBs, OCPs and PFASs (note that PFOS is displayed separately) from 1979 to 2007. Presented results are based on the results of Papers I and II for sera from men in the Tromsø Study.

Concentrations of most compounds declined following restrictions or bans on production and use implemented in many countries prior to or during the study period (Paper I and II). However, the magnitude of the decrease differed between contaminant classes. The time trends of PCBs were declining from 1979 and 1986, and median summed PCB concentrations in 2007 were 44% of those measured in 1979. The median concentration of DDT was reduced by 96% from 1979 to 2007, whereas the concentrations of chlordanes

and Mirex did not change considerably. The declines of many POPs, especially *p,p'*-DDT, were exponential and indicated non-linear rates of decrease across the study period. By contrast, the summed PFAS concentrations increased five-fold from 1979 to 2001 followed by a 25% decrease to 2007. Also, the longer chained PFCAs increased throughout the period. Hence, there are divergent time trends between PCBs, OCPs and PFASs which likely reflect the different exposure histories of PFASs as compared to those of PCBs and OCPs.

Estimates of historic production, emissions or use are displayed for PCBs, DDT and POSF in Figure 1, 2 and 3, respectively. Clearly, the characteristics of human trends resemble those of historic production and use relative to the sampling time. Although emission inventories are not available for all compounds, the past restrictions and bans on production and use of POPs have translated into declining human concentrations after a time-lag. These results demonstrate that regulatory initiatives have impacted human exposures. The response time before human concentrations of a POP are reduced following declining production and use differ between compounds. This time-lag likely depend on human elimination rates and the response time of human exposure media with regards to environmental fate and degradation rates of that POP (AMAP, 1998; Armitage et al., 2009; Bignert et al., 1998; Quinn et al., 2011).

The range of POPs in past and current commerce is wide and their respective histories of production and use have varied. Hence, along with compound-specific environmental fate, precursor chemistry, exposure pathways and human elimination rates this has resulted in complex and dynamic compositions of POPs in human blood. The most prevalent PCBs, OCPs and PFASs in sera from Northern Norwegian men in all sampling years were PFOS, *p,p'*-DDE, PCB-153, HCB (wet weight concentrations from Paper I and II), and this is in agreement with other Norwegian studies (AMAP, 2009; Haug et al., 2009; Sandanger et al., 2006; Thomsen et al., 2007). However, the relative contribution of each compound has changed from 1979 to 2007. Indeed, the time trends have differed both between and within POP groups.

Concentrations of *p,p'*-DDT, *p,p'*-DDE, PCB-153, PCB-180, PFOA and PFOS respectively decreased annually by 7.7%, 3.9%, 3.8%, 3.3%, 4.3% and 3.8% from their peak values. The steeper decline in *p,p'*-DDT compared to other compounds, along with an increasing *p,p'*-DDE/*p,p'*-DDT ratio which is sensitive to recent exposure to *p,p'*-DDT (Anda et al., 2007), demonstrate that the exposure to DDT was effectively reduced. Interestingly, the rate of decrease in concentrations appears similar for the other compounds mentioned above. The decline for PFOA and PFOS was only observed between the last two measurements (Paper

II), yet the rate of decrease appeared similar to those of the higher chlorinated PCB congeners and DDE. The decrease in concentrations of summed HCHs and HCB were more pronounced as compared to summed PCBs; however, toxaphenes decreased fairly parallel to PCBs (Paper I). No or minor changes were observed for concentration of chlordanes and Mirex. The apparent rates of decrease for PCBs, OCPs and PFASs in human serum likely relate to the varying degradation properties of compounds in human exposure media and the human body.

Although our sample size was small and time trends are represented by only five data points, the observations are unique because of repeated measurements in the same individuals, the long study period and the analyses of a total of 51 compounds in all samples. Also, statistical power to detect changes was satisfactory, storage effects were adjusted for, and all analyses were performed with the same methods.

5.2.2. Time trends within PCBs, OCPs and PFASs

Relative differences in concentration declines were also observed within POP groups and reflect the different properties within each contaminant class. Examples are illustrated below.

- The relative proportion of PCB 138, 153, and 180 to summed legacy POPs increased from 1979 to 2007 (Paper I) and this likely demonstrates their higher persistence in the human body relative to lesser chlorinated PCBs (Milbrath et al., 2009; Ritter et al., 2011; Shirai and Kissel, 1996).
- Concentrations of PFHxS increased steadily until 2001 but did not display a significant decrease from 2001 to 2007 (Paper II), even though production of this compound was phased out along with PFOS (Kannan et al., 2004). This divergence could be due to the longer elimination half-life of PFHxS relative to PFOS (Olsen et al., 2007a) and possibly reflect a relatively higher exposure of PFHxS through a food-chain exposure pathway compared to PFOS.
- PFNA, PFDA and PFUnDA concentrations increased from 1979 to 2007 (Paper II) and likely reflect their continued production after the phase out of POSF-production in 2000-2002 (Armitage et al., 2006), perhaps along with longer elimination half-lives and higher bioaccumulation abilities compared to shorter-chain PFCAs (Conder et al., 2008; Zhang et al., 2013b).

- Human elimination rates of branched isomers of PFOS have been shown to be shorter compared to the linear isomer (Benskin et al., 2009; Zhang et al., 2013b). However, the percentages of branched isomers in summed PFOS concentrations were relatively stable (~30%) in the Northern Norwegian male study group during 1979-2007 (Paper II). There was no time trend observed for the relative isomer contributions for the entire study group. However, unique time trends could be observed for each individual.

5.2.3. Individual variation in time trends

The overall time trends were evident in all individuals for most compounds although there was large variation between individuals with regards to concentrations themselves, rates of change and timing of peak concentrations. Especially, the widest concentration ranges and temporary concentration spikes for some persons were observed during peak years for PCB-153, PFOS and PFOA (Papers I and II). This likely demonstrates the amplified differences between low and high exposed individuals when exposure intensity is large. Correlations of any pair of consecutive measurements for many PCBs and OCPs became stronger during the study period (e.g. ρ = 0.44, 0.79, 0.87, and 0.89 between 1979 and 1986, 1986, and 1994, 1994 and 2001, and 2001 and 2007, respectively; Paper I), and this could indicate that exposure variability and intensity was reduced over time. A similar trend was observed between measurements of PFUnDA (Paper II). However, correlations were variable across the measurements for other PFASs, yet appeared stronger for the last two measurements compared to the first two. Together, these observations suggest that variation was high when exposure intensity was high and that correlations between two subsequent measurements became stronger following peak concentrations. The largest decreases were observed for individuals with the highest concentrations of PCB-153 (Paper I) and PFOS (Paper II), which is consistent with first order kinetics, and perhaps also reflect that certain POPs such as some PCBs can induce their own biotransformation enzymes (Shimada et al., 2002).

5.2.4. Regional, national and global comparisons

Prior to their ban or application restrictions in Norway, DDT was used as an insecticide, PCBs in building materials and electrical installations and PFOS in fire-fighting foam at airports. However, there has been no production of any of these compounds in Norway. In recent years, human exposure to these and related compounds in Northern Norway is likely linked to their historic emissions, long-range transport and presence in food items. Whereas exposure to many POPs has been linked to diet in recent years (see Section 1.5.3.), there is less knowledge of exposure sources during the years of most intense exposure.

Study design, age distribution and time of sampling relative to historic production and use must be considered when comparing concentrations and temporal trends in Papers I and II to other types of studies. The study subjects in Papers I and II were elderly men with high consumption of marine foods. These aspects also need to be kept in mind when making regional, national and international comparisons for this study group.

Compared to other Northern Norwegian studies also including younger age groups and women, our Tromsø male study subjects had generally higher concentrations of PCBs and OCPs (Furberg et al., 2002; Hansen et al., 2010; Rylander et al., 2009b; Sandanger et al., 2003) and PFASs (Rylander et al., 2009a; 2010). Sampling years in those studies varied from 1997 to 2005. Notably, POP concentrations in a coastal population in the Tromsø region with a high fish liver intake were in the same range as those in the present study for corresponding sampling years, although the summary statistics included women and persons who were younger (Sandanger et al., 2006). Furthermore, marine food intake (e.g. fat fish, fish liver, seagull eggs) has been demonstrated as a predictor of concentrations of PCBs, OCPs and PFASs in several of these studies (Furberg et al., 2002; Rylander et al., 2009a; 2009b; 2012; Sandanger et al., 2006). Together, this suggests that concentrations in our study subjects relate to the high consumption of marine food groups despite the lack of individual dietary information.

There are few longitudinal studies conducted among background-exposed populations. Time trends in concentrations of PCBs in the Northern Norway men were similar to those reported in pooled sera from the general Norwegian population during 1977 to 2003 (included females and younger age groups) (Thomsen et al., 2007). However, PCB concentrations were higher in our study subjects for all sampling years when compared to respective concentrations in the pooled sera (Thomsen et al., 2007). The time trends of several PFASs in our study group displayed many similarities to those reported in pooled

sera from men from the general Norwegian population (aged 40-50 at the time of each collection) during 1977-2006 (Haug et al., 2009). However, the slopes were steeper for PFOS, PFNA PFDA, PFUnDA in the years of increasing concentrations in our study, and the decrease for PFOS from 2001 on appeared less pronounced. These observed differences in time trends could partly be explained by enhanced and prolonged exposure to these compounds in our Northern Norwegian men, and possibly their expected higher fish consumption (Alexander et al., 2006; Norwegian Directorate of Health, 2010; Johansson and Solvoll, 1999).

When comparing temporal changes in our Northern Norwegian men with those reported in younger Swedish men, the concentrations of PCB-153, *p,p'*-DDE, and HCB and their temporal changes were comparable (Hagmar et al., 2006). By contrast, concentrations were lower and peaked later in our study subjects compared to those in two longitudinal cohorts conducted in the US Great Lakes area (Hovinga et al., 1992; Tee et al., 2003). On the other hand, concentrations were generally higher for PFOS, slightly lower for PFOA, and comparable for PFNA and PFHxS in our study group compared to those reported from cross-sectional studies in Germany and US (Kato et al., 2011; Olsen et al., 2012; Schröter-Kermani et al., 2012). Further, the decline in PFOS from 2001 to 2007 was less pronounced in the Northern Norwegian men compared those in these studies. Nevertheless, the temporal changes for PFOA, PFNA and PFHxS between 2001 and 2007 were comparable.

The time trends observed for the Northern Norwegian men are generally in line with observations in other studies although the decline appears slower. These similarities and differences could relate to continued higher intake rates due to the high consumption on marine food, along with geographical differences in environmental exposure intensities during the same time period.

5.2.5. Considerations of half-life calculations

Human half-lives were not specifically addressed in the evaluation of time trends in Paper I and II although the concept is relevant when exploring temporal aspects of human POP concentrations. Thus, this section presents considerations of half-life calculations and estimates from the results in Paper I and II that have not been presented in the papers.

Human body burdens of a bioaccumulative substance increase during times of constant or increasing exposures when the rate of intake exceeds the elimination rate. Human

elimination half-lives have often estimated from individuals experiencing high-exposure episodes (Olsen et al., 2007a; Seegal et al., 2010; Shirai and Kissel, 1996). Estimates of apparent human half-lives incorporate the aggregated effect of intrinsic elimination, on-going exposure, and body weight changes (Norén and Meironyté, 2000; Ritter et al., 2011; Wolff et al., 2000; Woodruff et al., 1994). From the mean concentrations at the peak year and the subsequent decreasing measurements in Northern Norwegian men, apparent half-lives could be calculated based on fitted exponential regression equations, specifically: 6.1, 10.8, and 19.8 years for *p,p'*-DDT, *p,p'*-DDE, and PCB-153, respectively. Similarly, estimated half-lives for PFOA and PFOS from the decline from 2001 to 2007 were 17.3 and 16.5 years, respectively. These estimates are crude and include uncertainties related to the method of estimation, especially for PFOS and PFOA estimates as they are determined from only two time points. Although the estimates presented are within the range of other longitudinal data (see Section 1.4.), they are among the higher values. This could imply prolonged exposure for the men in Northern Norway causing the decline to appear less steep. One explanation for this could be the relatively high intakes of these compounds through high consumption of marine food items and remoteness to urban and industrial sources.

If apparent half-lives were estimated for each person they would likely deviate from this group estimate as could be implicated from the considerable individual variation observed in time trends. Indeed, individual variation has been demonstrated for the serum elimination half-lives of PFOS in retired fluorochemical production workers (Olsen et al., 2007a). In that study, the group median half-life was 4.6 years although ranging from 2.4 to 21.7 years among all individuals. The large variations in individual curves observed in the Northern Norwegian men could be due to toxicokinetic variability and variations in diet between individuals. Half-lives are also dependent on initial concentration (Grandjean et al., 2008a; Shirai and Kissel, 1996) and vary as a function of age, smoking, and percent body fat (Milbrath et al., 2009). Hence, the estimates of apparent half-lives are likely dependent on the study population along with exposure intensity and duration.

5.2.6. Interpretations of time trends with regards to exposure pathways

Decreasing concentrations of a POP in human exposure media translate to declining concentrations of that POP in humans. Further, the rate of decrease reflects a combination of compound-specific persistence in the environment and elimination rates. For background exposed populations, it is likely that the sources of POP exposures are more diverse during periods of use. Accordingly, the largest variation and temporal spikes of concentrations of certain POPs were observed during years when concentrations peaked (Paper I and II). In the years after peak production, the relative importance of exposure through food-chains likely increases when near-field exposure sources are reduced. This might imply that the relative importance of food-chain related exposure has been higher for PCBs and OCPs in the study years than for PFASs, which could be related to the longer time passed since peak production and use for most PCBs and OCPs (Figure 5).

The time trends for PCBs and OCPs observed in wild-life and human dietary surveys (see Section 1.3.2.) are in agreeement with those observed in our study (Paper I). Further, the time trends of several PFASs in Northern Norwegian men (Paper II) are in accordance with decreasing trends in human dietary intakes in recent years (Johansson et al., 2014; Vestergren et al., 2012). Whereas the time trends of many PFASs are variable in wild-life monitoring, the observed continued increase of longer chained (C>8) PFCAs in our study group is in agreement with observations from such studies (Butt et al., 2010; Holmström et al., 2005; Holmström et al., 2010; Muir and de Wit, 2010; Roos et al., 2013). As environmental background exposure is likely becoming more important for PFASs, the discrepancy with wild-life trends to decrease in the coming years as near-field exposure sources (e.g. consumer products) are removed and peak production years become more distant (Vestergren and Cousins, 2009).

Moderate or strong correlations between many POPs and their similar percentages of decrease (see Section 5.2.1.) over time suggest similar environmental and human persistence and that their exposure pathways have changed little or concomitantly. Overall, the inter-compound correlations within the PCBs, OCPs and PFASs were strongest before and during peak years of expected exposure (Paper I and II) and likely reflect their common production and use.

The correlation between many compounds were strong throughout the study period or increased, and this suggests similar persistent properties and their co-exposure through environmental background concentrations (e.g. PCB-180 and HCB with PCB-153; Table 2).

However, some of the POPs evaluated (e.g. *β*-HCH; Table 2) were weaker but steadily correlated with PCB-153 concentrations during all sampling years, suggesting similar and unchanging environmental exposure pathways and similar rates of concentration decreases. Conversely, the correlations between some POPs decreased (e.g., *α*-HCH and PCB-149 with PCB-153; Table 2) and likely reflect their different persistence during decreasing exposures. Clearly, PFOA was not correlated to PCB-153 and suggests its exposure pathways are unrelated to those of many legacy POPs.

Table 2. Correlations between PCB-153 with ten selected POPs in the five survey years. The numbers represent the correlation coefficient (Spearman`s ρ) and bolded values are significant ($p<0.05$).

Sampling year	α-HCH	β-HCH	HCB	t-NC[a]	*p,p'*-DDE	PCB-149	PCB-180	PFOA	PFUnDA	PFOS
1979	**0.6**	**0.4**	**0.6**	**0.8**	**0.5**	**0.6**	**1.0**	0.2	**0.3**	**0.4**
1986	**0.5**	**0.6**	**0.8**	**0.8**	**0.8**	**0.6**	**0.9**	-0.2	**0.4**	0.3
1994	**0.4**	**0.4**	**0.8**	**0.8**	**0.7**	**0.4**	**1.0**	-0.2	**0.4**	0.3
2001	**0.3**	**0.4**	**0.7**	**0.8**	**0.7**	**0.4**	**0.9**	-0.3	0.3	0.2
2007	0.2	**0.4**	**0.8**	**0.8**	**0.7**	**0.3**	**0.9**	-0.1	**0.4**	**0.4**

[a]*trans*-nonachlor

The inter-correlation between PFNA, PFDA, PFUnDA and PFOS became stronger during the study period (Paper II). Further, the increasing PFNA/PFOA ratio observed appears to be an indication of the increasing influence of food-chain related exposure since PFNA>PFOA in wildlife studies (Vestergren and Cousins, 2009). This is in line with gradual co-exposure to these compounds during this period through environmental background concentrations as discussed above.

The human exposure history to PFASs has been more complex compared to PCBs because there is a variety of precursor compounds that can degrade to PFOA or PFOS. Enrichment of branched isomers (>30% branched) has been suggested as a biomarker of exposure to PFOS precursors (Martin et al., 2010). One explanation for the relatively constant proportions of branched PFOS isomers (~30%) observed in the Northern Norwegian men (Paper II) with time could be exposure to PFOS itself, rather than exposure to its precursors (Martin et al., 2010). Since FOSA is a precursor to PFOS and also the degradation product of other precursor compounds (Xu et al., 2004), the observed decline for FOSA could have

contributed to decreases in PFOS concentrations. Clearly, the contributions by precursor compounds to PFAS exposure remains to be further elucidated.

5.3. The age-period-cohort approach and POP trends

The repeated measurements described in Papers I and II allowed for an APC analysis. This approach revealed that calendar year of sampling was a stronger predictor for concentrations of PCB-153 and selected PFASs than age or birth cohorts. The longitudinal results demonstrate that PCB, OCP and PFAS concentrations did not increase as the men aged *per se*, but rather represents a periodic effect resembling trends of historic exposures based on past production and use as mentioned above.

Our study subjects were born in a narrow range of years during the early years of PCB emissions and well before the onset of large-scale PFAS production. Thus, large birth-cohort differences were not expected as the exposure (duration and intensity) to all persons was expected to be fairly similar at each sampling time point. Nevertheless, birth-cohort differences in concentrations were indicated for PCB-153 (and other PCBs and OCPs, although not presented; Paper I) and PFUnDA (Paper II), but not for PFOA and PFOS (Paper II). The differences between birth cohorts for PCB-153 and PFUnDA (Figure 12) were not large, although higher concentrations in the oldest birth quartiles could reflect more intense or prolonged exposure for these persons. One explanation could be relatively higher intake rates of POPs associated with higher fish consumption in the oldest age groups, which might be expected based on Norwegian population statistics (Alexander et al., 2006; Norwegian Directorate of Health, 2010; Johansson and Solvoll, 1999). Also, one could speculate that this observation for PCB-153 was related to the full overlap of the earliest born cohorts with the early PCB emissions. There were no differences between age or birth cohort quartiles for PFOS and PFOA, which could be due to similar magnitude of exposure for all birth cohorts. Also, the indicated birth cohort influence for PFUnDA could be due to more dependence on marine food as an exposure pathway compared to for PFOA and PFOS.

Age and period is confounded in the longitudinal design and thus, in addition to the periodic effect, weaker effects of age on individual temporal changes of PCBs, OCPs and PFASs cannot be ruled out. Potential changes related to aging are age-differentiated intake rates as has been shown for PFASs (Haug et al., 2010a; Tittlemier et al., 2007) or changes in toxicokinetic processes with age such as decreasing metabolic capacity. There have been indications of the latter in terms of elimination half-lives of PCBs in humans (Kreuzer et al., 1997; Milbrath et al., 2009).

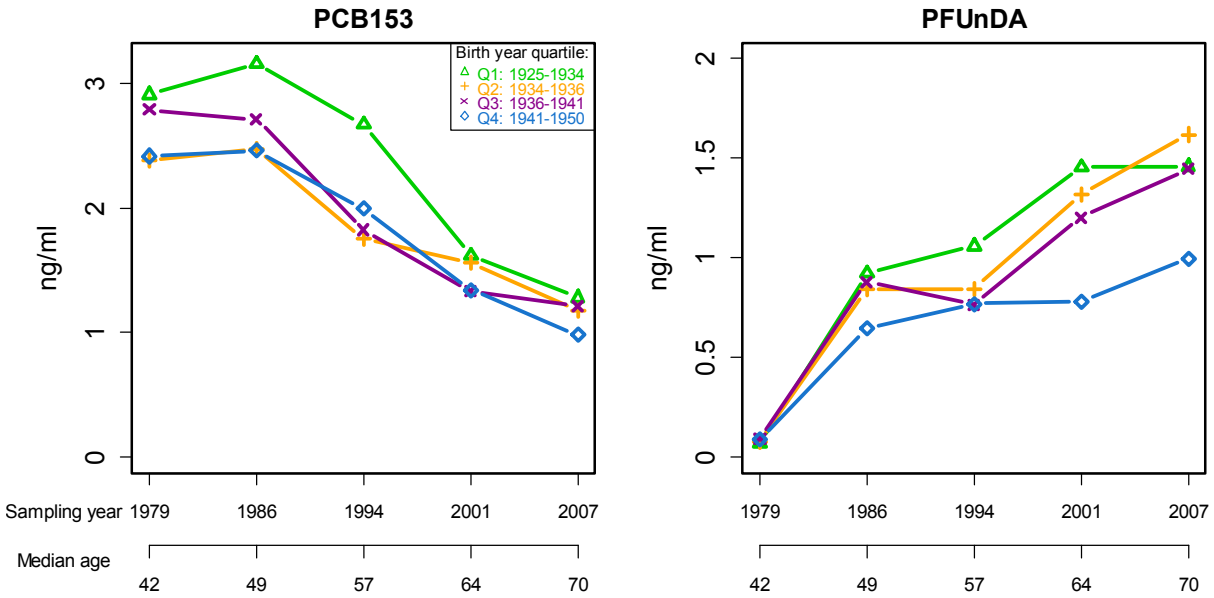

Figure 12. APC plots showing serum concentrations of PCB-153 and PFUnDA among birth cohorts according to sampling period. The graphs are based on the results of Papers I and II for sera from men in the Tromsø Study. In both groups, each line represents a birth year quartile.

Positive associations between concentrations of many legacy POP with age (Hardell et al., 2010; Mueller and Toms, 2010; Rylander et al., 1997; Wolff et al., 2005) or birth cohorts (Bjerregaard et al., 2001; Perry et al., 2005; Wolff et al., 2007) have been frequently reported in human cross-sectional studies conducted many years after peak exposures. Statements made in some studies referencing such associations to age are exemplified below.

- 'OCPs are persistent, broad spectrum toxicants and sequestered in lipid-rich tissues where their long half-life results in accumulation with age.' (Çok et al., 2012)
- 'POPs are lipophilic by nature. When consumed, they bioconcentrate in adipose tissue, and because of their long half-life, POPs accumulate with age and exposure.' (Nickerson, 2006)
- 'Because PCBs are resistant to metabolism in the body, they bioaccumulate as a person ages.' (Orloff et al., 2003)

In line with the statements above, one suggested explanation of higher POP concentrations in older age groups is longer time for bioaccumulation of these compounds when constantly exposed. However, the most likely explanation for increasing POP concentrations with increasing age in cross-sectional studies is birth-cohort differences in duration and

intensity of exposure and that older individuals lived through periods of more intense exposures compared to younger individuals (Alcock et al., 2000; Porta et al., 2008; Quinn and Wania, 2012; Ritter et al., 2011).

In contrast to legacy POPs, the newer POPs like PFASs have not shown a dependence on age in a number of studies (Calafat et al., 2007a; Calafat et al., 2007b; Harada et al., 2007; Olsen et al., 2008; Yeung et al., 2006), or have been either negative or positive depending on sampling year or sex (Haug et al., 2009; Kato et al., 2011). Studies of PFASs have been conducted closer to peak exposures in time (see Figure 5) compared to PCBs and OCPs. This might imply that exposure was recent for all age groups in such studies and that age associations reflect more recent exposures compared to studies of legacy POPs.

When the results for PCB-153 in Paper I were displayed as repeated cross-sections, positive relationships of concentrations with age were revealed that are in line with observations from cross-sectional studies despite the narrow age range. Cross-sectional organisation of PFOA, PFUnDA and PFOS results (Paper II) showed age-associations that varied between years. Thus, the correlations of POPs with age in cross-sectional studies are not equivalent to the statement that 'POPs increase with age' for each individual. Rather, the results underline that associations of POPs with age are conditional observations that must be understood in relation to historic production and use (Quinn and Wania, 2012). Furthermore, intraindividual and interindividual differences in age should be distinguished between longitudinal and cross-sectional studies, respectively. The interpretations of trends of POPs in human biomonitoring studies including a temporal aspect should consider study period relative to past production and use, as well as the human exposure pathways (Alcock et al., 2000; Quinn and Wania, 2012; Ritter et al., 2009). Furthermore, the study design and age structure of a study population must be regarded, and the observed trends will be influenced by compound-specific environmental persistence, exposure sources, exposure pathways, and elimination rates.

5.4. Achievements from mechanistic modelling

5.4.1. Group level predictive ability

The predictive ability of CoZMoMAN for group median concentrations was considered good with the best agreement observed for PCBs 153 and 180. Predicted median concentrations were comparable to those measured in: i) men from Northern Norway sampled during 1979-2007 (Paper I); ii) pregnant women from Northern Norway sampled during 2007-2009 (Paper III); and iii), postmenopausal women from Norway sampled in 2004 (Paper III). Also, the temporal changes in median measured concentrations during 1979 to 2007 in men from Northern Norway were reproduced by CoZMoMAN. This indicates that model parameterisation of temporal aspects, especially time-variant emission estimates, are realistic. Evidently, mechanistically derived intake estimates from terrestrial and marine food chains can adequately represent group level exposures of PCB concentrations.

5.4.2. Person-specific predictive ability

The overall predictive ability of individual predictions of PCB concentrations in pregnant and postmenopausal women was good compared to measured values (Paper III). However, precision was better for the pregnant Northern Norwegian women compared to the postmenopausal Norwegian women. Discrepancies between the predictions and measurements were associated with fish intake rates. It is likely that the fish consumption reported in questionnaires introduce variation into the model calculations due to recall problems when filling out questionnaires. Also, fish intake could be overestimated due to a predominance of fish-related questions. Body weight and consumption of seagull eggs were indicated as PCB predictors that should be incorporated in future simulations. The precision of person-specific PCB predictions using CoZMoMAN was similar to what has been demonstrated for pharmacokinetic modelling or statistical approaches (Bergkvist et al., 2012; Kvalem et al., 2012; Sonne et al., 2014). This is encouraging as the CoZMoMAN model incorporates calculations of human bioaccumulation based on emissions and environmental fate and requires information available in questionnaires.

5.4.3. Advances of mechanistic modelling

Human biomonitoring and effect studies have demonstrated the need for expanding exposure estimates from single measurements to understanding a person`s concentrations throughout life. Also, estimation of human exposure when measurements are fragmented and at sensitive life stages is of significance.

The mechanistic modelling using CoZMoMAN was able to reproduce PCB measurements for three adult study groups in Norway (Paper I and III). Furthermore, predictions of a person`s PCB concentrations in the past could be obtained from estimates of historic emissions along with information on personal characteristics and reproductive history (e.g. ingestion rates, growth rates, child births, breastfeeding). Life-course concentrations (based on group median inputs) for a man in the Tromsø study, a woman in the MISA study and a woman in the NOWAC study are depicted in Figure 13. The estimated emission trends for PCB-153 assumed by CoZMoMAN are also displayed. Clearly, the awareness of individual variation through life and differences between individuals in past exposures is of importance for epidemiological studies. Furthermore, estimation of individual exposures in the past obtained from questionnaire information and the CoZMoMAN model can be employed as exposure metrics in such studies. Similar approaches to achieving estimates of human exposures and interindividual differences in concentrations have previously been suggested (Bachelet et al., 2010; Verner et al., 2011) and these warrant further research in suitable effect studies.

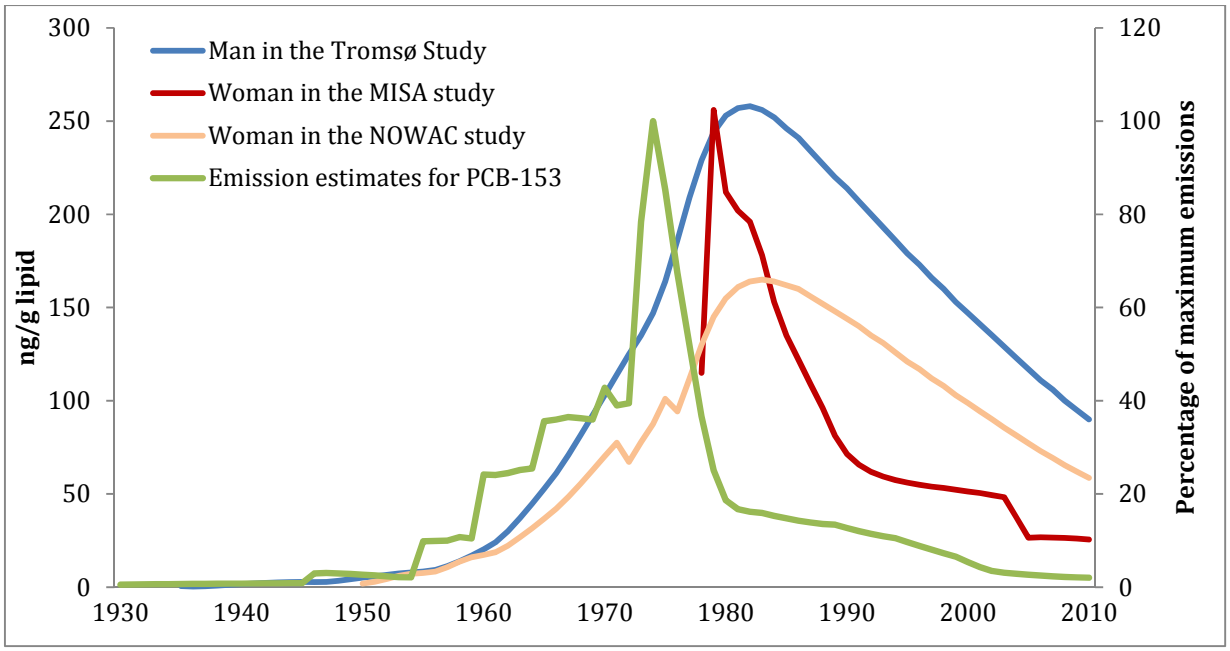

Figure 13. Life-course concentrations according to CoZMoMAN for the median man from the study group of men in Tromsø (Paper I, born in 1935), median woman from the NOWACs study group (Paper III, born in 1949) and median woman from the MISA study group (Paper III, born in 1978). Shown are also the time-variant emission estimates for PCB-153 in the CoZMoMAN model.

5.5. Human exposure characterization in epidemiological studies

Epidemiological effect studies address the potential association between an exposure and an outcome. These assessments rely on exposure measures to be representative and relevant for the aetiological exposure time window for the suspected effects (Ben-Shlomo and Kuh, 2002). As defined by the US National Research Council (2006), a biomarker of exposure to a chemical should have relevance for the outcome (biological plausibility and suspected mechanisms) and be possible to measure. Further, it should be sensitive (indicate the chemical if present) and specific (indicate the appropriate chemical). Still, how exposure is represented in terms of, for example, the time-variant intensity or integrated compound complexity varies.

Single measurements of blood POP concentrations are most often used as the exposure measurement in epidemiological studies (Lee and Jacobs, 2006; Steenland et al., 2010; Wigle et al., 2008; Wolff et al., 2000). Such measurements represent circulating biologically available concentrations and are good biomarkers of internal exposure doses; however, concentrations change with time, the sampling is invasive, and the physicochemical properties of compounds influence the partitioning to blood. Also, there are limitations as past or cumulative exposures are not necessarily strongly correlated to the single measurements (Paper III). The knowledge obtained from the repeated measurements in the longitudinal study (Paper I and II) demonstrates the importance of conducting studies of different designs.

Persons are often divided into quartiles according to POP concentrations as a classification of exposure level in effect studies (e.g. Demers et al., 2002). This includes a certain degree of misclassification as the quartile classification at the time of measurement does not necessarily agree with what could be assumed at the time when any effect arose. The inadequacy of single measurements as exposure metrics in epidemiological effect studies has been discussed (Bachelet et al., 2010; Heinzow and McLean, 1994; Paustenbach and Galbraith, 2006; Porta, 2012; Ritter and Arbuckle, 2007). Some authors have indicated important study features to consider (e.g. technology employed, study design, and biomarkers chosen) (Weis et al., 2005). Others have suggested potential approximations of past exposures (Bachelet et al., 2010; Verner et al., 2011) similar to that suggested from the mechanistic modelling using the CoZMoMAN model. Predicted life-course perspectives allow for assessment of past exposure for each person as well as indicated intergenerational differences (Quinn et al., 2011). Predicted exposures for foetuses and children are important for effect studies since effects potentially arise during sensitive life

periods (Boekelheide et al., 2012; Grandjean, 2008b; Wigle et al., 2008). For changes in concentrations throughout life and over time, APC effects in human POP concentrations had previously been proposed (Porta et al., 2008) and modelled (Alcock et al., 2000; Moser and McLachlan, 2002; Quinn et al., 2011; Ritter et al., 2009). Indeed, the results of Paper I and II provide empirical confirmation of such temporal effects. Furthermore, the findings of Paper I-III highlight that the understanding of temporal changes in human POP concentrations should be considered in the result interpretation of biomonitoring and effect studies.

The appropriate assessment of exposure in effect studies is further complicated by the fact that humans are exposed to a complex mixture of contaminants (Carpenter et al., 2002; Samet, 1995; Yang, 1998). Blood PCB-153 concentrations can be used as an indicator compound for the most persistent legacy POPs, but emerging contaminants with diverse exposure pathways may not correlate to the same extent (e.g. PFOA; Table 2). It is also likely that human body burdens also include chemicals in commerce that have not currently received the attention of researchers (Muir and Howard, 2006), and they could be future POPs based on persistence, bioaccumulation potential, and toxicity (Strempel et al., 2012). Clearly, the complexity of human exposure to POPs can continue to increase. Furthermore, interpretation of future monitoring studies should regard the temporal aspects of production and use of any chemical under study along with degradation rates in human exposure media and in humans.

6. Concluding remarks

Longitudinal serum data for PCBs, OCPs and PFASs in men from Northern Norway allowed for a novel perspective on how human concentrations of these chemicals have changed in relation to available information on historic production and use. Concentrations of POPs that were banned before or during the study period decreased in our study subjects. Further, the rates of decline of concentrations likely relate to a combination of emission reductions, persistence of contaminants in the environment and their human elimination rates. Currently, the circulating organochlorine burden of POPs is minor compared to that of organofluorines. The changing compositional patterns and inter-compound correlations likely reflect compound-specific temporal changes in concentrations in human exposure media and of exposure pathways.

Awareness of age-period-cohort effects is important for interpretations of human biomonitoring studies. Periodic trends were evident in the longitudinal results, with indications of birth cohort differences in concentrations of certain POPs. As the study subjects aged, concentrations reflected past production and use rather than an effect of age itself.

Mechanistic modelling using CoZMoMAN demonstrated reliable performance in three adult study groups. Predictions obtained from such models can serve as useful tools for assessing past, current and future exposures in human biomonitoring. Especially, predicted life-course concentrations can provide exposure metrics for the sensitive periods of life.

The research efforts described contribute to the understanding of human blood concentrations over time and during life for background exposed human populations in Norway. Also, the potential for mechanistic modelling to estimate past concentrations should be further explored in effect studies.

7. Future perspectives

Time trends of a larger number of emerging contaminants could have been addressed in the longitudinal sample set. In particular, the short-chained PFASs, perfluorobutanoic acid (PFBA) and perfluoropentanoic acid (PFPeA), were detected in three random samples from the Tromsø Study which indicates the potential for quantification of time trends also for these compounds. Additional longitudinal data of precursor compounds and isomer-specific analysis of branched PFOS could enhance our understanding of the importance of PFOS precursors for human exposure to PFASs as indicated by Martin et al. (2010). During the chemical analyses of the Tromsø study samples, a fraction containing phenolic compounds was extracted and stored. Analysis of these extracts can offer exploration of time trends of pentachlorophenol and hydroxylated PCB metabolites.

There are still knowledge gaps regarding the understanding of temporal changes in human concentrations of organic contaminants. The longitudinal study design offered new perspectives on relationships with time and age, and this awareness should be considered in future human biomonitoring efforts. Although repeated measurements are rare, the longitudinal design could be advantageous for future POP biomonitoring. A new study might include study groups of a fixed age group (e.g., 30 year old women, not the same individuals). Such monitoring could indicate temporal changes in POPs for women at reproductive ages and thus exposures for the unborn child across time.

Mechanistic modelling using CoZMoMAN could be further explored for other research hypothesis of human exposures. For example, model parameterisation for other compounds, additional food items and personal characteristics in the model framework could be pursued in the simulations. There is a need for predicted concentrations during foetal life, infancy and childhood, and thus the potential for employing model predictions as exposure metrics during these life stages should be explored.

This thesis has highlighted that time-variant estimates of production and use of POPs are crucial for a mechanistic interpretation of observed human exposure. It follows that there is a need for further efforts to establish reliable and up-to-date emission inventories for other organic contaminants of concern if the temporality in human concentrations is to be rationalized.

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Errata

Paper I

The second subheading in the Discussion “PCB-153 concentrations and aAPC effects” should have been “PCB-153 concentrations and APC effects”.

Appendix I

List of web links to letters of invitations and questionnaires in the Tromsø Study relevant in this work, Tromsø 2-6

The 1979 survey:

Letter of invitation: http://uit.no/Content/271751/T2_Invitation.pdf

Questionnaires: http://uit.no/Content/271760/T2_Q1.pdf

http://uit.no/Content/304040/T2_Q2.pdf

The 1986-1987 survey:

Letter of invitation: http://uit.no/Content/271752/T3_Invitation.pdf

Questionnaires: http://uit.no/Content/271762/T3_Q1.pdf

http://uit.no/Content/271763/T3_Q2.pdf

The 1994-1995 survey:

Letter of invitation: http://uit.no/Content/271754/T4_Invitation.pdf

Questionnaires: http://uit.no/Content/271764/T4_Q1.pdf

http://uit.no/Content/271765/T4_Q2_O70.pdf

The 2001-2002 survey:

Letter of invitation: http://uit.no/Content/271757/T5_Invitation.pdf

Questionnaires: http://uit.no/Content/271767/T5_Q1_O70.pdf

http://uit.no/Content/271769/T5_Q2.pdf

The 2007-2008 survey:

Letter of invitation: http://uit.no/Content/100339/Invitasjon_deltakelse_fase_1_t6.pdf

Information brochure: http://uit.no/Content/100340/Forespoersel_om_deltakelse_t6.pdf

Questionnaires: http://uit.no/Content/271770/T6_Q1.pdf

http://uit.no/Content/271771/T6_Q2.pdf

Appendix II

Web links to information pamphlet and questionnaires

in the Northern Norway Mother-and-Child Contaminant Cohort

Information pamphlet:

http://websim.arkivert.uit.no/getfile.php%3fPageId=6442%26FileId=13

Questionnaire answered at time of sampling:

http://websim.arkivert.uit.no/getfile.php%3fPageId=6442%26FileId=14

Main questionnaire:

http://websim.arkivert.uit.no/getfile.php%3fPageId=6442%26FileId=12

Appendix III

Web link to questionnaire

in the Norwegian Women and Cancer Study

The questionnaire that included the food frequency questions answered by the participants in the Norwegian Women and Cancer study:

http://site.uit.no/nowac/questionnaires-2/