Food and Agriculture Organization of the United Nations

30
FOOD SAFETY AND QUALITY SERIES

ISSN 2415-1173

# EXPOSURE TO ENDOCRINE DISRUPTING CHEMICALS

## CHANGES FROM 2002 TO 2024

# EXPOSURE TO ENDOCRINE DISRUPTING CHEMICALS

## CHANGES FROM 2002 TO 2024

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS
ROME, 2024

Required citation:
FAO. 2024. *Exposure to endocrine disrupting chemicals – Changes from 2002 to 2024.* Food Safety and Quality Series, No. 30. Rome. https://doi.org/10.4060/cd3005en



ISSN 2415-1173 [Print]
ISSN 2664-5246 [Online]

ISBN978-92-5-139296-6





Cover photos (from left to right):

Rome - Rice varieties on sale at a market, © FAO/Giulio Napolitano; Mauritius - School food programme, © FAO/Patrick Morin; Seibersdorf - A research scientist working in a Biotechnology Laboratory, © FAO/ Kai Wiedenhoefer.

Layout: Tomaso Lezzi

# CONTENTS

# TABLES

## FIGURES

# ACKNOWLEDGEMENTS

This publication was prepared by Peter Cressey, Science Leader at the Institute of Environmental Science and Research Limited New Zealand (ESR NZ) under the technical leadership and guidance of Angeliki Vlachou and Markus Lipp of the Agrifood Systems and Food Safety Division of the Food and Agriculture Organization of the United Nations (FAO).

The authors are grateful to experts who provided their insightful comments during the peer review process, in particular Abhishek Gautam (ESR NZ) and Vittorio Fattori (FAO).

The document was copy edited by Jeannie Marshall and graphic design was provided by Tomaso Lezzi.

Mauritius - School food programme

© FAO/Patrick Morin

# ABBREVIATIONS

| | |
|---|---|
| **APE** | alkylphenol ethoxylates |
| **BDE** | brominated diphenyl ether |
| **BP-3** | benzophenone-3 |
| **BPA** | bisphenol A |
| **BPF** | bisphenol F |
| **BPS** | bisphenol S |
| **CDC** | Centers for Disease Control and Prevention |
| **CHMS** | Canadian Health Measures Survey |
| **DDT** | dichlorodiphenyltrichloroethane |
| **DEHA** | di(2-ethylhexyl) adipate |
| **DEHP** | di(2-ethylhexyl) phthalate |
| **DEP** | diethyl phthalate |
| **DINCH** | di(isononyl) cyclohexane-1,2- dicarboxylate |
| **DL-PCB** | dioxin-like polychlorinated biphenyls |
| **DPHP** | di(2-propylheptyl) phthalate |
| **ECHA** | European Chemicals Agency |
| **EDC** | endocrine disrupting chemicals |
| **EDI** | estimated daily intake |
| **EFSA** | European Food Safety Authority |
| **ESB** | Environmental Specimen Bank (Germany) |
| **FAO** | Food and Agriculture Organization of the United Nations |
| **GC-HRMS** | gas chromatography-high resolution mass spectrometry |
| **GC-MS** | gas chromatography-mass spectrometry |
| **GMP** | Global Monitoring Plan |
| **GnRH** | gonadotropin-releasing hormone |
| **HBCDD** | hexabromocyclododecanes |
| **HBGV** | health-based guidance value |
| **HCH** | hexachlorocyclohexane |
| **HMW** | high molecular weight |
| **HQ** | hazard quotient |

| | |
|---|---|
| **NHANES** | National Health and Nutrition Examination Survey |
| **HPA** | hypothalamic-pituitary-adrenal |
| **HPG** | hypothalamic-pituitary-gonadal |
| **HPT** | hypothalamic-pituitary-thyroid |
| **ILO** | International Labour Organization |
| **IPCS** | International Programme on Chemical Safety |
| **LMW** | low molecular weight |
| **LOD** | limit of detection |
| **LOQ** | limit of quantification |
| **MISA** | Mother-and-Child Contaminant Cohort |
| **NBFR** | non-brominated flame retardants |
| **NHANES** | National Health and Nutrition Examination Survey (United States of America) |
| **NIEHS** | National institute of Environmental Health Sciences |
| **NZTDS** | New Zealand Total Diet Study |
| **OCP** | organochlorine pesticides |
| **PBDE** | polybrominated diphenyl ether |
| **PBPK** | physiologically-based pharmacokinetic |
| **PCB** | polychlorinated biphenyl |
| **PCDD** | polychlorinated dibenzo dioxins |
| **PCDD/F** | polychlorinated dibenzo dioxins/furans |
| **PFAS** | perfluorinated alkyl substance |
| **PFOA** | perfluorooctanoic acid |
| **POP** | persistent organic pollutants |
| **p,p'-DDT** | parent DDT |
| **REACH** | Registration, Evaluation, Authorisation and Restriction of Chemicals |
| **TEF** | toxic equivalency factors |
| **TEQ** | toxic equivalents |
| **UNEP** | United Nations Environment Programme |
| **VTG** | vitellogenin |
| **WHO** | World Health Organization |

# EXECUTIVE SUMMARY

In 2002, the World Health Organization (WHO), the International Labour Organization (ILO) and the United Nations Environment Programme (UNEP) commissioned the report titled *Global Assessment of the State-of-the-Science of Endocrine Disruptors* (Damstra *et al.*, eds., 2002). This report, commissioned by the Food and Agriculture Organization of the United Nations (FAO) addresses a somewhat narrower range of issues and is particularly focused on evidence suggesting that risk management measures put in place in the last four decades have resulted in decreased exposure to endocrine disrupting chemicals (EDCs). While FAO is primarily concerned with exposure to EDCs in diets, most of the available information on exposure trends is from human biomonitoring, which does not distinguish between routes of exposure.

There are a vast array of chemicals purported to be EDCs, but this report focuses on chemicals or groups of chemicals that have been consistently implicated as EDCs. There is a considerable overlap among chemicals considered to be EDCs and chemicals classified as persistent organic pollutants (POPs). The inclusion of chemicals in the Stockholm Convention has been the source of much of the information on human exposures currently available (UNEP, 2019).

This report is particularly focused on the exposure of human populations and food-producing animals to EDCs and more particularly on temporal trends in those exposures. The period since 2002 has seen many changes in the manufacture, use and control of many EDCs. Some of these changes have been driven by regulation, some by voluntary industry initiatives and some by increased awareness among consumers.

In general, there has been a downward trend in human food-producing animal exposure to EDCs where there have been specific regulatory controls placed on the manufacture and use of the chemical, where public health concerns have led to voluntary control measures by the manufacture or use industries, or where publicly available information has raised concerns in the general population. While all these mechanisms have been effective in reducing exposure to EDCs, they have not eliminated exposure. Exposure to many EDCs will continue for some time due to the incomplete application of control measures and the extreme environmental persistence of some EDCs.

Conclusions for specific chemicals or classes of chemicals are given below.

**Organochlorine compounds.** The manufacture and use of many organochlorine pesticides (OCPs) ceased in the 1980s and all studies summarized in this report have shown continuing decreases in the OCP content of food-producing animals and human exposure. The peak in human exposure to dichlorodiphenyltrichloroethane (DDT) before the ongoing decline may have occurred later in some African countries

(Linderholm *et al.*, 2010) where the use of DDT for vector control was allowed under an exemption to the Stockholm Convention (UNEP, 2019).

Animal concentrations and human exposure to polychlorinated dibenzo dioxins/furans (PCDD/F) and dioxin-like polychlorinated biphenyls (DL-PCBs) have similarly declined through the period considered in this study, except for northern China. There is evidence from two studies (Lu *et al.*, 2015 and Sun *et al.*, 2011) that exposure to the sum of PCDD/F and DL-PCBs was increasing through the late 2000s/early 2010s. Neither of the studies provided an explanation for this divergent trend.

**Polybrominated diphenyl ether.** Trends in concentrations of Polybrominated diphenyl ether (PBDE) congeners in animals and humans are complicated by the presence of multiple industrial formulations and the mixture of voluntary industry control and regulatory measures. Penta- and octa-brominated diphenyl ether (BDE) products were phased out earlier and this is reflected in the largely uniform decreases in congeners BDE-47, -99 and -100. While more recent studies show decreases in BDE-153 and -209 and hexabromocyclododecanes (HBCDDs), such trends are not always apparent in earlier studies. BDE-209 is the main congener in deca-BDE formulations, which were still in use later than the penta- and octa-BDE formulations. Similarly, the use of HBCDDs continued in some regions until recently.

**Phthalates.** While there is variation from study to study, overall there is good evidence to show that human exposure to low molecular weight (LMW) phthalates decreased across the period considered in this report. However, in some studies, decreases in exposure were not apparent until after regulatory action in Europe in 2013. While not always included in the studies, there is less evidence of decreases in exposure to the high molecular weight (HMW) phthalates that are not included in the European regulatory action. Several studies have shown that human exposure to phthalate substitutes, such as di(isononyl) cyclohexane-1,2-dicarboxylate (DINCH), is increasing.

**Bisphenols.** Decreases in exposure to bisphenol A (BPA) appear to have occurred earlier in Asia than in Europe and Northern America. While most studies have demonstrated decreases in BPA exposure, the decreases are often not substantial. While there is some evidence that substitution of BPA by other bisphenols may have occurred to some extent, no sustained trends in exposure to other bisphenols was apparent.

**Parabens, triclosan and benzophenone.** While use levels of these chemicals in cosmetic and consumer products are regulated in some countries, their use has not been banned and decreases seen in exposure, particularly for parabens and triclosan, are likely to be the result of public pressure and responses by manufacturers to that pressure. There is moderately consistent evidence for decreasing exposure to parabens and triclosan, particularly for methyl and propyl paraben. Unsurprisingly, most studies that have estimated trends in exposure to benzophenone-3 (BP-3) have reported increases. BP-3 is an active ingredient in sunscreen formulations and many countries have had active programmes encouraging the use of sunscreens.

**Alkyl phenols.** Only two studies were identified that considered trends in human exposure to alkyl phenols. The two studies, one in Germany and one in Japan, indicated decreases in human exposure to alkyl phenols after 2012.

**Perfluorinated alkyl substance.** Human exposure to the shorter chain perfluorinated alkyl substance (PFAS) appears to have decreased from about 2000 to 2008, with the peak of exposure varying between countries. There is limited evidence for decreased exposure to the longer chain PFAS and some indications of increases in exposure. There are relatively few studies on trends in the PFAS exposure of food-producing animals and the available studies give inconsistent indications of whether exposure is increasing or decreasing.

**Phytoestrogens.** Only two sources of information were found on trends in exposure to phytoestrogens, particularly the soy isoflavones, daidzein and genistein. There is little evidence of a trend in exposure to these chemicals. Data from the National Health and Nutrition Examination Survey (NHANES) in the United States of America are suggestive of increased exposure to daidzein. This may be due to increased use of soy products in processed foods.

Italy - Organic eggs

# CHAPTER 1
# INTRODUCTION

In 2002, the World Health Organization (WHO), the International Labour Organization (ILO) and the United Nations Environment Programme (UNEP) commissioned a report titled *Global Assessment of the State-of-the-Science of Endocrine Disruptors* (Damstra *et al.*, eds., 2002). UNEP and WHO commissioned a follow-up report in 2012 titled *State of the Science of Endocrine Disrupting Chemicals – 2012* (Bergman *et al.*, 2013). This report, commissioned by the Food and Agriculture Organization of the United Nations (FAO), addresses a somewhat narrower range of issues than the earlier reports and is particularly focused on evidence suggesting that risk management measures put in place in the last four decades have resulted in decreased exposure to endocrine disrupting chemicals (EDCs).

## 1.1 DEFINITIONS

While various definitions of endocrine disrupting substances have been posited, for consistency this report has adopted the definitions used in Damstra *et al.*, eds. (2002, p.1):

> An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations.

> A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations.

## 1.2 RELEVANT ASPECTS OF THE ENDOCRINE SYSTEM

The endocrine system was classically considered to consist only of glands that secreted hormones into the blood and were transported to distant target tissues, bound to specific cellular receptors, and produced characteristic actions (Damstra *et al.*, eds., 2002). However, a wider range of chemical regulators are now recognized.

The study of EDCs has tended to focus on three main aspects (axes) of the endocrine system, the:

> hypothalamic-pituitary-gonadal (HPG)

> hypothalamic-pituitary-thyroid (HPT)

> hypothalamic-pituitary-adrenal (HPA).

The HPG involves regulation of aspects of the body's reproductive functions through gonadotropin-releasing hormone (GnRH). The HPT stimulates general metabolic activity through the release of the thyroid hormones $T_3$ and $T_4$. The HPA regulates production of the glucocorticoid hormones, cortisol and corticosterone, which are involved in the body's response to stress, among other functions.

## 1.3 FREQUENTLY IDENTIFIED CLASSES OF ENDOCRINE DISRUPTING CHEMICALS

There is no single authoritative list of EDCs and the range of chemicals included in this definition varies depending on the source consulted. Table 1 lists chemicals or groups of chemicals that have been frequently classified as EDCs. The list of substances in the table is not intended to be exhaustive or definitive, however, the substances in Table 1 are generally agreed to have endocrine disrupting potential, are potentially present in the food supply and have been monitored in humans and/or foods and food-producing animals.

The European Chemicals Agency (ECHA) has established new hazard classes for chemicals placed on the European Union market under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (ECHA, 2023) such as: may cause endocrine disruption in humans (ED HH 1); suspected of causing endocrine disruption in humans (ED HH 2); may cause endocrine disruption in the environment (ED ENV 1); and suspected of causing endocrine disruption in the environment (ED ENV 2). This could lead to a more standardized classification of substances as EDCs, at least from a European perspective.

## 1.4 SCOPE OF THE CURRENT REPORT

This report has a particular focus on the exposure of human populations and food-producing animals to EDCs and, more particularly, on temporal trends in those exposures. While the Food and Agriculture Organization of the United Nations (FAO) is primarily concerned with exposure to EDCs from the diet, the bulk of the available information on exposure trends is from human biomonitoring, which does not distinguish between dietary and non-dietary exposure. There have been many changes since 2002 in the manufacture, use and control of many endocrine disrupting chemicals. Some of these changes have been driven by regulatory actions, some by voluntary industry initiatives and some by increased awareness among consumers.

TABLE 1 **CHEMICAL(S) FREQUENTLY IDENTIFIED AS ENDOCRINE DISRUPTING**

| CHEMICAL(S) | CHEMICAL TYPE | REFERENCES |
|---|---|---|
| Alkyl phenols | Industrial chemicals | (Demeneix & Slama, 2019; UNEP, 2017) |
| Atrazine | Herbicide | (Bergman *et al.*, 2013; Endocrine Society, 2022; NIEHS, 2023) |
| Benzophenones | Industrial chemicals | (Endocrine Society, 2022; UNEP, 2017) |
| Bisphenols (A, F, S) | Plasticizers | (Bergman *et al.*, 2013; Endocrine Society, 2022; Demeneix & Slama, 2019; La Merrill *et al.*, 2020; NIEHS, 2023) |
| DDT and metabolites | Insecticide | (Bergman *et al.*, 2013; Endocrine Society, 2022; La Merrill *et al.*, 2020) |
| Dioxins | Environmental contaminant | (Endocrine Society, 2022; NIEHS, 2023) |
| HBCDD | Flame retardant | (Bergman *et al.*, 2013; Endocrine Society, 2022; Demeneix & Slama, 2019) |
| Parabens | Antimicrobials | (Endocrine Society, 2022; Demeneix & Slama, 2019; UNEP, 2017) |
| PBDEs | Flame retardants | (Bergman *et al.*, 2013; Endocrine Society, 2022; Demeneix & Slama, 2019; NIEHS, 2023) |
| PCBs | Industrial chemical | (Bergman *et al.*, 2013; Endocrine Society, 2022; La Merrill *et al.*, 2020; NIEHS, 2023) |
| Perchlorate | Industrial chemicals | (La Merrill *et al.*, 2020; NIEHS, 2023) |
| PFAS | Industrial chemical | (Bergman *et al.*, 2013; Endocrine Society, 2022; Demeneix & Slama, 2019; NIEHS, 2023) |
| Phthalates | Plasticizers | (Bergman *et al.*, 2013; Endocrine Society, 2022; Demeneix & Slama, 2019; La Merrill *et al.*, 2020; NIEHS, 2023; UNEP, 2017) |
| Phytoestrogens | Natural plant substances | (NIEHS, 2023) |
| Triclosan | Antimicrobial | (Bergman *et al.*, 2013; Endocrine Society, 2022; Demeneix & Slama, 2019; NIEHS, 2023; UNEP, 2017) |

*Notes*: DDT: dichlorodiphenyltrichloroethane; HBCDD: hexabromocyclododecane; PBDEs: polybrominated diphenyl ethers; PCB: polychlorinated biphenyl; and PFAS: perfluorinated alkyl substances.

*Sources:* See References.

Kenya - A herd of buffalo grazing at the Meru National Park

# CHAPTER 2
# GENERAL EXPOSURE ISSUES

## 2.1 SOURCES OF ENDOCRINE DISRUPTING CHEMICALS

Since there are a diversity of EDCs, there are also a diversity of sources. EDCs may be introduced intentionally into the environment through such processes as the application of pesticides to crops. They may be naturally present in the environment as a normal component of plants (phytoestrogens) or unintentionally formed in the environment through processes such as combustion.

EDCs also enter the environment through the wear or breakdown of consumer items or as a component of domestic or industrial discharges (polybrominated diphenyl ethers, perfluorinated alkyl substances, parabens, alkyl phenols). Some EDCs enter our food supply because of migration from food packaging (bisphenol A, phthalates).

## 2.2 ROUTES OF EXPOSURE

Exposure to exogenous substances is usually considered to occur through three main routes:

> oral, through the ingestion of food, water, medicines, cosmetic preparations and environmental media, such as soil;

> dermal, through contact of the skin with medical or cosmetic preparations or environmental media, such as water and soil; and

> inhalation, through the presence of gaseous or particulate material in breathed air.

In fish, the gill epithelium is considered to be an additional route of exposure (Evans, 1987).

While the oral exposure route is generally considered to be the dominant route of exposure to EDCs for humans, there is little evidence comparing exposure to EDCs from different routes.

In a study conducted in Shanghai, China organochlorine pesticides (OCPs) were found in food, dust and air samples and exposure was determined to be through ingestion (food and dust), inhalation and dermal contact (Yu *et al.*, 2012). Diet was estimated to account for more than 98 percent of exposure to dichlorodiphenyltrichloroethane (DDT) and more than 95 percent of exposure to hexachlorocyclohexane (HCH) for both children and adults.

A Norwegian study examined associations between polyfluorinated alkyl substance (PFAS) in serum with food consumption and use of personal care products (Thépaut *et al.*, 2021). The PFAS detected in serum at the highest concentrations were positively associated with fish consumption, while concentrations of other PFAS were positively associated with the use of personal care products. It should be noted that two of the three personal care products considered (sunscreen, mouthwash and lip gloss/balm) are at least as likely to result in oral exposure as dermal exposure.

An integrated exposure and physiologically-based pharmacokinetic (PBPK) model was used to model multiroute exposure to phthalate, based on product phthalate concentrations (Wu *et al.*, 2021). The predicted distributions of urinary metabolites were shown to be in reasonable agreement with concentrations determined in the United States of America biomonitoring programme. The analysis revealed that contamination of food-by-food contact materials had the greatest impact on body burden for di(2-ethylhexyl) adipate (DEHA), di(2-ethylhexyl) phthalate (DEHP), di(isononyl) cyclohexane-1,2-dicarboxylate (DINCH), and di(2-propylheptyl) phthalate (DPHP), whereas the body burden of diethyl phthalate (DEP) was most sensitive to the concentration in personal care products.

A German study determined the polybrominated diphenyl ethers (PBDEs) in duplicate diets, indoor air and household dust of 50 study participants (Fromme *et al.*, 2009). A toxicokinetic model was used to relate the concentration in media to blood concentrations. It was estimated that diet was the dominant exposure route, accounting for 95–97 percent of exposure. Dermal exposure is not considered to be consequential for PBDEs (EFSA, 2011).

A Republic of Korea study determined concentrations of PBDEs in house dust and determined exposure from the ingestion and inhalation of dust (Kim *et al.*, 2016). The exposure estimates determined were combined with estimates of dietary exposure from other Republic of Korea studies to estimate the total exposure for toddlers and adults. Diet accounted for 63 percent and 94 percent of PBDE exposure for toddlers and adults, respectively.

A study in Shanghai, China estimated the exposure to PBDEs from inhalation, ingestion of dust, dermal absorption from dust and diet (Li *et al.*, 2015). When absorption via the various routes of exposure was considered, diet accounted for 60 percent of exposure for children and 68 percent of exposure for adults.

Lo *et al.* (2023) estimated inhalation and dermal exposure to the flame retardants hexabromocyclododecanes (HBCDDs) by determining their concentrations in air particulate and soil. Exposure estimates for these exposure routes were compared to a previous estimate of dietary exposure for the same location (Taiwan).

Exposure was estimated to be predominantly via the diet (79–91 percent), followed by dermal exposure (9–20 percent), with inhalation making a negligible contribution to exposure. The authors of this study noted that their estimate of dermal exposure was based on a worst-case concentration in soil.

Evaluations conducted by the European Food Safety Authority (EFSA) of chemicals in the food supply, including EDCs, primarily consider dietary exposure but also consider non-dietary exposure.

Oral (food and beverage, dust and toys) and dermal (thermal paper and cosmetics) exposure to bisphenol A (BPA) were compared using a PBPK model (EFSA, 2015). Oral exposures, from ingesting dust and mouthing toys, and dermal exposures, from cosmetics, were generally minor (<10 percent) compared to dietary exposure. High estimates of dermal exposure from contact with thermal paper were estimated to exceed dietary exposure; however, there was considerable uncertainty associated with the estimates of dermal exposure from this source.

In the assessment of dioxins and DL-PCBs, EFSA considered the available information on exposure from inhalation of ambient air, smoking, ingestion of soil, and dermal exposure from contact with soil (EFSA, 2018). It was concluded that non-dietary exposure generally contributed less than 10 percent to human daily dioxin and DL-PCB exposure.

EFSA reported an assessment conducted by ECHA that estimated exposure to four phthalates from the indoor environment (air inhalation and dust ingestion), food (environmental contamination and food contact material) and articles (e.g. sandals, erasers and toys) (EFSA, 2019). The distribution of exposures among the three sources/routes depended on the phthalate and the population group and the scenario (typical or reasonable worst case). In most cases, articles were the major contributors to phthalate exposure, followed by food and the indoor environment.

Swaziland - A crop of sunhemp

# CHAPTER 3
# APPROACHES TO EXPOSURE ASSESSMENT

Exposure to endocrine disrupting chemicals or chemicals (EDCs) in general can be estimated by the two main classes of methods: indirect and direct. Indirect methods estimate the external exposure from knowledge of the concentration of the substance in the environment (including food) and knowledge of human choices and behaviours that influence their intake rates of environmental media. Direct methods determine the concentration of the substance in human bodily fluids (blood, urine, breastmilk) or tissues (hair, nails).

## 3.1 INDIRECT METHODS

Indirect methods determine the exposure dose that meets the external surface of the body (external dose). For oral exposure, this will be the dose that enters the mouth, for inhalation, the dose that enters the lungs, for dermal, the dose that ends up on the skin. These external doses can be converted to internal doses if information is available on the rate of absorption of the substance from the gastrointestinal tract, the lungs and through the skin. If route specific absorption data is not available, default values may be applied. For oral and inhalation absorption, default values are usually 100 percent.

At the highest level, exposure determined by indirect methods is a function of the exposure intensity (concentration) and the intake rate (for example, food consumption amount, breathing rate or amount of skin exposed). The exposure estimate is usually normalized by dividing by the body weight of the exposed individual or the mean or typical body weight of the exposed group.

In many cases, the high-level parameters that define exposure are not able to be measured directly or are not easily measured and must be derived from secondary factors. For example, a young child's exposure to plasticizers from mouthing toys will depend on the concentration of the plasticizer in the toy, the rate at which the plasticizer is extracted by human saliva and the frequency and duration of mouthing events.

### 3.1.1 AGGREGATE AND CUMULATIVE EXPOSURE ASSESSMENT

Aggregate exposure assessment refers to the estimation of exposure to a single chemical from multiple sources and routes of exposure (FAO and WHO, 2009; International Programme on Chemical Safety (IPCS) and WHO, 2009). For example, consideration of exposure to DEHP due to its presence in the diet, drinking water, air and household dust would be considered to be an aggregate exposure assessment.

Cumulative exposure assessment refers to an estimation of exposure to multiple chemicals by a single or by multiple routes of exposure (FAO and WHO, 2009; IPCS and WHO, 2009). Cumulative exposure assessment is usually only carried out when the chemicals have a common mode of action, and their toxicological effects can be considered to be additive. An example of a cumulative exposure assessment is in the consideration of organophosphorus and carbamate insecticides that all act by inhibiting acetylcholinesterase (Boon *et al.*, 2008; Jardim *et al.*, 2018). Initiatives are also underway to develop approaches to the risk assessment of the combined exposure to chemical mixtures (FAO/WHO, 2019)

A cumulative exposure assessment usually requires information on the relative potency of the different chemicals in causing the common mode of action. One of the best characterized examples of the use of potency factors in a cumulative exposure assessment is the use of toxic equivalency factors (TEFs) in the assessment of exposure to dioxins, dibenzofurans and dioxin-like PCBs (DeVito *et al.*, 2024).

## 3.2 DIRECT METHODS

Direct methods for determining exposure involve the measurement of the chemical or a metabolite of the chemical in bodily fluids or tissues. These measurements are often referred to as biomarkers of exposure. Depending on the distribution, metabolism and elimination of the chemical, a particular biomarker may be indicative of recent exposure or may be indicative of chronic exposure.

The use of biomarkers to estimate internal exposure offers some advantages over estimates of external exposure to monitor trends in populations over time and geographic regions. Biomarkers integrate exposure over time from multiple sources. In a causal sense, they are also "closer" to adverse health effects of interest than are other types of exposure estimates.

# CHAPTER 4
# METHODS USED IN THIS STUDY

The information summarized in the following sections are from studies in the scientific literature or from publicly available databases. Literature searches were carried out in Web of Science and PubMed. Each search included a combination of three components:

> temporal dimension such as (temporal OR time OR change OR trend);

> matrix such as (blood OR serum OR plasma OR urine OR milk); and

> analyte such as (perfluor* OR polyfluor* OR PFOA OR PFOS).

A separate set of searches was made to identify studies in Indigenous or First Nations populations using the search string (indigenous OR first nation OR aborigin* OR indian).

Inclusion/exclusion criteria were:

> articles in English;

> including at least one of the EDCs or EDC groups listed in Table 1;

> including repeated measures over a time period of at least five years (studies over a shorter time period were considered if the measures bracketed the implementation of a relevant regulatory measure);

> final date for the time series was after 2002; and

> presented a measure of exposure, either directly or indirectly determined.

The studies presented in the current report are not an exhaustive collection of those available in the literature and have been selected to include:

> studies with a wide temporal range;

> more recent studies where multiple studies are available from the same country; and

> as wide as possible geographical representation.


Chad - A poultry farm worker

# CHAPTER 5
# TRENDS IN HUMAN EXPOSURE TO ENDOCRINE DISRUPTING CHEMICALS

The literature on EDCs is now extensive. This literature review does not represent an exhaustive systematic review of all the available literature. However, as much as possible, the studies summarized in the following sections are representative of the literature and give priority to studies that compare measures of exposure over an extended period (>5 years). Trends over shorter periods have generally only been included when the time period brackets a risk management measure such as the phasing out of the chemical(s) under consideration. Additionally, as this report seeks to assess changes since the 2002 report, studies with a final date before 2002 were not considered.

## 5.1 ORGANOCHLORINE COMPOUNDS

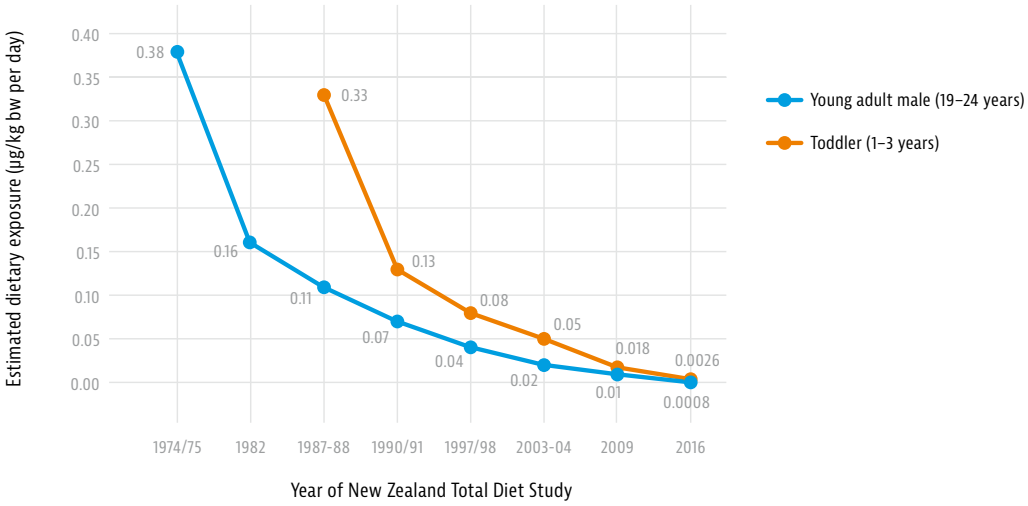
Organochlorine compounds include so-called legacy compounds, formerly used as pesticides or industrial chemicals, or compounds formed during natural or industrial processes such as dioxins. All these classes of compounds are characterized by long environmental persistence.

### 5.1.1 INDIRECT EVIDENCE

While a number of well-established total diet study programmes operate in various countries, few provide longitudinal exposure information for EDCs. However, several programmes provide good longitudinal dietary exposure information on "legacy" organochlorine compounds such as DDT and dieldrin.

The New Zealand Total Diet Study (NZTDS) includes nine completed studies since 1974. Organochlorine compounds have been included in the analyte list for all completed studies. The trend in estimated dietary exposure to total DDT (sum of exposure to parent compound and metabolites) for two representative age groups is shown in Figure 1, demonstrating a clear and sustained decrease in dietary exposure to these compounds with time.

FIGURE 1. **DIETARY EXPOSURE TO TOTAL DICHLORODIPHENYLTRICHLOROETHANE (DDT) FOR YOUNG ADULT MALES (19–24 YEARS) AND TODDLERS (1–3 YEARS), NEW ZEALAND TOTAL DIET STUDY (1974/75–2016)**




*Source:* **Pearson, A., Gibbs, M., Lau, K., Edmonds, J., Alexander, D. & Nicolas, J.** 2018. *2016 New Zealand Total Diet Study.* Wellington, New Zealand, Ministry for Primary Industries. https://www.mpi.govt.nz/dmsdocument/43177-2016-NZ-Total-Diet-Study-with-Appendices-report-

The Japanese total diet study included an analysis of dioxins (PCDD/F and DL-PCBs) in 14 food groups and an estimation of dietary exposure over the period 1998–2015 (Tsutsumi *et al.*, 2018). A cumulative exposure to dioxins is often expressed in terms of toxic equivalents (TEQs), derived by applying toxic equivalency factors (TEFs) to the exposures to the individual substance.

The TEF is an expression of the toxicity of the substance relative to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (Van den Berg *et al.*, 2006). Dietary exposure decreased steadily from 1.8 and 1.9 pg TEQ/kg bw per day, in 1998 and 1999, respectively, to 0.54 pg TEQ/kg bw per day in 2016. Dioxins present in fish and shellfish were the major contributor to dietary dioxin exposure.

Although the dioxin content of this food group decreased from 1998 to 2016, the contribution of the food group to dietary exposure increased from about 70 percent in 1998 to almost 90 percent in 2016.

### 5.1.2 DIRECT EVIDENCE

#### Blood/serum/plasma

Serum samples collected under the NHANES at two yearly cycles from 2005 to 2016 were analysed for OCPs by gas chromatography-mass spectrometry (GC-MS) (Li *et al.*, 2022). Survey weights were applied and least squares geometric mean concentrations determined for each survey cycle. Results are summarized in Table 2. While concentrations of all OCPs show a steady temporal decline, it is also clear that these compounds will take a long time to completely disappear from the biosphere.

TABLE 2 **ORGANOCHLORINE PESTICIDE RESIDUES IN SERUM OF THE POPULATION OF THE UNITED STATES OF AMERICA, 2005–2016**

| SUBSTANCE | LEAST SQUARES GEOMETRIC MEAN CONCENTRATION, µg/kg LIPID | | | | | | CHANGE (% per cycle) |
|---|---|---|---|---|---|---|---|
| | 2005–2006 | 2007–2008 | 2009–2010 | 2011–2012 | 2013–2014 | 2015–2016 | |
| β-HCH | 7.4 | 6.3 | 5.3 | 4.6 | 3.9 | 3.3 | -15 |
| HCB | 9.6 | 9.5 | 9.3 | 9.2 | 9.0 | 8.9 | -1.6 |
| p,p'-DDE | 440 | 380 | 320 | 279 | 230 | 200 | -15 |
| p,p'-DDT | 6.4 | 5.5 | 4.7 | 4.0 | 3.5 | 3.0 | -14 |
| Trans-nonachlor | 14 | 12 | 11 | 10 | 9.5 | 8.6 | -8.7 |

*Notes*: DDT: HCH: hexachlorocyclohexane; HCB: hexachlorobenzene; DDE: dichlorodiphenyldichloroethylene; and DDT: dichlorodiphenyltrichloroethane.

*Source:* **Li, M.M., Wang, R., Su, C., Li, J.W. & Wu, Z.Y.** 2022. Temporal Trends of Exposure to Organochlorine Pesticides in the United States: A population study from 2005 to 2016. *International Journal of Environmental Research and Public Health*, 19(7): 3862. https://doi.org/10.3390/ijerph19073862

During 1993 to 2007, 537 clinical samples (392 blood and 145 adipose tissue) were collected as components of various human cancer studies conducted in Sweden (Hardell *et al.*, 2010). Samples were analysed for PCBs and OCPs by GC-MS. After adjustment for specimen type and gender, body mass index and age of subjects, changes in percent per year were estimated. Statistically significant ($p<0.001$) trends were reported for the sum of PCBs (-7.2 percent per year), HCB (-8.8 percent per year), DDE (-13.5 percent per year) and the sum of chlordanes (-10.3 percent per year).

Serum samples from 33 male police officers in Guinea-Bissau were collected on up to five occasions (1990–1991, 1993–1995, 1997–1999, 2001–2003 and 2005–2007) (Linderholm *et al.*, 2010). Samples were pooled in up to six composite samples at each time point and analysed for organochlorine pesticides and PCBs by GC-MS. Mean concentrations of selected contaminants, across pools, are summarized in Table 3. Clear declines in serum concentrations of legacy pesticides and PCBs are apparent.

©FAO/Jenna Jadin

Balkh – Milk is collected daily and fat tested by trained workers

However, the decline in concentrations of parent DDT (p,p'-DDT) was only apparent after 2000. Although the authors of this study reported that they had no information on pesticide usage patterns in Guinea-Bissau, DDT was used for vector control in Africa more recently than in other parts of the world due to exemptions under the Stockholm Convention (UNEP, 2019).

TABLE 3 **TRENDS IN THE CONCENTRATIONS OF SELECTED ORGANOCHLORINE COMPOUNDS IN THE SERUM OF ADULT MALES FROM GUINEA-BISSAU, 1990–2007**

| SUBSTANCE | MEAN SERUM CONCENTRATION, µg/kg LIPID[a] | | | | |
|---|---|---|---|---|---|
| | 1990–1991 | 1993–1995 | 1997–1999 | 2001–2003 | 2005–2007 |
| p,p'-DDT | 783 | 838 | 840 | 384 | 216 |
| p,p'-DDE | 3433 | 2700 | 2520 | 1640 | 1460 |
| p,p'-DDD | 32 | 32 | 33 | 11 | 6 |
| β-HCH | 177 | 128 | 66 | 41 | 38 |
| γ-HCH | 128 | 10 | 8 | 11 | 8 |
| PCB-138 | 53 | 38 | 35 | 27 | 21 |
| PCB-153 | 65 | 54 | 46 | 38 | 30 |
| PCB-170 | 19 | 14 | 13 | 11 | 9 |
| PCB-180 | 59 | 51 | 46 | 40 | 31 |
| PCB-187 | 15 | 11.6 | 9.8 | 9.7 | 7.3 |
| $\Sigma PCB_5$ | 210 | 168 | 148 | 126 | 96 |

*Notes:* [a] For pools where the concentration of the contaminant was below the limit of detection, the value was set equal to the limit of detection for the calculation of mean values. $\Sigma PCB_5$: sum of the concentrations of 5 PCBs; HCH: hexachlorocyclohexane; and PCB: polychlorinated biphenyl.

*Source:* **Linderholm, L., Biague, A., Månsson, F., Norrgren, H., Bergman, Å. & Jakobsson, K.** 2010. Human exposure to persistent organic pollutants in West Africa — A temporal trend study from Guinea-Bissau. *Environment International*, 36(7): 675–682. https://doi.org/10.1016/j.envint.2010.04.020

Pooled samples of human blood serum were collected in metropolitan South East Queensland, Australia in 2002–2003, 2006–2007, 2008–2009, 2010–2011 and 2012–2013 and analysed for legacy OCPs by gas chromatography-high resolution mass spectrometry (GC-HRMS) (Thomas *et al.*, 2017). Five OCPs were detected across all time periods, with mean concentrations trending downward over time. A summary of the findings are included in Table 4.

TABLE 4 **ORGANOCHLORINE PESTICIDES IN POOLED AUSTRALIAN HUMAN SERUM SAMPLES, 2002–2013**

| SUBSTANCE | MEAN CONCENTRATION, µg/kg LIPID | | | | |
|---|---|---|---|---|---|
| | 2002–2003 | 2006–2007 | 2008–2009 | 2010–2011 | 2012–2013 |
| HCB | 39 | 9.0 | 15 | 10 | 9.7 |
| β-HCH | 15 | 11 | 12 | 7.1 | 6.1 |
| Trans-nonachlor | 13 | 4.7 | 6.4 | 5.8 | 4.8 |
| p,p'-DDE | 500 | 230 | 290 | 230 | 220 |
| p,p'-DDT | 6.8 | 4.7 | 5.4 | 4.3 | 4.0 |

*Notes:* HCB: hexachlorobenzene; HCH: hexachlorocyclohexane; DDE: dichlorodiphenyldichloroethylene; and DDT: dichlorodiphenyltrichloroethane.

*Source:* **Thomas, A., Toms, L-M.L., Harden, F.A., Hobson, P., White, N.M., Mengersen, K.L. & Mueller, J.F.** 2017. Concentrations of organochlorine pesticides in pooled human serum by age and gender. *Environmental Research*, 154: 10–18. https://doi.org/10.1016/j.envres.2016.12.009

The Mother-and-Child Contaminant Cohort (MISA)[1] study in northern Norway included a collection of blood samples from mothers during 2007–2009 (MISA 1) and 2017–2019 (MISA 2) (Xu *et al.*, 2022). Analyses were performed on 62 samples from MISA 1 and on 38 samples from MISA 2 for organochlorine pesticides, PCDD/F, DL-PCBs and chlorinated paraffins by GC-MS. The geometric mean concentration of PCDD/F and DL-PCBs, expressed as 2005 WHO TEQ decreased from 24.6 pg TEQ/L in 2007–2009 to 6.5 pg TEQ/L in 2017–2019. Geometric mean concentrations of HCB decreased from 0.09 to 0.05 µg/L wet weight in the same period, while p,p'-DDE concentrations decreased from 0.26 to 0.09 µg/L wet weight.

## BREAST MILK

From the 1980s onwards, national studies of the organochlorine content of human breast milk have been used to study human exposure to a range of persistent environmental contaminants, including persistent potential EDCs (Tarkowski and Yrjänheikki, 1989). A number of countries have performed such surveys periodically and have since included an analysis of further persistent environmental contaminants into the programmes ('t Mannetje *et al.*, 2013 and Fromme *et al.*, 2022). Much of this activity was coordinated by WHO/UNEP in seven coordinated studies between 1987 and 2019.

WHO and UNEP developed protocols for national breast milk studies (Tarkowski and Yrjänheikki, 1989). From 2000–2019, five rounds of breast milk surveillance were coordinated. Additionally, participating countries prepared a single composite breast milk sample that was considered to represent the average levels of POPs in human milk for a country or subpopulation of that country at the time of sampling (Malisch *et al.*, 2023e).

These composite samples were then analysed by reference laboratories. Trend analyses of the results from these composite samples were recently published, based on data from countries that had participated in more than one round of the programme (Malisch *et al.*, 2023d; Malisch *et al.*, 2023c; Malisch *et al.*, 2023b). The analysis additionally included summary statistics from the earlier rounds (1987–1988 and 1992–1993) (Table 5).

[1] In Norwegian, the name of the study is Miljøgifter i svangerskapet og i ammeperioden (MISA)

TABLE 5 **SUMMARY OF SELECTED RESULTS FROM THE WORLD HEALTH ORGANIZATION AND UNITED NATIONS ENVIRONMENT PROGRAMME COORDINATED BREAST MILK STUDIES, 1987–2019**

| COMPOUND | MEDIAN CONCENTRATION (RANGE), µg/kg LIPID | | | | | | | Median annual decrease (%) |
|---|---|---|---|---|---|---|---|---|
| | 1987–1988 | 1992–1993 | 2000–2003 | 2004–2007 | 2008–2011 | 2012–2015 | 2016–2019 | |
| Number of countries | 7 | 14 | 24 | 11 | 36 | 15 | 33 | |
| $\Sigma PCB_6$ | 211 (62–762) | 275 (56–801) | 123 (16–502) | 66 (10–376) | 23 (4–79) | 36 (2–158) | 14 (1–109) | 7.9 |
| WHO-PCDD/F-TEQ | 16.9 (5.4–42.2) | 11.9 (8.3–26.0) | 7.3 (3.1–18.0) | 4.8 (2.9–8.9) | 3.9 (1.3–12.1) | 3.8 (1.0–8.6) | 2.7 (1.0–10.0) | 4.0 |
| DDT complex | | | 445 (129–1580) | 324 (29–2830) | 465 (56–8490) | 297 (64–23,500) | 125 (17–7100) | 6.6 |
| Beta-HCH | | | 25.3 (5.8–1020) | 10.2 (<0.5–36.5) | 5.7 (0.7–845) | 14.7 (<0.5–375) | 2.4 (<0.5–41.6) | 9.6 |
| HCB | | | 16.4 (3.3-76.0) | 12.0 (2.8-47.4) | 5.3 (1.4-154) | 7.6 (1.0-46.7) | 3.3 (1.3-34.0) | 5.8 |
| Dieldrin | | | 3.7 (<0.5–8.0) | 1.8 (<0.5–6.7) | 2.2 (<0.5–37.8) | 0.9 (<0.5–11.7) | 1.3 (<0.5–5.8) | - |
| $\Sigma PBDE_6$ | | | 2.6 (0.7–223) | 2.6 (0.8–21.9) | 2.0 (0.3–62.7) | 1.1 (0.6–7.4) | 1.4 (0.3–107) | - |

*Notes:* $\Sigma PCB_6$: the sum of six indicator non-dioxin-like PCBs; WHO-PCDD/F-TEQ: concentration of dioxins and dibenzofurans, expressed as TEQ, using 2005 WHO TEF; DDT complex: sum of p,p'-DDT, o,p'-DDT, p,p'=DDD and p,p'-DDE; and $\Sigma PCB_6$: sum of six PBDE (BDE-47, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183).

*Sources:* See References.

Surveys of human breast milk, performed in accordance with the WHO coordinated survey protocol (Malisch *et al.*, 2023e) were conducted in New Zealand in 1988 (Bates *et al.*, 1994), 1998 (Bates, 2002) and 2008 ('t Mannetje *et al.*, 2013). Representative results across the three studies are summarized in Table 6.

TABLE 6 **TRENDS IN THE ORGANOCHLORINE CONTENT OF BREAST MILK IN NEW ZEALAND, 1988–2008**

| COMPOUND | MEAN CONCENTRATION, µg/kg LIPID | | |
|---|---|---|---|
| | 1988 | 1998 | 2008 |
| p,p'-DDT | 77 | 26 | 5.0 |
| p,p'-DDE | 1900 | 630 | 380 |
| Dieldrin | 47 | 15 | 10 |
| HCB | 32 | 11 | 6.7 |
| PCB-74 | 3.9 | 2.3 | 1.5 |
| PCB-118 | 7.2 | 3.2 | 1.3 |
| PCB-138 | 27 | 9.6 | 4.8 |
| PCB-153 | 44 | 9.8 | 5.6 |
| PCB-170 | 7.4 | 3.7 | 1.4 |
| PCB-180 | 18 | 5.9 | 2.9 |
| PCDD/PCDF (TEQ) | 17 | 5.3 | 3.5 |

*Notes*: DDT: dichlorodiphenyltrichloroethane ; DDE: dichlorodiphenyldichloroethylene ; HCB: hexachlorobenzene ; PCB: polychlorinated biphenyl ; PCDD: polychlorinated dibenzodioxins ; PCDF: polychlorinated dibenzofurans ; and TEQ: toxic equivalents.

*Sources:* **'t Mannetje, A., Coakley, J., Bridgen, P., Brooks, C., Harrad, S., Smith, A.H., Pearce, N. & Douwes, J.** 2013. Current concentrations, temporal trends and determinants of persistent organic pollutants in breast milk of New Zealand women. *Science of the Total Environment*, 458: 399–407. https://doi.org/10.1016/j.scitotenv.2013.04.055; **Bates, M.N., Hannah, D.J., Buckland, S.J., Taucher, J.A. & Van Maanen, T.** 1994. Chlorinated organic contaminants in breast milk of New Zealand women. *Environmental Health Perspectives*, 102: 211–217. https://doi.org/10.1289/ehp.94102s1211; and **Bates, M., Thomson, B. & Garrett, N.** 2002. Reduction in organochlorine levels in the milk of New Zealand women. *Archives of Environmental Health*, 57: 591–597. https://doi.org/10.1080/00039890209602093

Between 2005 and 2007, breast milk samples were collected from 13 primiparous women living in Rome, Italy and analysed for PCBs by GC-MS (Alivernini *et al.*, 2011). The results were compared to the results of previous breast milk studies carried out in Italy in 1987 (Larsen *et al.*, 1994) and 2000–2001 (Ingelido *et al.*, 2007). Representative results from the three surveys are summarized in Table 7.

TABLE 7 **SELECTED POLYCHLORINATED BIPHENYLS IN THE BREAST MILK OF ITALIAN WOMEN, 1987–2007**

| SUBSTANCE | MEAN CONCENTRATION, µg/kg LIPID | | |
|---|---|---|---|
| | 1987 | 2000–2001 | 2005–2007[a] |
| PCB CONGENERS | | | |
| 118 | 32.7 | 14.1 | 10.6 |
| 153 | 111 | 77 | 53.5 |
| 170 | 26.0 | 21 | 16.2 |
| 180 | 53.9 | 56 | 32.1 |
| 183 | 11.7 | 6.1 | 3.0 |
| 187 | 20.8 | 15 | 6.4 |

*Notes:* [a] To improve sensitivity, the individual samples in the 2005–2007 study were pooled and the sample volume reduced. The results presented here are for the single pooled sample. PCB: polychlorinated biphenyl.

*Sources:* **Alivernini, S., Battistelli, C.L. & Turrio-Baldassarri, L.** 2011. Human Milk as a Vector and an Indicator of Exposure to PCBs and PBDEs: Temporal Trend of Samples Collected in Rome. *Bulletin of Environmental Contamination and Toxicology*, 87(1): 21–25. https://doi.org/10.1007/s00128-011-0262-7; **Ingelido, A.M., Ballard, T., Dellatte, E., di Domenico, A., Ferri, F., Fulgenzi, A.R., Herrmann, T. *et al.*** 2007. Polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) in milk from Italian women living in Rome and Venice. *Chemosphere*, 67(9): S301–S306. https://doi.org/10.1016/j.chemosphere.2006.05.111; and **Larsen, B.R., Turriobaldassarri, L., Nilsson, T., Iacovella, N., Didomenico, A., Montagna, M. & Facchetti, S.** 1994. Toxic PCB congeners and organochlorine pesticides in Italian human milk. *Ecotoxicology and Environmental Safety*, 28(1): 1–13. https://doi.org/10.1006/eesa.1994.1029

Pooled human breast milk samples from the Swedish Environmental Specimen Bank from 1972 to 2011 were analysed by GC-HRMS to examine trends in the body burden of PCDD/F and PCBs (Fång *et al.*, 2013). Representative results are summarized in Table 8. The data indicate a sustained decrease in these classes of environmental organochlorine contaminants over the study period.

TABLE 8 **POLYCHLORINATED DIBENZODIOXINS/POLYCHLORINATED DIBENZOFURANS AND POLYCHLORINATED BIPHENYLS IN THE BREAST MILK OF SWEDISH WOMEN, 1972–2011**

| SUBSTANCE | CONCENTRATION, ng/kg LIPID | | | | | |
|---|---|---|---|---|---|---|
| | 1972 | 1980 | 1990 | 2000[a] | 2007[a] | 2011[a] |
| 2,3,7,8-TCDD | <2.8 | 3.4 | 1.8 | 0.50 | 0.49 | 0.36 |
| OctaCDD | 430 | 330 | 240 | 77 | 49 | 36 |
| ΣPCDD/F (WHO-TEQ2005) | 26 | 23 | 14 | 6.5 | 4.2 | 2.9 |
| ΣDL-PCB (WHO-TEQ2005) | 30 | 21 | 12 | 5.9 | 4.4 | 2.2 |
| Total TEQ (WHO-TEQ2005) | 56 | 44 | 26 | 13 | 8.6 | 5.1 |

*Notes:* [a] Results of two samples were presented for each of 2000, 2007 and 2011. Concentrations presented here are the mean of the two values. PCDD: polychlorinated dibenzodioxins; PCDF: polychlorinated dibenzofurans; TCDD: tetrachloro dibenzodioxin; DL-PCB: dioxin-like polychlorinated biphenyls; and WHO-TEQ2005: toxic equivalents calculated using the WHO 2005 toxic equivalence factors.

*Source:* **Fång, J., Nyberg, E., Bignert, A. & Bergman, Å.** 2013. Temporal trends of polychlorinated dibenzo-p-dioxins and dibenzofurans and dioxin-like polychlorinated biphenyls in mothers' milk from Sweden, 1972–2011. *Environment International*, 60: 224–231. https://doi.org/10.1016/j.envint.2013.08.019

Primiparous nursing mothers in Uppsala, Sweden were recruited between 1996 and 2006 to donate breast milk samples to be analysed for PCBs and dioxins by GC-MS (Lignell *et al.*, 2009). Although individual concentrations were not reported for this study, the rate of decrease of substance concentrations were assessed by linear regression and multiple regression. For the simple linear regression, concentrations of PCBs in breast milk decreased during the period of 1996 to 2006 from 1.6 percent per year (PCB-169) to 8.2 percent per year (PCB-118). All PCDDs determined decreased during the period by 5.1 percent per year (1,2,3,7,8-PeCDD) to 9 percent per year (1,2,3,4,6,7,8-HpCDD). More modest, but consistent decreases were seen in concentrations of PCDFs. Total TEQs decreased at a rate of 5.5 percent per year.

In an extension of that study to cover the period of 1996 to 2017, changes in the rate of decrease of persistent organic pollutants were examined (Gyllenhammar *et al.*, 2021). While the overall rate of decrease in breast milk concentration of total TEQs was little changed (5.7 percent per year), the study suggested that the decrease was biphasic, with a rate 6 percent per year prior to 2008 and a rate of 1.6 percent per year after 2008. For OCPs (p,p'-DDT, p,p'-DDE, β-HCH, oxychlordane, and trans-nonachlor) no change in the rate of concentrations decrease in breast milk was apparent, with rates in the range 6.6–10 percent per year. For HCB, a change point of 2009 was identified, with rates of 6.7 percent and 3.8 percent per year, before and after this date, respectively.

Breast milk samples were collected from primiparous nursing mothers in Tarragona County, Spain in 1998, 2002, 2007 and 2012 and analysed for PCDD/F and PCB by GC-HRMS (Schuhmacher *et al.*, 2013). The area is potentially impacted by discharges from a hazardous waste incinerator. A steady decrease was seen in concentrations of the organochlorine contaminants across the period considered. The mean sum of PCDD/F and PCBs, expressed as WHO 2005 TEQ, decreased from 29.7 ng TEQ/kg lipid in 1998 to 20.0 (2002), 16.6 (2007) and 7.3 ng TEQ/kg lipid (2012), equating to a 75 percent decrease across the study period.

Breast milk samples were collected from 50 primiparous nursing mothers in Chișinău, Republic of Moldova during 2008–2009 and again in 2014–2015, and a single pooled sample for each time period was analysed for persistent organochlorine compounds by a WHO reference laboratory (Tirsina *et al.*, 2017). While decreases of up to 70 percent in concentrations of organochlorines between the two time periods were observed, it appears that organochlorine pesticides were still in active use in the Republic of Moldova over this period. Representative results are summarized in Table 9.

TABLE 9 **CONCENTRATIONS OF SELECTED PERSISTENT ORGANOCHLORINE COMPOUNDS IN POOLED BREAST MILK, REPUBLIC OF MOLDOVA, 2008–2009 AND 2014–2015**

| SUBSTANCE | CONCENTRATION, µg/kg LIPID | | CHANGE (%) |
|---|---|---|---|
| | 2008–2009 | 2014–2015 | |
| p,p'-DDT | 69.9 | 64.6 | -7.5 |
| p,p'-DDE | 1560 | 990 | -37 |
| HCB | 154 | 47 | -69 |
| B-HCH | 480 | 150 | -68 |
| $\Sigma PCB_6$ | 66.9 | 35.9 | -46 |
| PCDD/F and DL-PCB-WHO TEQ (ng/kg lipid) | 14.9 | 9.0 | -39 |

*Notes*: DDT: dichlorodiphenyltrichloroethane; DDE: dichlorodiphenyldichloroethylene; HCB: hexachlorobenzene; HCH: hexachlorocyclohexane; $\Sigma PCB_6$: the sum of six indicator non-dioxin-like PCBs, PCDD/F; and DL-PCB-WHO TEQ: concentration of dioxins, dibenzofurans and dioxin-like PCBs, expressed as TEQ, using 2005 WHO TEF.

*Source:* **Tirsina, A., Sircu, R., Pinzaru, I. & Bahnarel, I.** 2017. Changes over time in persistent organic pollutants (POPs) concentrations in human milk in the Republic of Moldova. *Toxicological & Environmental Chemistry*, 99(5–6): 1007–1019. https://doi.org/10.1080/02772248.2017.1287469

Samples of breast milk were collected at a maternity hospital in Hebei province in northern China during 2002–2003 (30 samples) and in 2006–2007 (20 samples) and analysed for PCDD/F and DL-PCB by GC-HRMS (Sun *et al.*, 2011). The mean total concentration, expressed in terms of WHO 2005 TEQ, increased from 4.5 ng TEQ/kg lipid at the earlier time point to 6.2 ng TEQ/kg lipid in 2006–2007. Concentrations of some PCDD/F increased, while others decreased. However, concentrations of all DL-PCB in breast milk increased over the period 2002–2007. Although the concentration of total PCDD/F and DL-PCBs in breast milk in 2007 was similar to concentrations observed in other countries at about the same time, the upward trend in concentrations contrasts with declines seen in other countries.

Further support for an upward trend in exposure to dioxins comes from the study of Lu *et al.*, 2015. Breast milk samples from primiparous nursing mothers ($n$ = 150) were collected in Shanghai during 2011–2012 and analysed for PCDD/F and DL-PCB by GC-HRMS. Most of the mothers were recent immigrants to Shanghai from other provinces. Survey results were grouped by province of origin and compared to results of a national survey conducted in 2007, with comparative data available for eight provinces. For all provinces, mean exposure to PCDD/F and DL-PCBs had increased between 2007 and 2012. The highest exposures were in Shanghai with mean concentrations in breast milk, expressed as WHO 2005 TEQ, increasing from 8.5 to 18.2 ng TEQ/kg lipid. Percentage increases ranged from 24 percent (Shanxi) to 190 percent (Heilongjiang).

Breast milk samples were collected from healthy primiparous mothers recruited annually, between 1998 and 2015, throughout Japan and analysed for PCDD/F and PCBs by GC-MS (Ae *et al.*, 2018). Between 21 and 415 mothers provided breast milk each year. The mean concentration of total PCDD/F and PCBs in breast milk, expressed as WHO 2005 TEQ, decreased over the entire study period from

20.8 ng TEQ/kg lipid in 1998 to 8.7 ng TEQ/kg lipid in 2015. The decreasing trend was apparent for each of PCDDs, PCDFs and coplanar PCBs and for different age ranges of mothers (20–25, 26–30 and >30 years).

## 5.2 BROMINATED FLAME RETARDANTS

Polybrominated diphenyl ethers (PBDEs) and isomers of hexabromocyclododecane (HBCDD) are flame retardants added to a wide range of consumer products. For the PBDE, three main products have been used with differing proportions of brominated diphenyl ether (BDE) congeners:

> penta-BDE, congeners BDE-47 and BDE-99 are most abundant;

> octa-BDE, congeners BDE-153 and BDE-183 are most abundant; and

> deca-BDE, BDE-209 is most abundant.

Commercial HBCDD is composed of three main diastereoisomers, α, β and γ.

### 5.2.1 META-ANALYSES

Studies ($n$ = 207) on PBDE and HBCDD in human breast milk were reviewed to determine if the available evidence supported the effectiveness of regulatory action (van der Schyff *et al.*, 2023). Overall, the highest concentrations of PBDE were reported in Northern America, while the highest concentrations of HBCDD were reported in Asia and Oceania. Data were considered in terms of an overall linear trend, as well as by "breakpoint analysis" in which the temporal data was considered to be composed of two trend patterns: usually an earlier increasing pattern and a later decreasing or plateauing pattern. The analyses were reported on a congener basis.

**BDE-47.** Decreasing trends were apparent in most geographical regions for the concentration of BDE-47 in breast milk. Breakpoint analysis suggested that the decrease began in approximately 1990–1995 in Europe and Asia, 2003–2005 in Northern America and Oceania, and after 2015 in Latin America and the Caribbean.

**BDE-99.** Decreasing trends were apparent in most geographical regions for the concentration of BDE-99 in breast milk. Breakpoint analysis suggested that the decrease began in approximately 1995–2000 in Europe and Asia, 2000–2005 in Northern America and Oceania, and after 2015 in Latin America and the Caribbean. It should be noted that BDE-99 has a longer elimination half-life in humans than BDE-47, which may have contributed to the later breakpoint for this congener.

**BDE-153.** The available data provide little evidence for an overall decreasing trend in PDE-153 concentrations in breast milk, except possibly in Oceania. Breakpoint suggested that BDE-153 concentrations peaked in Asia and Europe in approximately 1990 and have been stable since then. In Northern America the breakpoint was later, about 2003–2004, followed by a steady decrease.

**BDE-209.** Less information was available on this congener. The available evidence suggests breast milk concentrations have remained fairly stable since about 2005.

**HBCDD.** The overall linear trend in HBCDD breast milk concentration suggests little change over time in most regions, with a possible increase in Asia and Europe and a decrease in Africa. Breakpoint analysis suggested a decrease in Asia from about 2000 and a plateauing in Europe from about 2010.

Another meta-analysis of blood and breast milk concentration of PBDE considered worldwide trends for the period 2000–2016 (Meng *et al.*, 2021). At a global level, no significant trend was observed in blood PBDE concentrations over this period and no significant difference was seen between the periods 2000–2009 and 2010–2016. However, significant regional differences in blood PBDE concentrations were observed, with median concentrations in European studies decreasing from 8.4 to 3.4 µg/kg lipid for 2000–2009 and 2010–2016, respectively. No significant decreases were observed for Asia or North America. Although there appeared to be an overall downward trend in the PBDE concentrations of breast milk, no significant differences between concentrations in 2000–2009 and 2010–2015 were apparent at a global or regional level.

### 5.2.2 INDIRECT EVIDENCE

During the period of March–June 2006, food samples were purchased in 12 cities in Catalonia, Spain and analysed for PBDEs by GC-MS (Domingo *et al.*, 2008). Food consumption information was taken from a nutrition survey conducted in 2002–2003 (details not provided). Dietary exposure to the sum of PBDE congeners was estimated for a standard 70 kg adult male and compared to an equivalent estimate derived in 2006. Estimated dietary exposure decreased from 1.4 ng/kg bw per day in 2000 to 1.1 ng/kg bw per day in 2006. However, this decrease will include not only contributions from decreased levels of PBDE contamination in the environment, but also decreases in the mean amounts of many foods consumed by the Catalan population.

During 2020 and 2021, foods of animal origin were sampled from three supermarkets in Birmingham, United Kingdom of Great Britain and Northern Ireland and analysed for PBDE, HBCDD and non-brominated flame retardants (NBFR) by either GC-MS (PBDE and NBFR) or liquid chromatography-tandem mass spectrometry (LC-MS/MS) (HBCDD) (Ma *et al.*, 2023). Food consumption information from the National Diet and Nutrition Survey Years 1–11, 2008–2019 was used to estimate dietary exposure. Estimates of dietary exposure were compared to equivalent estimates from a survey conducted in 2015. For toddlers (0–3 years) and adults (18+ years), mean estimates of dietary exposure to the sum of eight PBDEs decreased from 4.2 to 0.7–1.3 ng/kg bw per day and 1.8 to 0.3–0.4 ng/kg bw per day, respectively, from 2015 to 2020–2021. Similar decreases in estimated mean dietary exposure to HBCDDs were observed, from 0.88 to 0.07–0.18 ng/kg bw per day and 0.44 to 0.04–0.07 ng/kg bw per day for toddlers and adults, respectively. There were corresponding 2 to 3-fold increases in dietary exposure to NBFRs.

### 5.2.3 DIRECT EVIDENCE

#### Blood/serum/plasma

First-time mothers in Uppsala, Sweden were recruited each year over the period 1996–2010 (Darnerud *et al.*, 2015). Serum samples ($n$ = 412 across the complete study) were pooled into three annual samples and analysed for PBDE and HBCDD by GC-MS. Linear regression analyses demonstrated significant changes in serum concentrations ($p$<0.05) of BDE-47 (-7.1 percent per year), BDE-99 (-16 percent per year), BDE-100 (-5.3 percent per year) and HBCDD (-6.9 percent per year). Change in concentrations of the most commonly detected PBDEs (BDE-153 and BDE-209) were not statistically significant.

Blood samples were collected from students aged 9 to 11 years in Baden-Württemberg, Germany during 2002–2003, 2004–2005, 2005–2006 and 2008–2009 (162 to 770 blood samples per period) (Link *et al.*, 2012). Samples were pooled, with between 5 and 67 individual samples per pool, and analysed for PBDE by GC-HRMS. Weighted arithmetic mean concentrations by year decreased or stayed the same for BDEs 47, 85, 99, 100, 153, 154 and 183. However, concentrations of the deca-brominated BDE-209 increased during the period 2002–2009.

A cohort (n = 334) of children of African American or Dominican ethnicity were enrolled between 1996 and 2006 in New York City, United States (Cowell *et al.*, 2019). Blood samples were taken at birth and at 2, 3, 5, 7 and 9 years of age and analysed for PBDEs by GC-MS. When only results from samples taken in the post-natal period were considered, the rates of decrease of BDE-47, -99, -100 and -153 were 13, 13, 11 and 11 percent per year, respectively. Blood concentrations at earlier times were likely to have been influenced by maternal transfer, while concentrations of PBDEs in samples taken in the post-natal period were considered to predominantly reflect environmental exposure. While decreases in environmental levels of PBDEs are likely responsible for much of the observed decrease in blood PBDE concentrations, changes in diet and activity patterns may also have had an impact. In a date-stratified model, the decrease of BDE-47 concentrations occurred at a greater rate over the period 2006–2012 (16 percent per year) than during 1998–2005 (5 percent per year). This is consistent with the voluntary industry phase-out of penta-BDE in 2004.

Serum samples were collected from residents of Weifang City, Shandong Province, China in 2014 ($n$ = 490) and 2015 ($n$ = 452) and analysed for a range of brominated flame retardants by gas chromatography-tandem mass spectrometry (GC-MS/MS) (Ma *et al.*, 2017). Results were compared with those from equivalent studies conducted in Shandong Province in 2007, 2011 and 2013. Mean serum concentrations of the sum of eight PBDE ($\Sigma_8$ PBDE) and the dominant congener BDE-209 decreased monotonically from 2007 to 2015, from a mean of 440 µg/kg lipid weight for BDE-209 in 2007 to a mean of 26 µg/kg lipid weight in 2015. While decreases in other congeners (BDE-28, -47, -99, -100, -153, -154 and -183) were less consistent, in all cases, the 2015 concentrations were substantially below the 2007 concentrations.

Serum samples from 33 male police officers in Guinea-Bissau were collected on up to five occasions (1990–1991, 1993–1995, 1997–1999, 2001–2003 and 2005–2007) (Linderholm *et al.*, 2010). Samples were pooled into up to six composite samples at each time point and analysed for PBDEs by GC-MS. Mean concentrations, across pools, are summarized in Table 10. No trend is apparent in serum concentrations of PBDE congeners. This is not surprising as the phasing out of penta- and octa-PBDEs did not occur until 2004, while the use of deca-PBDEs, including BDE-209, continued after that date.

TABLE 10 **TRENDS IN THE CONCENTRATIONS OF SELECTED POLYBROMINATED DIPHENYL ETHERS IN THE SERUM OF ADULT MALES FROM GUINEA-BISSAU, 1990–2007**

| SUBSTANCE | MEAN CONCENTRATION, µg/kg[a] | | | | |
|---|---|---|---|---|---|
| | 1990–1991 | 1993–1995 | 1997–1999 | 2001–2003 | 2005–2007 |
| BDE-153 | 0.26 | 0.27 | 0.21 | 0.29 | 0.25 |
| BDE-209 | 3.5 | 6.6 | 3.2 | 2.8 | 4.7 |

*Notes:* [a] For pools where the concentration of the contaminant was below the limit of detection, the value was set equal to the limit of detection for the calculation of mean values. BDE: brominated diphenyl ether.

*Source:* **Linderholm, L., Biague, A., Månsson, F., Norrgren, H., Bergman, Å. & Jakobsson, K.** 2010. Human exposure to persistent organic pollutants in West Africa — A temporal trend study from Guinea-Bissau. *Environment International*, 36(7): 675–682. https://doi.org/10.1016/j.envint.2010.04.020

PBDE concentrations were determined by GC-MS in 249 pooled serum samples collected in South East Queensland, Australia between 2002 and 2013 (Toms *et al.*, 2018). Trends were assessed for four congeners (BDE-47, -99, -100 and -153) and for the sum of the congeners. Assessments were also segmented by the age of the individuals in the serum pools. Significant ($p<0.001$) decreases in concentrations of all congeners were observed for the 0–4 years age group, with rates of decrease of 5.3 to 11.9 percent per year. Lower, but significant decreases were seen in the 5–15 years group for all congeners, except BDE-153. Trends in concentrations of all congeners in all age groups were downward, except for BDE-153. Concentrations of this congener trended upward for all age groups greater than 15 years and the upward trend was significant for those older than 30 years. Importation and manufacture of penta- and octa-BDEs was banned in Australia in 2007, however, many sources of exposure are likely to remain for many years.

HBCDD concentrations were determined by LC-MS/MS in 67 pooled serum samples collected in South East Queensland, Australia between 2002 and 2015 (Drage *et al.*, 2017). The mean concentration of the sum of HBCDD isomers in adult pooled sera increased from 1.2 in 2002, to 4.4 (2004), 4.7 (2006) and 7.9 (2008) µg/kg lipid, before decreasing to 3.0 µg/kg lipid in 2010. While the authors of this study did not report mean HBCDD concentrations for the more recent time periods, these can be calculated from the information provided in the publication. Assigning a value of LOD/2 to results below the limit of detection, the mean total HBCDD concentrations for 2012–2013 and 2014–2015 were 4.4 and 2.8 µg/kg lipid, respectively. The mean for the 2012–2013 data set is impacted by a single very high result

(36 µg/kg lipid) and the associated median concentrations are 2.5 and 1.7 µg/kg lipid, respectively. While importation of HBCDD to Australia as powder or granules ceased in 2010, its use in the form of liquid dispersions continues.

### Breast milk

Surveillance of breast milk for PBDE has been carried out on three occasions (2005, 2011 and 2014) in Beijing, China (Chen *et al.*, 2019). Penta-BDE and octa-BDE have been banned from production, importation and use in China since 2014, but deca-BDE production and use in China is currently permissible. While there was a clear decrease in the median concentrations of some congeners across the three surveys (BDE-47, BDE-99, BDE-100, BDE-183), little change was seen in the median concentration of the main congeners (BDE-153, BDE-209), with the median concentration of BDE-209 increasing from 1.95 to 2.2 µg/kg lipid between 2011 and 2014.

In what appears to be a follow-on from the study of Chen *et al.* (2019), breast milk samples were collected from 105 Beijing-resident nursing mothers during 2018 and analysed for brominated flame retardants by GC-MS/MS (Zhao and Shi, 2021). Results were compared to those of previous studies conducted in Beijing in 2011 and 2014. Clear decreasing trends in the concentrations of ΣPBDEs (sum of all PBDEs) and the marker compound BDE-209 were apparent between 2014 and 2018 but not between 2011 and 2014. There was a significant increase in HBCDDs between 2011 and 2014 and again between 2014 and 2018. The authors noted that HBCDD was scheduled for phase-out at the end of 2021.

Pooled samples of human breast milk from nursing mothers in Stockholm, Sweden, covering the period 1980 to 2004, were analysed for PBDEs and HBCDD (Fängström *et al.*, 2008). Concentrations of most PBDE congeners in the pools increased from 1980 to be fairly stable across the period 1990–2001 before declining. A less distinct trend was apparent for BDE-153 and HBCDD. Representative concentrations are summarised in Table 11.

TABLE 11 **CONCENTRATIONS OF POLYBROMINATED DIPHENYL ETHER AND HEXABROMOCYCLODODECANES IN POOLED BREAST MILK SAMPLES, STOCKHOLM, SWEDEN, 1980–2004**

| SUBSTANCE | CONCENTRATION, µg/kg LIPID | | | | | |
|---|---|---|---|---|---|---|
| | 1980 | 1992 | 2001 | 2002 | 2003 | 2004 |
| BDE-47 | 0.12 | 1.4 | 1.8 | 1.4 | 1.2 | 0.93 |
| BDE-99 | 0.06 | 0.48 | 0.57 | 0.33 | 0.29 | 0.26 |
| BDE-100 | 0.04 | 0.31 | 0.63 | 0.27 | 0.31 | 0.29 |
| BDE-153 | 0.04 | 0.48 | 1.3 | 0.72 | 1.1 | 0.92 |
| HBCDD | 0.08 | 0.29 | 0.54 | 0.60 | 0.49 | 0.39 |

*Notes*: BDE: brominated diphenyl ether and HBCDD: hexabromocyclododecane.

*Source:* **Fängström, B., Athanassiadis, I., Odsjö, T., Norén, K. & Bergman, Å.** 2008. Temporal trends of polybrominated diphenyl ethers and hexabromocyclododecane in milk from Stockholm mothers, 1980–2004. *Molecular Nutrition & Food Research*, 52(2): 187–193. https://doi.org/10.1002/mnfr.200700182

Primiparous nursing mothers from Uppsala, Sweden were recruited during the period 1996 to 2017 and donated breast milk samples for analysis of PBDEs and HBCDDs by GC-MS (Gyllenhammar *et al.*, 2021). Although individual concentrations were not reported for this study, the rates of decrease of substance concentrations were assessed by regression analysis. Concentrations of BDE-47, -99, -100 and -153 decreased across the study period. The decrease in concentrations of BDE-153 (0.3 percent per year) was not significant, but when the trend was considered in two separate time periods, before and after 2004, the respective rates – an increase at 5.8 percent per year before 2004 and a decrease at 4.3 percent per year after 2004, were significant. Concentrations of the decabrominated BDE (BDE-209) increased across the time course of the study (4.7 percent per year), although this increase was not statistically significant ($p = 0.49$). Total HBCDDs decreased significantly at 6.5 percent per year across the course of the study.

Breast milk samples were collected from primiparous nursing mothers in Tarragona County, Spain in 2002, 2007 and 2012 and analysed for PBDE by GC-HRMS (Schuhmacher *et al.*, 2013). Results were expressed as the sum of 15 BDE congeners. The area is potentially impacted by discharges from a hazardous waste incinerator. Little difference was seen in the mean PBDE concentration in breast milk collected in 2002 and 2007, with mean concentrations of 2.4 and 2.5 µg/kg lipid, respectively. However, a 50 percent decrease in breast milk ΣPBDE concentrations was observed between 2007 and 2012, with a mean concentration at the later time point of 1.2 µg/kg lipid.

Sixteen pooled human breast milk samples were collected from primiparous nursing mothers in Galway and Dublin, Ireland during 2017–2018 (Wemken *et al.*, 2020). The number of individual samples per pool ranged from 3 to 10. PBDE and HBCDD were analysed by GC-MS/MS and LC-MS/MS, respectively. Results were compared to an equivalent survey carried out in 2011. Compared to the 2011 survey, concentrations were significantly lower for BDE-47 (medians 0.50 and 1.1 µg/kg lipid for 2017–2018 and 2011, respectively), BDE-99 (medians <0.2 and 0.27 µg/kg lipid), BDE-100 (medians <0.2 and 0.31 µg/kg lipid), BDE-153 (medians 0.71 and 1.0 µg/kg lipid), and ΣHBCDD (medians 1.8 and 2.9 µg/kg lipid). Concentrations of BDE-209 (medians 1.4 and 0.77 µg/kg lipid) were not significantly different. These findings are largely consistent with the legislative bans in Ireland on the use of penta- and octa-PDEs. The lack of decrease in BDE-209 concentrations was attributed to the later implementation of restrictions on the manufacture and use of deca-BDE. Restrictions on the manufacture and use of HBCDD was also noted to have occurred more recently.

Individual human milk samples from 1993 and 2001 to 2009 collected throughout Australia were combined into regional and annual pools of 4 to 10 samples and analysed for PBDEs and HBCDDs by GC-MS and LC-MS/MS, respectively (Toms *et al.*, 2012). Representative results are summarized in Table 12. Penta- and octa-BDE use was banned in Australia in 2004 and concentrations of the related congeners in human breast milk decreased from that time. HBCDD use was still permitted at the time of this study but has since been prohibited with limited exceptions.

TABLE 12 **CONCENTRATIONS OF POLYBROMINATED DIPHENYL ETHER AND HEXABROMOCYCLODODECANES IN POOLED BREAST MILK SAMPLES, STOCKHOLM, SWEDEN, 1980–2004**

| SUBSTANCE | CONCENTRATION, µg/kg LIPID | | | | | |
|---|---|---|---|---|---|---|
| | 1993 | 2002–2003 | 2003–2004 | 2006 | 2007–2008 | 2009 |
| BDE-47 | 4.4-5.6 | 4.0-11.5 | 9.3 | 8.5 | 2.5-3.0 | 1.4 |
| BDE-99 | 3.5-5.1 | 1.5-4.5 | 2.8 | 1.7 | 0.6-0.9 | 0.6 |
| BDE-153 | 1.4 | 1.0-3.3 | 4.5 | 1.5 | 1.6-2.0 | 1.3 |
| $\Sigma PBDE_4$ | 6.7-8.7 | 4.0-15.8 | 12.4 | 9.9 | 2.5-3.0 | 2.6 |
| ΣHBCDD | NQ-19 | NQ-11 | NQ | 5 | 12-15 | 2.5 |

*Notes*: BDE: brominated diphenyl ether; HBCDD: hexabromocyclododecane; $\Sigma PBDE_4$: sum of BDE-47, -99, -100 and -153, ΣHBCDD: sum of α-, β- and γ-HBCDD; NQ: not quantified.

*Source:* **Toms, L-M.L., Guerra, P., Eljarrat, E., Barceló, D., Harden, F.A., Hobson, P., Sjodin, A., Ryan, E. & Mueller, J.F.** 2012. Brominated flame retardants in the Australian population: 1993–2009. *Chemosphere*, 89(4): 398–403. https://doi.org/https://doi.org/10.1016/j.chemosphere.2012.05.053

Nationally representative samples of human breast milk were collected in Canada during 1992 ($n$ = 72), 2002 ($n$ = 98) and 2005 ($n$ = 34) and analysed for PBDE by GC-MS (Ryan and Rawn, 2014). Summary statistics for selected congeners and the sums of congeners are included in Table 13. The trend in concentrations of PBDE congeners in Canadian breast milk is complex, with mean concentrations of some congeners increasing across all three time periods, while others increased between 1992 and 2002 and decreased between 2002 and 2005. This suggests a transition from penta-PBDE, containing predominantly BDE-47, -99 and -100, to octa-BDE, containing predominantly BDE-183. BDE-209, the predominant congener in deca-BDE, was not determined in this study.

TABLE 13 **POLYBROMINATED DIPHENYL ETHER IN CANADIAN BREAST MILK, 1992, 2002 AND 2005**

| SUBSTANCE | MEAN CONCENTRATION (RANGE), µg/kg LIPID | | |
|---|---|---|---|
| | 1992 | 2002 | 2005 |
| BDE-28 | 0.40 (0.02-12.3) | 1.7 (0.03-13.1) | 2.9 (0.32-25.9) |
| BDE-47 | 8.3 (0.2-328) | 30.2 (0.08-526) | 23.0 (2.3-189) |
| BDE-99 | 4.4 (0.03-189) | 10.9 (0.05-299) | 5.8 (0.32-56) |
| BDE-100 | 1.2 (0.03-45) | 8.3 (0.06-148) | 6.7 (0.23-141) |
| BDE-153 | 0.60 (0.03-13.8) | 8.2 (0.09-153) | 8.9 (0.18-166) |
| BDE-154 | 0.19 (0.005-7.3) | 0.89 (0.002-23.1) | 0.55 (0.02-9.6) |
| BDE-183 | 0.27 (0.02-1.6) | 0.22 (0.003-2.0) | 2.0 (0.03-21.0) |
| $\Sigma_7$ PBDE | 15.3 (0.55-596) | 60.4 (0.84-956) | 48.2 (3.7-576) |

*Notes*: PBDE: polybrominated diphenyl ether; BDE: brominated diphenyl ether; and Σ7 PBDE: sum of the concentration of BDE-28,47,99,100,153,154,183.

*Source:* **Ryan, J.J. & Rawn, D.F.K.** 2014. The brominated flame retardants, PBDEs and HBCD, in Canadian human milk samples collected from 1992 to 2005; concentrations and trends. *Environment International*, 70: 1–8. https://doi.org/10.1016/j.envint.2014.04.020

Breast milk samples were collected from 50 primiparous nursing mothers in Chișinău, Republic of Moldova during 2008–2009 and again in 2014–2015 and a single pooled sample for each time period was analysed for PBDEs by a WHO reference laboratory (Tirsina *et al.*, 2017). Results are summarized in Table 14. While the absolute concentrations of PBDE congeners in breast milk in the Republic of Moldova are low compared to other country studies reviewed in this section, there is a strongly increasing trend during a period when other countries were observing decreases.

TABLE 14 **CONCENTRATIONS OF SELECTED POLYBROMINATED DIPHENYL ETHER, BROMINATED DIPHENYL ETHER IN POOLED BREAST MILK, REPUBLIC OF MOLDOVA, 2008–2009 AND 2014–2015**

| SUBSTANCE | CONCENTRATION ng/kg LIPID | | CHANGE (%) |
|---|---|---|---|
| | 2008–2009 | 2014–2015 | |
| BDE-28 | 35.0 | 49.3 | +41 |
| BDE-47 | 415 | 755 | +82 |
| BDE-99 | 104 | 502 | +380 |
| BDE-100 | 113 | 163 | +44 |
| BDE-153 | 95 | 219 | +130 |

*Notes*: PBDE: polybrominated diphenyl ether; BDE: brominated diphenyl ether.

*Source:* **Tirsina, A., Sircu, R., Pinzaru, I. & Bahnarel, I.** 2017. Changes over time in persistent organic pollutants (POP) concentrations in human milk in the Republic of Moldova. *Toxicological & Environmental Chemistry*, 99(5-6): 1007–1019. https://doi.org/10.1080/02772248.2017.1287469

Breast milk samples from healthy nursing mothers in Osaka, Japan were collected and pooled into year (1973–2006) and age-group composites and analysed for HBCDD by LC-MS/MS (Kakimoto *et al.*, 2008). HBCDD isomers were first detected in breast milk samples in 1988. From 1993 to 2006, the mean of the sum of the HBCDD isomers was fairly constant in the range 1.0–4.0 µg/kg lipid. No strong trend was apparent during this time, although concentrations in the three most recent years (2004–2006) decreased from 2.3 to 1.6 to 1.4 µg/kg lipid, suggestive of a decreasing trend.

Between 2005 and 2007, breast milk samples were collected from 13 primiparous women living in Rome, Italy and analysed for PBDEs by GC-MS (Alivernini *et al.*, 2011). The results were compared to the results of a previous breast milk study carried out in Italy in 2000–2001 (Ingelido *et al.*, 2007). Representative results from the two surveys are summarized in Table 15. The production and use of penta- and octa-PBDEs in the European Union was phased out in 2004, with restrictions for deca-PBDEs coming into effect in subsequent years (EFSA, 2024).

TABLE 15 **SELECTED POLYCHLORINATED BIPHENYLS IN THE BREAST MILK OF ITALIAN WOMEN, 1987–2007**

| SUBSTANCE | MEAN CONCENTRATION, µg/kg LIPID | |
|---|---|---|
| | 2000–2001 | 2005–2007 |
| PBDE CONGENERS[a] | | |
| BDE-28 | 0.082 | 0.065 |
| BDE-47 | 1.9 | 0.75 |
| BDE-100 | 0.48 | <0.03 |
| BDE-153 | 0.47 | 0.48 |

*Notes*: [a] To improve sensitivity, the individual samples in the 2005–2007 study were pooled and the sample volume reduced. The results presented here are for the single pooled sample. PBDE: polybrominated diphenyl ether and BDE: brominated diphenyl ether.

*Sources:* **Alivernini, S., Battistelli, C.L. & Turrio-Baldassarri, L.** 2011. Human Milk as a Vector and an Indicator of Exposure to PCBs and PBDEs: Temporal Trend of Samples Collected in Rome. *Bulletin of Environmental Contamination and Toxicology*, 87(1): 21–25. https://doi.org/10.1007/s00128-011-0262-7; and **Ingelido, A.M., Ballard, T., Dellatte, E., di Domenico, A., Ferri, F., Fulgenzi, A.R., Herrmann, T. *et al.*** 2007. Polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) in milk from Italian women living in Rome and Venice. *Chemosphere*, 67(9): S301–S306. https://doi.org/10.1016/j.chemosphere.2006.05.111

## 5.3 PHTHALATES

Phthalates or phthalate esters are esters of phthalic acid and have been used as plasticizers. Phthalates are usually characterized by their molecular weight. Phthalates are analysed in human clinical samples as their metabolites, with some phthalates having multiple metabolites. The use of phthalates has been phased out in many countries and they have been substituted with terephthalates and 1,2-cyclohexane dicarboxylic acid diisononyl ester (DINCH). The major phthalates, phthalate substitutes and their metabolites are shown in Table 16.

©FAO/Florita Botts

China - Powdered pesticides

TABLE 16 **MAJOR PHTHALATES, PHTHALATE SUBSTITUTES AND THEIR METABOLITES**

| SUBSTANCE | ACRONYM | MOLECULAR WEIGHT CLASS | METABOLITE(S) | METABOLITE ACRONYM(S) |
|---|---|---|---|---|
| PHTHALATES | | | | |
| Dimethyl phthalate | DMP | LMW | Monomethyl phthalate | MMP |
| Diethyl phthalate | DEP | LMW | Monoethyl phthalate | MEP |
| Diisobutyl phthalate | DiBP | LMW | Monoisobutyl phthalate<br>2-hydroxy-monoisobutyl phthalate | MiBP<br>2-OH-MiBP |
| Di-n-butyl phthalate | DnBP | LMW | Mono-n-butyl phthalate<br>3-hydroxy-mono-n-butyl phthalate | MnBP<br>3OH-MnBP |
| Butylbenzyl phthalate | BBzP | LMW | Monobenzyl phthalate | MBzP |
| Dicyclohexyl phthalate | DCHP | LMW | Monocyclohexyl phthalate | MCHP |
| Di-n-pentyl phthalate | DnPeP | LMW | Mono-n-pentyl phthalate | MnPeP |
| Di(2-ethylhexyl) phthalate | DEHP | HMW | Mono(2-ethylhexyl) phthalate<br>Mono(2-ethyl-5-hydroxy-hexyl) phthalate<br>Mono(2-ethyl-5-oxo-hexyl) phthalate<br>Mono(2-ethyl5-carboxy-pentyl) phthalate | MEHP<br>MEHHP<br>MEOHP<br>MECPP |
| Diisononyl phthalate | DiNP | HMW | 7-hydroxy-monomethyloctyl phthalate<br>7-oxo-monomethyloctyl phthalate<br>7-carboxy-monomethylheptyl phthalate | OH-MiNP<br>oxo-MiNP<br>cx-MiNP |
| Diisodeceyl phthalate | DiDP | HMW | 6-hydroxy-monopropylheptyl phthalate | OH-MiDP |
| PHTHALATE SUBSTITUTES | | | | |
| Di(2-ethylhexyl) terephthalate | DEHTP | SUB | mono-2-ethyl-5-hydrohexyl terephthalate<br>mono-2-ethyl-5-carboxypentyl terephthalate | MEHHTP<br>MECPTP |
| Cyclohexane-1,2-dicarboxylic acid diisononyl ester | DINCH | SUB | Cyclohexane-1,2-dicarboxylic acid monohydroxy isononyl ester<br>Cyclohexane-1,2-dicarboxylic acid monocarboxy isooctyl ester | MHiNCH<br><br>MCOCH |

*Notes*: LMW: low molecular weight; HMW: high molecular weight; and SUB: substitute.

### 5.3.1 META-ANALYSES

Worldwide geographical and temporal patterns of exposure to DEHP were examined based on a literature search (Qu *et al.*, 2022). Similar trends were demonstrated across different geographical regions, with mean estimates of exposure decreasing from 3–5 µg/kg bw per day before 2000 to approximately 1.5–2.5 µg/kg bw per day during 2015–2017. This publication also presented information on DEHP production volumes, which decreased to a minimum of about 100 000 tonnes in 2013 before increasing to about 300 000 tonnes in 2018.

### 5.3.2 DIRECT EVIDENCE

Due to their toxicity to reproduction, phthalates were included in the European Union list for authorization, with four phthalates (DEHP, DnBP, BBzP and DiBP) added to Annex IV of Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) in 2013.

Literature data (2000–2010) and data from two European projects, DEMOCOPHES (2011–2012) and HBM4EU (2014–2021) were combined to examine temporal trends in exposure to prioritized contaminants, including phthalates and phthalate substitutes (DINCH) (Rodriguez Martin *et al.*, 2023). Median urinary concentrations of a number of phthalate metabolites in children 5–12 years old decreased steadily from 2004 to 2016, then appeared to remain approximately stable through to 2020. While a number of regulatory measures were implemented from 2008 onwards, it is not obvious that any particular measure has produced a change in the human phthalate burden. Urinary concentrations of the DEP metabolite, MEP decreased sharply after 2014, but began to increase again after 2017. Urinary metabolite concentrations of DiNP in children 5 to 12 years old decreased steadily after 2010 to about 2018. This may have been due to the ban on phthalate use in cosmetic products in 2008. Urinary concentration of phthalate substitute (DINCH) metabolites in children 5 to 12 years old increased until about 2015, then stayed stable or decreased slightly.

In a study in the Netherlands of 500 individuals with impaired fasting glucose, urine samples were taken at recruitment in 2009–2013 and at a follow up point during 2014–2016 (van der Meer *et al.*, 2021). Urine samples were analysed for phthalate metabolites, providing two measures of temporal trend, (1) comparison of participants at recruitment and approximately four-year follow-up, and (2) urinary samples collected across the years 2009–2016. Selected results from both comparisons are summarized in Table 17. With the exception of MMP, both approaches demonstrated statistically significant decreases in urinary concentrations of all phthalate metabolites. The more gradual and constant decreases in urinary concentrations of phthalate metabolites were thought to reflect the wider range of regulatory measures implemented over time.

TABLE 17 **PHTHALATE METABOLITES IN THE URINE OF DUTCH SUBJECTS WITH IMPAIRED FASTING GLUCOSE, 2009–2016**

| SUBSTANCE | MEDIAN CONCENTRATION, µg/24 HOURS | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | B | F[a] | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 |
| MMP | 0.96 | 0.78 | 1.2 | 2.4 | 1.8 | 1.4 | 1.6 | 1.6 | 1.1 | 1.1 |
| MEP | 50 | 31 | 111 | 92 | 112 | 83 | 82 | 61 | 46 | 73 |
| MiBP | 20 | 14 | 43 | 43 | 33 | 32 | 30 | 25 | 24 | 23 |
| MnBP | 16 | 13 | 33 | 32 | 28 | 27 | 26 | 24 | 21 | 19 |
| MEHHP | 8.8 | 5.8 | 21 | 19 | 16 | 13 | 13 | 10 | 9.6 | 9.1 |
| MBzP | 3.7 | 2.0 | 8.8 | 7.6 | 5.9 | 5.9 | 5.6 | 4.0 | 3.5 | 3.1 |

*Notes*: [a] Follow-up samples were taken approximately four years after recruitment samples. B: baseline; F: follow-up; MMP: monomethyl phthalate; MEP: monoethyl phthalate; MiBP: monoisobutyl phthalate; MnBP: mono-n-butyl phthalate; MEHHP: mono-(2-ethyl-5-hydroxy-hexyl) phthalate (major metabolite of di(2-ethylhexyl) phthalate); and MBzP: monobenzyl phthalate.

*Source:* **van der Meer, T.P., Chung, M.K., van Faassen, M., Makris, K.C., van Beek, A.P., Kema, I.P., Wolffenbuttel, B.H.R., van Vliet-Ostaptchouk, J.V. & Patel, C.J.** 2021. Temporal exposure and consistency of endocrine disrupting chemicals in a longitudinal study of individuals with impaired fasting glucose. *Environmental Research*, 197: 110901. https://doi.org/10.1016/j.envres.2021.110901

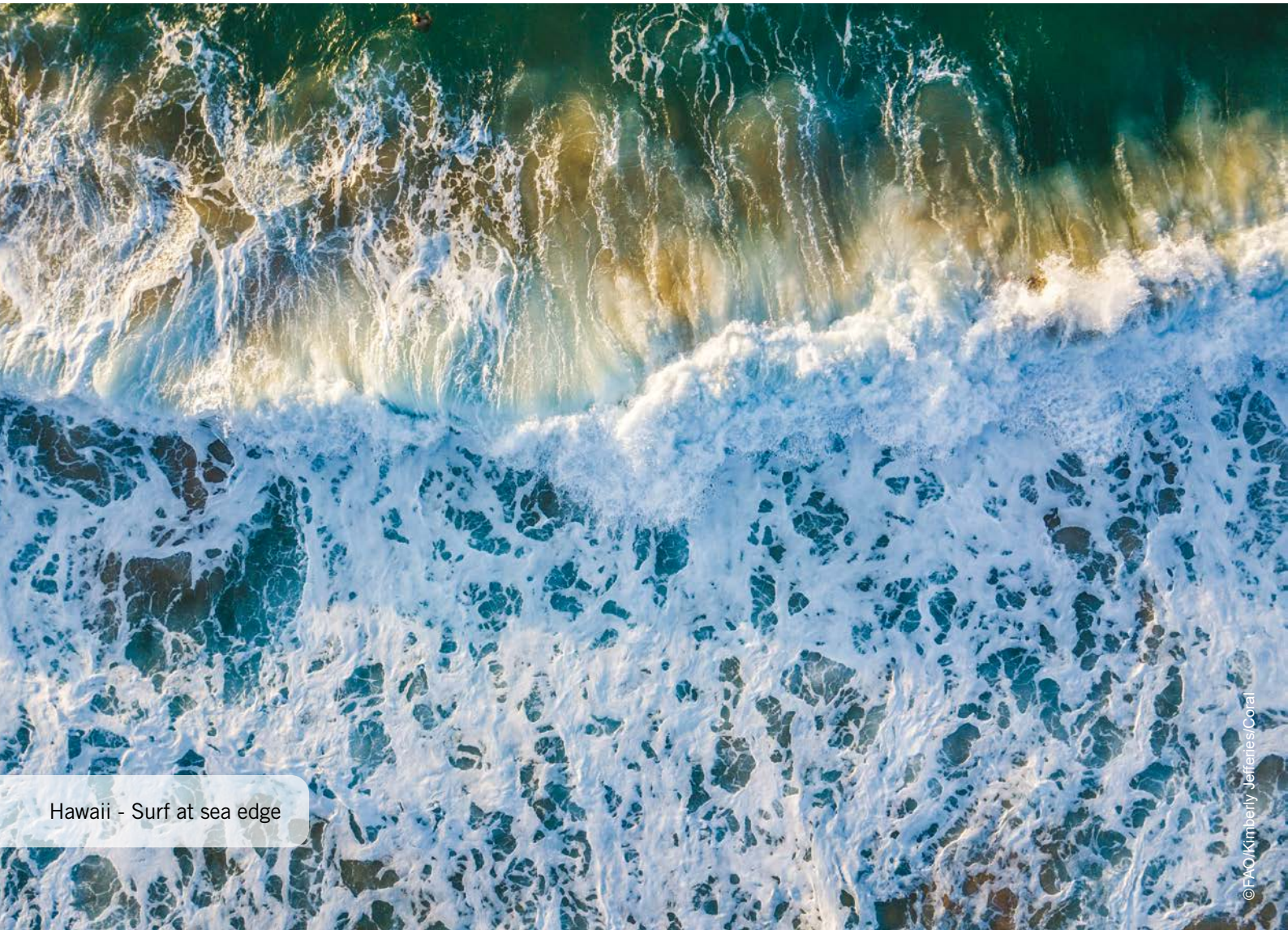
Two cohorts of volunteers were enrolled in central Italy in 2011 ($n$ = 157) and 2016 ($n$ = 171) and spot urine samples collected for phthalate analysis (Tranfo *et al.*, 2018). Samples were analysed by HPLC-MS/MS for metabolites of the four phthalates in Annex IV of REACH. The results are summarized in Table 18.

TABLE 18 **PHTHALATES IN THE URINE OF ITALIAN VOLUNTEERS, 2011 AND 2016**

| PHTHALATE | METABOLITES ANALYSED | MEAN CONCENTRATION, µg/g CREATININE | | | |
|---|---|---|---|---|---|
| | | MALES | | FEMALES | |
| | | 2011 | 2016 | 2011 | 2016 |
| DEHP | MEHP + MEHHP | 21.1 | 5.7 | 20.9 | 5.9 |
| DnBP | MnBP | 57.7 | 1.4 | 54.5 | 1.3 |
| BBzP | MBzP | 14.5 | 0.9 | 15.0 | 1.3 |
| DEP | MEP | 143 | 98 | 300 | 188 |

*Notes*: DEHP: di(2-ethylhexyl) phthalate; DnBP: di-n-butyl phthalate; BBzP: butylbenzyl phthalate; DEP: diethyl phthalate; MEHP: mono(2-ethylhexyl) phthalate; MEHHP: mono(2-ethyl-5-hydroxy-hexyl) phthalate; MnBP: mono-n-butyl phthalate; MBzP: monobenzyl phthalate; and MEP: monoethyl phthalate.

*Source:* **Tranfo, G., Caporossi, L., Pigini, D., Capanna, S., Papaleo, B. & Paci, E.** 2018. Temporal Trends of Urinary Phthalate Concentrations in Two Populations: Effects of REACH Authorization after Five Years. *International Journal of Environmental Research and Public Health*, 15(9): 1950. https://doi.org/10.3390/ijerph15091950



Hawaii - Surf at sea edge

A study carried out in Boston, Massachusetts in the United States examined phthalate metabolites and phthalate replacements in the urine of volunteers at two-year intervals between 2000 and 2017 (Jiang *et al.*, 2023). The number of urine samples analysed at each timepoint ranged from 94 (2000–2001) to 1 390 (2010–2011). A variety of trend patterns were observed, with the mean urinary concentrations of some contaminants decreasing monotonically across the course of the monitoring, while others increased to a peak during 2006–2009 before decreasing. As expected, urinary concentrations of metabolites of phthalate substitutes (DINCH and terephthalates) increased during the period 2010 to 2017. Representative data from this study are summarized in Table 19.

TABLE 19 **TRENDS IN URINARY CONCENTRATIONS OF SELECTED PHTHALATE METABOLITES AND METABOLITES OF PHTHALATE SUBSTITUTES, BOSTON, 2000–2017**

| SUBSTANCE | MEAN CONCENTRATION (95% CI), µg/L | | | | CHANGE PER YEAR (%) |
|---|---|---|---|---|---|
| | 2000–2001 | 2006–2007 | 2012–2013 | 2016–2017 | |
| PHTHALATE METABOLITES | | | | | |
| MEP | 109 (59–138) | 70 (61– 81) | 32 (28–37) | 22 (18–26) | -11.5 |
| MnBP | 8.4 (6.6–10.7) | 13.2 (12.0–14.5) | 8.1 (7.4–8.8) | 6.7 (6.0–7.4) | -3.3 |
| MBzP | 3.7 (2.9–4.7) | 3.3 (2.9–3.7) | 2.9 (2.6–3.2) | 2.2 (1.9–2.5) | -3.0 |
| MEHP | 3.8 (2.9–5.0) | 5.4 (4.8–6.0) | 1.4 (1.3–1.53) | 1.2 (1.1–1.3) | -11.9 |
| MECPTP | | | 8.1 (6.3–10.5) | 39.6 (33.9–46.3) | +45.1 |
| PHTHALATE SUBSTITUTE (DINCH) METABOLITES | | | | | |
| MHiNCH | | | 0.35 (0.33–0.37) | 0.78 (0.69–0.87) | +20.0 |
| MCOCH | | | 0.38 (0.37–0.39) | 0.69 (0.63–0.75) | +16.2 |

*Notes*: MEP: monoethyl phthalate; MnBP: mono-n-butyl phthalate; MBzP: monobenzyl phthalate; MEHP: mono(2-ethylhexyl) phthalate; MECPTP: mono-2-ethyl-5-carboxypentyl terephthalate; MHiNCH: cyclohexane-1,2-dicarboxylic acid monohydroxy isononyl ester; and MCOCH: cyclohexane-1,2-dicarboxylic acid monocarboxyisooctyl ester.

*Source:* **Jiang, V.S., Calafat, A.M., Williams, P.L., Chavarro, J.E., Ford, J.B., Souter, I., Hauser, R. & Mínguez-Alarcón, L.** 2023. Temporal trends in urinary concentrations of phenols, phthalate metabolites and phthalate replacements between 2000 and 2017 in Boston, MA. *Science of the Total Environment*, 898: 165353. https://doi.org/10.1016/j.scitotenv.2023.165353

A human biomonitoring study was carried out in 2015 within an adult population living in Liège, Belgium (Pirard and Charlier, 2022). Some phthalate metabolites were measured in the urine of 252 participants. An awareness campaign was initiated by the provincial authorities of Liège over the period 2014–2016. Three years later in 2018, 92 of the initial participants again provided urine samples, and the levels of phthalate metabolites and phthalate substitutes (DINCH) were determined for comparison with the earlier time point (Table 20).

TABLE 20 **COMPARISON OF CONCENTRATIONS OF PHTHALATE METABOLITES AND METABOLITES OF PHTHALATE SUBSTITUTES IN THE URINE OF A BELGIAN COHORT, 2015 AND 2018**

| SUBSTANCE | FREQUENCY OF DETECTION, % | | MEDIAN CONCENTRATION (P95), µg/L | |
|---|---|---|---|---|
| | 2015 | 2018 | 2015 | 2018 |
| PHTHALATE METABOLITES | | | | |
| MEP | 95.7 | 97.8 | 21.3 (320) | 20.4 (690) |
| MnBP | 97.8 | 97.8 | 19.0 (63) | 11.8 (77) |
| MBzP | 89.1 | 81.5 | 3.2 (18) | 1.9 (13) |
| 5-oxo-MEHP | 92.4 | 85.9 | 2.7 (12.9) | 1.9 (7.8) |
| 5-OH-MEHP | 96.7 | 96.7 | 3.8 (17) | 2.9 (13) |
| MEHP | 62.0 | 47.8 | 1.1 (6.6) | <LOQ (3.8) |
| cx-MiNP | 95.6 | 91.1 | 3.7 (38) | 3.4 (15) |
| OH-MiDP | 31.0 | 27.8 | <LOQ (4.8) | <LOQ (2.4) |
| DINCH METABOLITES | | | | |
| OH-MINCH | 24.1 | 35.6 | <LOQ (10) | <LOQ (36) |
| cx-MINCH | 19.5 | 34.4 | <LOQ (9.1) | <LOQ (24) |

*Notes*: P95: 95th percentile; MEP: monoethyl phthalate; MnBP: mono-n-butyl phthalate; MBzP: monobenzyl phthalate; MEHP: mono (2-ethylhexyl) phthalate; cx-MiNP: 7-carboxy-(mono-methyl-heptyl) phthalate; OH-MiDP: 6-hydroxy-monopropylheptyl phthalate; OH-MINCH: cyclohexane-1,2-dicarboxylate-mono-(7-hydroxy-4-methyl)octyl ester; and cx-MINCH: cyclohexane-1,2-dicarboxylate-mono-(7- carboxylate-4-methyl)heptyl ester.

*Source:* **Pirard, C. & Charlier, C.** 2022. Urinary levels of parabens, phthalate metabolites, bisphenol A and plasticizer alternatives in a Belgian population: Time trend or impact of an awareness campaign? *Environmental Research*, 214: 113852. https://doi.org/10.1016/j.envres.2022.113852

While the period across which these trends were considered is relatively narrow (three years), there is evidence for decreased exposure to some phthalates and suggestive evidence for the uptake of replacement chemicals for phthalates.

Urine samples from the German Environmental Specimen Bank (ESB) (60/year) for the years 2007, 2009, 2011, 2013 and 2015 were analysed for phthalate metabolites and the results were combined with those from studies covering the periods 1988 to 2003 and 2002 to 2008 (Koch *et al.*, 2017). Representative data for the major phthalate metabolites are summarized in Table 21. Regulatory changes affecting the production of phthalates occurred in Europe in 2013. While downward trends in urinary levels of phthalates are apparent before this time, decreases between 2013 and 2015 are appreciable.

TABLE 21 **TRENDS IN URINARY PHTHALATE METABOLITES FOR GERMANS AGED 20–29 YEARS, 1988–2015**

| PHTHALATE | METABOLITE | MEDIAN CONCENTRATION, µg/L | | | | | |
|---|---|---|---|---|---|---|---|
| | | 1988 | 1998 | 2007 | 2011 | 2013 | 2015 |
| DMP | MMP | - | - | 8.0 | 4.4 | 3.5 | 2.8 |
| DEP | MEP | - | - | 53.6 | 17.9 | 20.9 | 13.5 |
| DiBP | MiBP | 29.3 | 36.5 | 19.3 | 20.3 | 16.4 | 9.8 |
| DnBP | MnBP | 178 | 79.2 | 16.4 | 14.8 | 11.2 | 8.0 |
| BBzP | MBzP | 7.8 | 7.5 | 2.9 | 3.3 | 2.0 | 1.2 |
| DEHP | MEHHP | 27.8 | 17.0 | 10.8 | 7.5 | 5.7 | 4.2 |
| DiNP | OH-MiNP | 1.5 | 2.1 | 2.2 | 2.9 | 2.5 | 2.4 |
| DiDP/DPHP | OH-MiDP | - | - | 0.7 | 1.0 | 0.8 | 0.8 |

*Notes*: DMP: dimethyl phthalate; MMP: monomethyl phthalate; DEP: diethyl phthalate; MEP: monoethyl phthalate; DiBP: di(isobutyl) phthalate, MiBP: mono(isobutyl) phthalate, DnBP: di(n-butyl) phthalate; MnBP: mono-n-butyl phthalate; BBzP: butylbenzyl phthalate; MBzP: monobenzyl phthalate; DEHP: di(2-ethylhexyl) phthalate; MEHHP: mono-(2-ethyl-5-hydroxyhexyl) phthalate; DiNP: di(isononyl) phthalate; OH-MiNP: 7-OH-mono-methyloctyl phthalate; DiDP: diisodecyl phthalate; DPHP: di(propylheptyl) phthalate; and OH-MiDP: 6-OH-monopropylheptyl phthalate.

*Source:* **Koch, H.M., Rüther, M., Schütze, A., Conrad, A., Pälmke, C., Apel, P., Brüning, T. & Kolossa-Gehring, M.** 2017. Phthalate metabolites in 24-h urine samples of the German Environmental Specimen Bank (ESB) from 1988 to 2015 and a comparison with US NHANES data from 1999 to 2012. *International Journal of Hygiene and Environmental Health*, 220(2, Part A): 130–141. https://doi.org/10.1016/j.ijheh.2016.11.003

As part of the Swedish SELMA study, morning void urine samples were collected from pregnant women during 2007–2010 and analysed for phthalate metabolites by LC-MS/MS (Shu *et al.*, 2018). The results are summarized in Table 22. For DEHP and DiNP, which have multiple commonly-detected metabolites, a summary metric, the molar sum of the metabolites expressed as the parent compound, was derived. While there is some evidence for decreases in urinary levels of metabolites of some shorter chain phthalates (DEP, DEHP), for other phthalates there is either no evidence of a trend or evidence for an increasing trend. Major European regulatory measures to restrict production and use of phthalates postdate this study. However, this study shows a clear increasing trend in urinary levels of the metabolite of the phthalate substitute, di(isononyl) cyclohexane dicarboxylate (DiNCH, metabolite MONiCH).

TABLE 22 **PHTHALATE METABOLITES IN THE URINE OF PREGNANT SWEDISH WOMEN, 2007–2010**

| SUBSTANCE | LEAST SQUARES GEOMETRIC MEAN CONCENTRATION, µg/L | | | |
|---|---|---|---|---|
| | 2007 | 2008 | 2009 | 2010 |
| MEP | 66 | 73 | 67 | 59 |
| MnBP | 65 | 71 | 65 | 76 |
| MBzP | 15 | 17 | 16 | 18 |
| ΣDEHP | 74 | 79 | 65 | 62 |
| ΣDiNP | 22 | 25 | 28 | 31 |
| MCiNP | 0.58 | 0.64 | 0.73 | 0.79 |
| MHiDP | 1.02 | 1.23 | 1.32 | 1.37 |
| MONiCH | 0.19 | 0.26 | 0.39 | 0.60 |

*Notes*: MEP: monoethyl phthalate; MnBP: mono-n-butyl phthalate; MBzP: monobenzyl phthalate; ΣDEHP: molar sum of metabolites of di(2-ethylhexyl) phthalate; ΣDiNP: molar sum of metabolites of di(isononyl) phthalate; MCiNP: mono(carboxyisononyl) phthalate; MHiDP: mono(hydroxyisononyl) phthalate; and MoiNCH: mono(oxoisononyl) cyclohexanecarboxylic acid.

*Source:* **KShu, H., Jönsson, B.A.G., Gennings, C., Svensson, Å., Nånberg, E., Lindh, C.H., Knutz, M., Takaro, T.K. & Bornehag, C-G.** 2018. Temporal trends of phthalate exposures during 2007–2010 in Swedish pregnant women. *Journal of Exposure Science & Environmental Epidemiology*, 28(5): 437–447. https://doi.org/10.1038/s41370-018-0020-6

Urine samples were provided by women aged 25–80 years, living in Kyoto, Japan (Lyu *et al.*, 2022). Samples were collected in each of 1993, 2000, 2003, 2009, 2011 and 2016, with 10 to 26 samples collected each year, for a total of 132 samples. Samples were analysed for phthalates by LC-MS/MS. Results are summarized in Table 23. Two trends are apparent: for the metabolites of the lower molecular weight, phthalates concentrations in urine appear to decrease after 2009, while for the higher molecular weight species, no particular trend is apparent across the period 2000–2016.

TABLE 23 **PHTHALATE METABOLITES IN THE URINE OF WOMEN, KYOTO, JAPAN, 1993–2016**

| SUBSTANCE | MEDIAN CONCENTRATION, mg/kg CREATININE | | | | | |
|---|---|---|---|---|---|---|
| | 1993 | 2000 | 2003 | 2009 | 2010 | 2016 |
| MMP | 14.5 | 2.3 | 5.3 | 8.8 | 7.0 | 2.8 |
| MEP | 25.1 | 24.7 | 44.2 | 75.2 | 7.7 | 9.7 |
| MnBP | 42.0 | 3.9 | 1.8 | 6.6 | 3.2 | ND |
| MiBP | 43.6 | 3.0 | ND | 5.7 | ND | ND |
| MBzP | 7.7 | 1.6 | 2.2 | 4.6 | 2.3 | 1.3 |
| MEHHP | 30.3 | 9.7 | 12.2 | 12.1 | 14.1 | 12.4 |
| MECPP | 26.6 | 11.5 | 19.5 | 9.6 | 15.8 | 9.4 |
| MCMHP | 14.6 | 5.5 | 9.7 | 3.9 | 7.2 | 8.3 |

*Notes*: MMP: monomethyl phthalate; MEP: monoethyl phthalate; MnBP: mono-n-butyl phthalate; MiBP: mono(isobutyl) phthalate; MBzP: monobenzyl phthalate; MEHHP: mono-(2-ethyl-5-hydroxyhexyl) phthalate; MECPP: mono(2-ethyl-5-carboxypentyl) phthalate; and MCMHP: mono[(2-carboxymethyl)hexyl] phthalate.

*Source:* **Lyu, Z., Harada, K.H., Kim, S., Fujitani, T., Cao, Y., Hitomi, T., Fujii, Y., Kho, Y. & Choi, K.** 2022. Exposure to phthalate esters in Japanese females in Kyoto, Japan from 1993 to 2016: Temporal trends and associated health risks. *Environment International*, 165: 107288. https://doi.org/10.1016/j.envint.2022.107288

## 5.4 BISPHENOLS

Bisphenols are chemicals made up of two phenol molecules joined at the para position to a bridging moiety. Bisphenol A (BPA, propyl bridging group) is primarily used as a co-monomer in the production of polycarbonate plastics. BPA is also used in the production of some resins. Due to concerns about its estrogenicity, BPA has been replaced in some instances by other bisphenols: bisphenol F (BPF, methyl bridging group) and bisphenol S (BPS, sulfonyl bridging group).

### 5.4.1 META-ANALYSES

A systematic review and meta-analysis of BPA in human breast milk classified included studies into two time periods: 2000–2010 and 2011–2020 (Iribarne-Durán *et al.*, 2022). The analysis concluded that the arithmetic mean of BPA concentrations in breast milk samples from the later time period (1.81 µg/L) was substantially higher than in the earlier period (1.01 µg/L). It should be noted that most studies that considered trends in the human body burden of BPA, reviewed as part of the current report, used urine as the matrix for determining BPA exposure. It is uncertain whether the matrix influences the assessment of trends.

### 5.4.2 INDIRECT EVIDENCE

Estimates of dietary exposure to BPA were derived from concentrations of BPA in foods collected in France over the period 2007–2009 and in 2015 (Gorecki *et al.*, 2017). Food consumption information was taken from the second individual and national study on food consumption (INCA 2). For the adult (>18 years) population, the mean lower bound-upper bound (95th percentile lower bound–upper bound) estimate of dietary exposure to BPA decreased from 0.038–0.040 (0.077–0.087) µg/kg bw per day based on samples collected over the period 2007–2009 to 0.034–0.035 (0.067–0.074) µg/kg bw per day for samples collected in 2014. Similar changes were estimated for children (3–17 years) with exposure decreasing from 0.053–0.056 (0.119–0.141) µg/kg bw per day to 0.048–0.050 (0.109–0.123) µg/kg bw per day.

### 5.4.3 DIRECT EVIDENCE

Literature data (2000–2010) and data from two European projects, DEMOCOPHES (2011–2012) and HBM4EU (2014–2021) were combined to examine temporal trends in exposure to prioritized contaminants, including BPA, BPS and BPF (Rodriguez Martin *et al.*, 2023). Median urinary concentrations of BPA in women 24–52 years increased over the period 2004 to 2012 to a peak of approximately 1.8 mg/kg creatinine before decreasing to approximately 1.0 mg/kg creatinine in 2020. The decrease closely followed regulatory restrictions in the European Union. Median urinary concentrations of BPF increased to a peak of approximately 0.6 mg/kg creatinine in 2015, before decreasing to negligible levels in 2020. Median bisphenol S concentrations peaked in about 2015, decreased over the next two years and seem to be increasing again.

The BPA body burden of the German population from 1995 to 2009 was assessed by examining 600 24-hour urine samples and corresponding plasma samples by LC-MS/MS (Koch *et al.*, 2012). No trend in urinary BPA concentrations was apparent, with geometric mean concentrations in the range 1.54 to 1.98 mg/kg creatinine across the course of the study and geometric mean BPA concentrations in 1995 and 2009 of 1.81 and 1.73 mg/kg creatinine, respectively. BPA concentrations were mostly below the limit of detection (LOD) in plasma samples.

In a study in the Netherlands of 500 individuals with impaired fasting glucose, urine samples were taken at recruitment in 2009–2013 and at a follow up point during 2014–2016 (van der Meer *et al.*, 2021). Urine samples were analysed for bisphenols, providing two measures of temporal trend: (1) comparison of participants at recruitment and approximately 4-year follow-up; and (2) urinary samples collected across the years 2009–2016. Results from both comparisons are summarized for bisphenols A, F and S in Table 24. Both approaches demonstrated a statistically significant decrease in urinary BPA concentrations but no BPF. A sharp decrease in urinary BPA concentrations was apparent between 2014 and 2015, which is coincident with EFSA's reassessment of BPA and a substantial reduction in the tolerable daily intake (EFSA, 2015).

TABLE 24 **BISPHENOLS IN THE URINE OF DUTCH SUBJECTS WITH IMPAIRED FASTING GLUCOSE, 2009–2016**

| SUBSTANCE | MEDIAN CONCENTRATION, µg/24 HOURS | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | B | FA | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 |
| BPA | 1.1 | 0.77 | 2.3 | 2.3 | 1.7 | 1.4 | 1.8 | 1.8 | 0.9 | 1.2 |
| BPF | 0.29 | 0.25 | 0.49 | 0.68 | 0.46 | 0.50 | 0.45 | 0.57 | 0.44 | 0.46 |
| BPS | <LOD | <LOD | - | - | - | - | - | - | - | - |

*Notes:* [a] Follow-up samples were taken approximately four years after recruitment samples. B: baseline; F: follow-up; BPA: bisphenol A; BPF: bisphenol F; BPS: bisphenol S; and LOD: limit of detection.

*Source:* **van der Meer, T.P., Chung, M.K., van Faassen, M., Makris, K.C., van Beek, A.P., Kema, I.P., Wolffenbuttel, B.H.R., van Vliet-Ostaptchouk, J.V. & Patel, C.J.** 2021. Temporal exposure and consistency of endocrine disrupting chemicals in a longitudinal study of individuals with impaired fasting glucose. *Environmental Research*, 197: 110901. https://doi.org/10.1016/j.envres.2021.110901

A human biomonitoring study was carried out in 2015 within an adult population living in Liège, Belgium (Pirard and Charlier, 2022). Bisphenol A and other bisphenols were measured in the urine of 252 participants. An awareness campaign was initiated by the provincial authorities of Liège and spread over 2014–2016. In 2018, 92 of the initial participants again provided urine samples and the levels of BPA and bisphenol alternatives (bisphenol S, F, Z, P) were determined and compared to those obtained in 2015 to assess the time trends (Table 25).

TABLE 25 **COMPARISON OF CONCENTRATIONS OF BISPHENOLS IN THE URINE OF A BELGIAN COHORT, 2015 AND 2018**

| SUBSTANCE | FREQUENCY OF DETECTION, % | | MEDIAN CONCENTRATION (P95), µg/L | |
|---|---|---|---|---|
| | 2015 | 2018 | 2015 | 2018 |
| BISPHENOLS | | | | |
| Bisphenol A | 74.4 | 77.8 | 0.82 (3.3) | 0.79 (8.0) |
| Bisphenol F | 38.4 | 57.8 | <LOQ (0.67) | 0.12 (1.4) |
| Bisphenol P | 1.2 | 16.7 | <LOQ (<LOQ) | <LOQ (0.72) |
| Bisphenol S | 24.4 | 45.6 | <LOQ (0.56) | <LOQ (1.6) |
| Bisphenol Z | 10.5 | 22.2 | <LOQ (0.12) | <LOQ (0.85) |

*Source:* **Pirard, C. & Charlier, C.** 2022. Urinary levels of parabens, phthalate metabolites, bisphenol A and plasticizer alternatives in a Belgian population: Time trend or impact of an awareness campaign? *Environmental Research*, 214: 113852. https://doi.org/10.1016/j.envres.2022.113852

Urine samples were collected from primiparous mothers in Uppsala, Sweden during the period 2009–2014 and analysed for BPA by LC-MS/MS (Gyllenhammar *et al.*, 2017). While summary statistics of urinary BPA concentrations by year were not reported, the rate of change in urinary BPA was reported to be -9.8 percent per year.

In a similar study carried out in Puerto Rico during 2011–2016, 2 166 urine samples were collected from 1 003 pregnant women (134–498 samples per year) and analysed for bisphenols (Ashrap *et al.*, 2018). Time trends are presented graphically in this publication and show a decreasing trend for BPA and an increasing trend for the BPA substitute bisphenol S, while no clear trend was apparent for bisphenol F.

Spot urine samples were collected from 133 healthy Japanese women (25–80 years of age) from the Kyoto area in six year-based cohorts of 10 to 26 women (1993, 2000, 2003, 2009, 2011 and 2016) (Lyu *et al.*, 2023). Samples were analysed by LC-MS/MS for 10 bisphenols. The most commonly detected bisphenols were A, E and F, detected in 65.4, 66.2 and 76.7 percent of samples, respectively. Exposure to bisphenols was calculated from the urinary concentrations. The median estimated daily intake (EDI) for BPA decreased monotonically from 0.038 µg/kg bw per day in 1993 to 0.003 µg/kg bw per day in 2016. For BPE and BPF, no clear trend was apparent, although for both bisphenols the median EDI in 2016 (0.025 and 0.016 µg/kg bw per day, respectively) were greater than in 1993 (0.004 and 0.002 µg/kg bw per day, respectively). Phthalate metabolites were determined in urine samples by LC-MS/MS.

Morning void urine samples were collected from 7-year-old children in Hokkaido, Japan during the period 2012–2017 and analysed for seven bisphenols by GC-MS/MS (Gys *et al.*, 2020). A statistically significant negative trend in BPA concentrations was observed across the study period, with urinary BPA concentrations decreasing by 6.5 percent per year. The detection frequency of the BPA substitutes, bisphenol F and bisphenol S, increased, although no trend was apparent in urinary concentrations of these substances. BPA was phased out of use in baby bottle, polycarbonate tableware and thermal paper during 2000–2001.

The modest decreases in urinary BPA concentrations in the period 2012–2017 may have been because more substantive decreases occurred at earlier time points. The mean urinary BPA concentrations determined in this study (about 1 mg/kg creatinine) are similar to those reported in the Canadian and United States populations (Table 36 and Table 37) for the same time period.

In a study carried out in Shanghai, China over 2006–2019, human colostrum samples were collected from mothers within 3–5 days of delivery and analysed for bisphenols by LC-MS/MS (Zhang *et al.*, 2024). Of the four years (2006, 2010, 2013 and 2019), approximately 20 samples per year were analysed for the first three years, with 71 analysed for 2019. Only three bisphenols (A, S and F) were consistently detected across all years. There was no evidence of a trend in colostrum concentrations of BPS and BPF. For BPA, there was a substantial decrease in concentrations between 2010 and 2013, with mean/median concentration in 2006 and 2010 of 6.8/1.9 and 3.5/3.2 µg/L, respectively, and in 2013 and 2019 of 0.10/0.11 and 0.22/0.12 µg/L, respectively. Zhang *et al.* (2024) noted that the use of BPA had been prohibited or restricted in China since 2011, but provided no further details of the regulatory actions. Colostrum is an unusual matrix for biomonitoring and paired analysis of colostrum and urine samples from 2019 found no significant correlation in BPA concentrations.

A study carried out in Boston, United States examined bisphenols A and F in the urine of volunteers at two-yearly intervals between 2000 and 2017 (Jiang *et al.*, 2023). The number of urine samples analysed at each timepoint ranged from 94 (2000–2001) to 1390 (2010–2011). Urinary concentrations of bisphenol A increased to a peak at about 2006–2009 before decreasing. As expected, urinary concentrations of bisphenol F were not detected before 2012. Representative data from this study are summarized in Table 26.

TABLE 26 **TRENDS IN URINARY CONCENTRATIONS OF SELECTED PHTHALATE METABOLITES AND METABOLITES OF PHTHALATE SUBSTITUTES, BOSTON, 2000–2017**

| SUBSTANCE | MEAN CONCENTRATION (95% CI), µg/L | | | | CHANGE PER YEAR (%) |
|---|---|---|---|---|---|
| | 2000–2001 | 2006–2007 | 2012–2013 | 2016–2017 | |
| PHENOLS | | | | | |
| Bisphenol A | 0.78 (0.64–0.96) | 1.40 (1.30–1.52) | 0.86 (0.80–0.93) | 0.58 (0.53–0.63) | -6.3 |
| Bisphenol F | | | 0.23 (0.20–0.28) | 0.31 (0.28–0.34) | +6.0 |

*Source:* **Jiang, V.S., Calafat, A.M., Williams, P.L., Chavarro, J.E., Ford, J.B., Souter, I., Hauser, R. & Mínguez-Alarcón, L.** 2023. Temporal trends in urinary concentrations of phenols, phthalate metabolites and phthalate replacements between 2000 and 2017 in Boston, MA. *Science of the Total Environment*, 898: 165353. https://doi.org/10.1016/j.scitotenv.2023.165353

Urine samples (total $n$ = 760) were collected from pregnant women in California, United States between 2007 and 2014 and analysed for bisphenol A by LC-MS/MS (Kim *et al.*, 2021). BPA was consistently detected in urine samples. No clear trend in BPA concentrations was apparent, with geometric mean urinary concentrations in the range of 1.03–1.44 µg/L during 2007–2013 before decreasing to 0.78 µg/L in 2014.

## 5.5 PARABENS, TRICLOSAN AND BENZOPHENONES

Methyl-, ethyl-, propyl-, butyl- and benzyl-paraben and triclosan have been used as antimicrobials mainly in personal care products, cosmetics, cleaning products and paints. Benzophenone is a component of many sunscreen products.

### 5.5.1 META-ANALYSES

A systematic review and meta-analysis of parabens and benzophenone-3 (BP-3) in human breast milk classified included studies grouped into two time periods: 2000–2010 and 2011–2020 (Iribarne-Durán *et al.*, 2022). The analysis concluded that concentrations in breast milk samples had decreased for methyl paraben (6.3 and 1.2 µg/L for 2000–2010 and 2011–2020, respectively) and propyl paraben (0.65 and 0.27 µg/L, respectively). However, arithmetic mean concentrations had increased for ethyl paraben (0.45 and 0.86 µg/L, respectively), butyl paraben (0.02 and 0.07 µg/L, respectively) and BP-3 (1.4 and 74 µg/L, respectively). However, the following sections suggest the urine is a more common matrix for assessing human exposure to these compounds.

A meta-analysis of human biomonitoring studies of BP-3 was conducted (Mustieles *et al.*, 2023). Most of the studies included in the meta-analysis determined BP-3 in urine. Studies were grouped into four time periods: 1996–2003, 2004–2008, 2009–2013 and 2014–2019. The results of this study are somewhat difficult to interpret as two different analytical approaches, a meta-analysis and a meta-regression, were applied. The meta-analysis shows an increase in mean urinary concentration of BP-3 from the earliest time period (8.9 mg/kg creatinine) to the second time point (11.9 mg/kg creatine) before a steady decrease over the latter two time points (8.5 and 3.8 mg/kg creatinine, respectively). However, the meta-regression, which considered all factors simultaneously, indicated a steady increase in urinary BP-3 compared to the reference (1996–2003) time point, with estimates of 1.9, 6.4 and 7.4 mg/kg creatinine for 2004–2008, 2009–2013 and 2014–2019, respectively. The authors of the study noted that the increase appeared to be in Asian and southern European studies, while urinary BP-3 concentrations were stable across the time course of the study for Northern American and northern and western European populations.

### 5.5.2 DIRECT EVIDENCE

Urine samples (n = 660) from the German EBS, collected from 1995 to 2012, were analysed for parabens by LC-MS/MS (Moos *et al.*, 2015). Methyl, ethyl and n-propyl parabens were the most frequently detected. There were no statistically significant trends in urinary paraben concentrations, except for methyl paraben. The median urinary concentration of methyl paraben increased from 34 mg/kg creatinine in 1995 to 80.1 mg/kg creatinine in 2012.

In a study in the Netherlands of 500 individuals with impaired fasting glucose, urine samples were taken at recruitment in 2009–2013 and at a follow up point during

2014–2016 (van der Meer *et al.*, 2021). Urine samples were analysed for parabens, providing two measures of temporal trend: (1) comparison of participants at recruitment and approximately 4-year follow-up; and (2) urinary samples collected across the years 2009–2016. Results from both comparisons are summarized in Table 27. Both approaches demonstrated statistically significant decreases in urinary concentrations of all parabens, except benzyl paraben, which wasn't detected. Decreases appear to mirror regulatory changes affecting use of parabens in the European Union in 2014, which banned the use of longer chain parabens and established maximum use levels for all parabens.

TABLE 27 **PARABENS IN THE URINE OF DUTCH SUBJECTS WITH IMPAIRED FASTING GLUCOSE, 2009–2016**

| SUBSTANCE | MEDIAN CONCENTRATION, µg/24 HOURS | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | B | F[a] | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 |
| MeP | 12.3 | 4.8 | 31 | 34 | 14 | 17 | 11 | 9.8 | 6.1 | 7.3 |
| EtP | 1.2 | 0.76 | 1.9 | 3.1 | 2.4 | 1.9 | 1.1 | 1.7 | 0.88 | 1.7 |
| PrP | 1.2 | 0.21 | 6.1 | 3.4 | 1.4 | 1.6 | 0.52 | 0.76 | 0.14 | 0.27 |
| n-BuP | 0.07 | <LOD | 0.20 | 0.27 | 0.10 | 0.11 | 0.14 | 0.10 | 0.10 | 0.09 |
| BzP | <LOD | <LOD | - | - | - | - | - | - | - | - |

*Notes:* [a] Follow-up samples were taken approximately four years after recruitment samples. B: baseline; F: follow-up; MeP: methyl paraben; EtP: ethyl paraben; PrP: propyl paraben; n-BuP: n-butyl paraben; and BzP: benzyl paraben.

*Source:* **van der Meer, T.P., Chung, M.K., van Faassen, M., Makris, K.C., van Beek, A.P., Kema, I.P., Wolffenbuttel, B.H.R., van Vliet-Ostaptchouk, J.V. & Patel, C.J.** 2021. Temporal exposure and consistency of endocrine disrupting chemicals in a longitudinal study of individuals with impaired fasting glucose. *Environmental Research*, 197: 110901. https://doi.org/10.1016/j.envres.2021.110901

Urine samples (total n = 760) were collected from pregnant women in California, United States between 2007 and 2014 and analysed for parabens by LC-MS/MS (Kim *et al.*, 2021). Only methyl-, ethyl- and propyl-paraben were consistently detected in urine samples, with butyl-paraben detected in less than 35 percent of samples. Representative results from the study are summarized in Table 28. Though there is some variability from year-to-year, the results of this study largely indicate a decrease in exposure to these potential EDCs during the period 2007 to 2014.

TABLE 28 **PARABENS IN THE URINE OF PREGNANT WOMEN, CALIFORNIA, 2007–2014**

| SUBSTANCE | GEOMETRIC MEAN URINARY CONCENTRATION (µg/L) | | | | |
|---|---|---|---|---|---|
| | 2007 | 2009 | 2011 | 2013 | 2014 |
| **Sample size** | 51 | 180 | 67 | 106 | 57 |
| Methyl paraben | 111 | 38 | 36 | 23 | 21 |
| Ethyl paraben | 2.0 | 1.3 | 0.9 | 1.0 | 1.2 |
| Propyl paraben | 18 | 7.6 | 7.0 | 4.5 | 5.4 |

*Source:* **Kim, K., Shin, H.M., Busgang, S.A., Barr, D.B., Panuwet, P., Schmidt, R.J., Hertz-Picciotto, I. & Bennett, D.H.** 2021. Temporal trends of phenol, paraben, and triclocarban exposure in California pregnant women during 2007–2014. *Environmental Science & Technology*, 55(16): 11155–11165. https://doi.org/10.1021/acs.est.1c01564

In a study carried out in Puerto Rico over 2011–2016, 2 166 urine samples were collected from 1 003 pregnant women (134–498 samples per year) and analysed for parabens, triclosan and BP-3 (Ashrap *et al.*, 2018). Time trends are presented graphically in this publication and show a decreasing trend for the four parabens (methyl, ethyl, propyl and butyl). No clear trend was apparent for BP-3 or triclosan.

A human biomonitoring study was carried out in 2015 within an adult population living in Liège, Belgium (Pirard and Charlier, 2022). Parabens were measured in the urine of 252 participants. An awareness campaign was initiated by the provincial authorities of Liège and spread over 2014–2016. In 2018, 92 of the initial participants again provided urine samples, and the levels of parabens were determined and compared to those obtained in 2015 to assess time trends (Table 29).

TABLE 29 **COMPARISON OF CONCENTRATIONS OF BISPHENOLS IN THE URINE OF A BELGIAN COHORT, 2015 AND 2018**

| SUBSTANCE | FREQUENCY OF DETECTION, % | | MEDIAN CONCENTRATION (P95), µg/L | |
|---|---|---|---|---|
| | 2015 | 2018 | 2015 | 2018 |
| PARABENS | | | | |
| Methyl paraben | 83.7 | 83.7 | 9.1 (250) | 3.6 (130) |
| Ethyl paraben | 77.2 | 62.0 | 1.1 (37) | 0.6 (19) |
| Propyl paraben | 25.0 | 28.3 | <LOQ (51) | <LOQ (16) |
| Butyl paraben | 9.8 | 4.3 | <LOQ (2.9) | <LOQ (<LOQ) |

*Notes:* P95: 95th percentile; and LOQ: limit of quantification.

*Source:* **Pirard, C. & Charlier, C.** 2022. Urinary levels of parabens, phthalate metabolites, bisphenol A and plasticizer alternatives in a Belgian population: Time trend or impact of an awareness campaign? *Environmental Research*, 214: 113852. https://doi.org/10.1016/j.envres.2022.113852

A study carried out in Boston, United States examined phenols in the urine of volunteers and presented data for two-year intervals between 2000 and 2017 (Jiang *et al.*, 2023). The number of urine samples analysed at each timepoint ranged from 94 (2000–2001) to 1 390 (2010–2011). Urinary concentrations of parabens increased to a peak at about 2006–2009 before decreasing. Triclosan was only monitored at the two later time points, with a decrease in urinary concentrations apparent. Representative data from this study are summarized in Table 30.

TABLE 30 **TRENDS IN URINARY CONCENTRATIONS OF SELECTED PHTHALATE METABOLITES AND METABOLITES OF PHTHALATE SUBSTITUTES, BOSTON, 2000–2017**

| SUBSTANCE | MEAN CONCENTRATION (95% CI), µg/L | | | | CHANGE PER YEAR (%) |
|---|---|---|---|---|---|
| | 2000–2001 | 2006–2007 | 2012–2013 | 2016–2017 | |
| Methyl paraben | 41.5 (31.0–55.7) | 99.0 (85.5–115) | 67.6 (59.2–77.3) | 37.8 (31.4–44.9) | -5.4 |
| Propyl paraben | 9.8 (6.5–14.7) | 18.6 (15.2–22.7) | 9.4 (7.8–11.4) | 4.3 (3.3–5.5) | -10.2 |
| Butyl paraben | 0.33 (0.26–0.43) | 1.3 (1.0–1.6) | 0.36 (0.31–0.43) | 0.15 (0.12–0.19) | -14.2 |
| Triclosan | | | 12.4 (10.1–15.4) | 5.4 (4.2–6.9) | -18.8 |

*Source:* **Jiang, V.S., Calafat, A.M., Williams, P.L., Chavarro, J.E., Ford, J.B., Souter, I., Hauser, R. & Mínguez-Alarcón, L.** 2023. Temporal trends in urinary concentrations of phenols, phthalate metabolites and phthalate replacements between 2000 and 2017 in Boston, MA. *Science of the Total Environment*, 898: 165353. https://doi.org/10.1016/j.scitotenv.2023.165353

Urine samples were collected from primiparous mothers in Uppsala, Sweden during the period 2009–2014 and analysed for triclosan by LC-MS/MS (Gyllenhammar *et al.*, 2017). While summary statistics of urinary triclosan concentrations by year were not reported, the rate of change in urinary triclosan was reported to be -24 percent per year.

Urine samples collected during five cycles (2003–2012) of the NHANES in the United States were analysed for triclosan and BP-3 by LC-MS/MS (Han, Lim and Hong, 2016). Least squares geometric means of triclosan increased from 2003–2004 to 2005–2006 (13.3 to 18.8 µg/L, creatinine adjusted), before decreasing across the next three 2-year cycles (15.2 to 14.9 to 12.5 µg/L, creatinine adjusted). BP-3 followed an exactly opposite trend, decreasing from 2003–2004 to 2005–2006 (24.0 to 19.2 µg/L, creatinine adjusted) and then increasing across the next three 2-year cycles (19.9 to 24.2 to 25.7 µg/L, creatinine adjusted). These trends were largely consistent across gender and age groups. As no regulatory controls on these substances had been implemented in the time period considered, it was suggested that the trends were due to increased public awareness of the potential detrimental effects of triclosan and the positive effects of benzophenone-containing sunscreens.

## 5.6 ALKYL PHENOLS

Alkyl phenols, in the form of alkylphenol ethoxylates (APEs) are non-ionic surfactants. APEs are made up of the hydrophobic alkylphenol moiety, an alkane (usually eight or nine carbons) bound by hydrogen bonds to a water-soluble polyethoxylate chain. APEs were a common component of household detergents.

### 5.6.1 DIRECT EVIDENCE

The German ESB includes samples of human urine collected since 1991 (Ringbeck *et al.*, 2022a). Samples taken in a particular year include 60 24-hour urine samples

(30 male/30 female), collected from students aged 20–29 years. Samples from 11 years over the years 1991–2021 analysed for the nonylphenol (NP) metabolites OH-NP and oxo-NP by LC-MS/MS. The metabolite OH-NP was the dominant species detected. Urinary metabolite concentrations were used to estimate dietary exposure. Estimated dietary exposure was reasonably stable in the period 1991–2009, with geometric mean estimates in the range 0.15–0.18 µg/kg bw per day. During the period 2012 to 2021, the geometric mean estimate of dietary exposure decreased from 0.14 to 0.04 µg/kg bw per day. Across the entire time range, estimated dietary exposure decreased by 76 percent. Alkylphenol use in Germany reduced through a voluntary manufacturing phase out by approximately 85 percent between 1986 and 1997, although NP remains a high production volume chemical worldwide.

From 2 451 urine samples provide by 7-year-old Japanese children participating in the Hokkaido Study on Environment and Children's Health, samples from 30 children in each of the birth years 2012 to 2017 were analysed for metabolites of the plasticizer nonylphenol (Ringbeck *et al.*, 2022b). Metabolite concentrations were determined by LC-MS/MS. Urinary metabolite concentrations were then converted to dietary exposures. While numerical values for mean dietary nonylphenol exposure by birth year were not reported, the authors of the study reported a statistically significant decreasing trend ($p<0.01$) for the period 2012 to 2017.

## 5.7 PERFLUORINATED COMPOUNDS

Perfluorinated or perfluoroalkylated substances (PFASs) are highly fluorinated aliphatic compounds with high thermal and chemical stability, as well as high surface activity. PFASs are used in a range of industrial and chemical applications, including textiles, paper, packaging materials, paints and varnishes, and fire-extinguishing liquids (EFSA, 2012). Several PFASs are recognized as environmentally persistent organic pollutants (POPs) (UNEP, 2019).

### 5.7.1 INDIRECT EVIDENCE

Food samples were collected from grocery store chains in Swedish cities and combined in food consumption proportions to give a single pooled food sample for each of the years 1999, 2005 and 2010 (Gebbink *et al.*, 2015). Samples were analysed for PFAS by LC-MS/MS. Dietary exposure was estimated by multiplying food pool concentrations by the annual mean weight of food consumed in Sweden. Dietary exposures estimated were then converted to daily estimates and normalized using an adult body weight of 73.7 kg. Estimates of dietary exposure for the main PFAS for the three years are summarized in Table 31. Results from the indirect estimation of PFAS exposure are qualitatively similar to direct estimates, with exposure to the shorter chain PFAS decreasing, while exposure to the longer chain PFAS increased. However, estimates for perfluorooctanoic acid (PFOA) are anomalous in this respect, indicating a decrease between 1999 and 2005, followed by an increase between 2005 and 2010.

TABLE 31 **ESTIMATED DIETARY EXPOSURE TO SELECTED PERFLUOROALKYLATED SUBSTANCES BY SWEDISH ADULTS, 1999, 2005 AND 2010**

| SUBSTANCE | ESTIMATED DIETARY EXPOSURE, ng/kg bw per day | | |
|---|---|---|---|
| | 1999 | 2005 | 2010 |
| PFHxS | 0.055 | 0.026 | 0.020 |
| ΣPFOS | 1.6 | 0.86 | 0.73 |
| PFOA | 0.13 | 0.043 | 0.15 |
| PFNA | 0.19 | 0.44 | 0.42 |
| PFDA | 0.043 | 0.058 | 0.066 |
| PFUnDA | 0.070 | 0.13 | 0.17 |
| PFDoDA | 0.032 | 0.028 | 0.026 |

*Notes:* PFHxS: perfluorohexanesulfonic acid; ΣPFOS: perfluorooctanesulfonic acid, sum of branched and linear isomers; PFOA: perfluorooctanoic acid; PFNA: perfluorononanoic acid; PFDA: perfluorodecanoic acid; PFUnDA: perfluoroundecanoic acid; and PFDoDA: perfluorododecanoic acid.

*Source:* **Gebbink, W.A., Glynn, A., Darnerud, P.O. & Berger, U.** 2015. Perfluoroalkyl acids and their precursors in Swedish food: The relative importance of direct and indirect dietary exposure. *Environmental Pollution*, 198: 108–115. http://dx.doi.org/10.1016/j.envpol.2014.12.022

## 5.7.2 DIRECT EVIDENCE

### Blood serum/plasma

Data on PFAS concentrations in serum from the NHANES in the United States were used to compare body burdens in 2003–2004 to those in 2013–2014 (Dong *et al.*, 2019). PFAS concentrations were determined by LC-MS/MS. Significant decreases in median serum concentrations were observed for perfluorooctanoic acid (PFOA) (3.7 to 1.8 µg/L), perfluorooctanesulfonic acid (PFOS) (19.2 to 4.7 µg/L), perfluorohexansulfonic acid (PFHxS) (1.7 to 1.3 µg/L) and perfluorononanoic acid (PFNA) (0.8 to 0.6 µg/L)

Pooled human sera collected in South East Queensland, Australia during 2002–2003, 2006–2007, 2008–2009 and 2010–2011 were analysed for PFAS by isotope dilution LC-MS/MS (Toms *et al.*, 2014). A summary of the analytical results is included in Table 32. As with other studies summarized in this report, there is a clear downward trend in serum concentration of PFOS and PFOA but more equivocal information on trends in concentrations of PFHxS and PFNA. The decreasing trends in concentrations of PFOS and PFOA were consistent across all age groups considered in this study (0-4, 5-15 and >16 years).

TABLE 32 **SELECTED PERFLUOROALKYLATED SUBSTANCES CONCENTRATIONS IN POOLED HUMAN SERA FROM SOUTH EAST QUEENSLAND, AUSTRALIA, 2002–2011**

| SUBSTANCE | MEAN CONCENTRATION (RANGE), µg/L | | | |
|---|---|---|---|---|
| | 2002–2003 | 2006–2007 | 2008–2009 | 2010–2011 |
| NUMBER OF POOLED SAMPLES | 26 | 84 | 24 | 24 |
| PFOS | 25.9 (19.1-36.1) | 15.2 (5.0-28.5) | 11.9 (5.3-19.2) | 10.2 (4.4-17.4) |
| PFOA | 10.2 (7.0-14.5) | 6.4 (0.8-9.1) | 5.2 (2.8-7.3) | 4.5 (3.1-6.5) |
| PFHxS | 4.3 (2.0-12.8) | 3.1 (ND-11.3) | 2.9 (1.2-5.7) | 3.3 (1.4-5.4) |
| PFNA | 0.5 (0.4-0.7) | 0.8 (0.1-1.4) | 1.2 (0.9-1.6) | 0.7 (0.6-0.9) |

*Notes:* PFOS: perfluorooctanesulfonic acid; PFOA: perfluorooctanoic acid; PFHxS: perfluorohexanesulfonic acid; and PFNA: perfluorononanoic acid.

*Source:* **Toms, L-M.L., Thompson, J., Rotander, A., Hobson, P., Calafat, A.M., Kato, K., Ye, X., Broomhall, S., Harden, F. & Mueller, J.F.** 2014. Decline in perfluorooctane sulfonate and perfluorooctanoate serum concentrations in an Australian population from 2002 to 2011. *Environment International*, 71: 74–80. https://doi.org/10.1016/j.envint.2014.05.019

Samples of human blood plasma (n = 100) from the German Environmental Specimen Bank, collected from 2009 to 2019, were analysed for 37 PFAS by UHPLC-HRMS (Göckener *et al.*, 2020). Results were combined with those from an earlier survey (1982–2010) to examine temporal trends. Detection frequencies only allowed for the examination of trends for four PFAS. Serum PFOA concentrations reached a peak in about 1990, then decreased steadily to a median concentration <2 µg/L by 2017. No trend in concentrations of PFNA was apparent, with peaks in about 1990 and 2005. Median concentrations were <1 µg/L across the entire period considered. PFHxS concentration in serum increased to about 2000, then decreased steadily to a median of 0.9 µg/L in 2019. Linear PFOS serum concentrations decreased from a peak in the late 1980s with a median concentration of 3.1 µg/L reached in 2019.

From a study involving adult males from Tromsø in northern Norway on five occasions (1979, 1986–1987, 1994–1995, 2001 and 2007–2008), 53 participants were identified who had participated in three or more rounds of the study and for whom there was sufficient stored blood for analysis (Nøst *et al.*, 2014). Samples (n = 254) of serum were analysed for PFAS by LC-MS/MS. For PFOA and PFOS, median concentrations reached a peak in 2001 before significantly decreasing in 2007–2008. A similar pattern was apparent for PFHxS and perfluoroheptanesulfonic acid (PFHpS) but the decrease at 2007–2008 was not significant. Median concentrations of PFNA and perfluorodecanoic acid (PFDA) increased significant across all time periods, while for perfluoroundecanoic acid (PFUnDA) a similar trend was apparent, but period-to-period changes were not always significantly different. Median concentrations for the main PFAS are summarized in Table 33.

TABLE 33 **PERFLUOROALKYLATED SUBSTANCES IN SERUM OF ADULT MALES, NORTHERN NORWAY, 1979–2008**

| SUBSTANCE | MEDIAN CONCENTRATION, µg/L | | | | |
|---|---|---|---|---|---|
| | 1979 | 1986–1987 | 1994–1995 | 2001 | 2007–2008 |
| Number of serum samples | 53 | 52 | 48 | 49 | 52 |
| PFHxS | 0.2 | 0.7 | 1.5 | 2.0 | 1.9 |
| PFHpS | 0.2 | 0.5 | 0.6 | 0.8 | 0.7 |
| PFOA | 0.9 | 2.5 | 3.9 | 4.2 | 3.1 |
| ΣPFOS | 8.6 | 23 | 37 | 43 | 33 |
| PFNA | 0.1 | 0.5 | 0.8 | 1.1 | 1.5 |
| PFDA | 0.1 | 0.3 | 0.5 | 0.7 | 0.8 |
| PFUnDA | 0.1 | 0.8 | 0.8 | 1.1 | 1.3 |

*Notes:* PFHxS: perfluorohexanesulfonic acid; PFHpS: perfluoroheptanesulfonic acid; PFOA: perfluorooctanoic acid; ΣPFOS: perfluorooctanesulfonic acid, sum of branched and linear isomers; PFNA: perfluorononanoic acid; PFDA: perfluorodecanoic acid; and PFUnDA: perfluoroundecanoic acid.

*Source:* **Nøst, T.H., Vestergren, R., Berg, V., Nieboer, E., Odland, J.Ø. & Sandanger, T.M.** 2014. 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. *Environment International*, 67: 43–53. https://doi.org/10.1016/j.envint.2014.02.011

## Breast milk

As part of the Global Monitoring Plan (GMP) under the Stockholm Convention, samples of human breast milk from 59 countries were analysed for PFAS (Fiedler *et al.*, 2022). Results of analyses were grouped by United Nations Regional Groups of Member States (Africa, Asia-Pacific, Central and Eastern Europe, Latin America and the Caribbean, and Western Europe and Other) and three time periods (2005–2009, 2010–2014 and 2015–2019). For the three primary PFASs (PFOS, PFOA and PFHxS) a consistent overall trend was apparent with mean and median concentrations increasing from 2005–2009 to 2010–2014 and decreasing from 2010–2014 to 2015–2019. Summary statistics are shown in Table 34. Over all three time periods, the highest mean concentration of PFOS was in the Central and Eastern European group, for PFOA in the Western European and Other group and for PFHxS in the Asian group. Of the other PFASs, only perfluorobutanoic acid (PFBA) and PFNA were detected in samples from all five geographic groups, with the highest mean concentrations in the Asian and Central and Eastern European groups, respectively.

TABLE 34 **SUMMARY STATISTICS FROM SELECTED PERFLUOROALKYLATED SUBSTANCES IN HUMAN BREAST MILK FROM 59 COUNTRIES, 2005–2009, 2010–2014 AND 2015–2019**

| SUBSTANCE | MEAN CONCENTRATION (RANGE), ng/kg LIPID | | |
|---|---|---|---|
| | 2005–2009 | 2010–2014 | 2015–2019 |
| Number of national pooled samples | 17 | 19 | 50 |
| ΣPFOS | 24.8 (7.9–62.7) | 33.6 (9.4–83.3) | 20.7 (0–212) |
| PFOA | 26.6 (12.8–63.4) | 28.0 (12.6–57.8) | 18.3 (6.2–48.8) |
| PFHxS | 0.82 (0–7.6) | 4.2 (0–34.8) | 3.0 (0–111) |

*Notes:* PFOS: perfluorooctanesulfonic acid; PFOA: perfluorooctanoic acid; and PFHxS; perfluorohexanesulfonic acid.

*Source:* **Fiedler, H., Sadia, M., Krauss, T., Baabish, A. & Yeung, L.W.Y.** 2022. Perfluoroalkane acids in human milk under the global monitoring plan of the Stockholm Convention on Persistent Organic Pollutants (2008–2019). *Frontiers of Environmental Science & Engineering*, 16(10): 132. https://doi.org/10.1007/s11783-022-1541-8

Pooled human milk samples (15 to 116 individual samples per pool) from healthy Swedish mothers, collected in Stockholm from 1972 to 2008, were analysed for the three most prevalent PFASs (PFOS, PFOA and PFHxS) (Sundström *et al.*, 2011). A similar temporal pattern was apparent for all three compounds, with reasonably low concentrations in 1972 (23, 19 and <5 ng/L for PFOS, PFOA and PFHxS, respectively) increasing to a steady state between 1988 and 2004 (179–234, 98–139 and 11–28 ng/L for PFOS, PFOA and PFHxS, respectively) before decreasing from 2004 to 2008 (75, 74 and 14 ng/L for PFOS, PFOA and PFHxS, respectively, in 2008). The authors noted that this pattern was consistent with the occurrence of these compounds in human serum and with the institution of voluntary and regulatory controls on their use.

The study of Sundström *et al.* (2011) was subsequently extended to the year 2016, and also included breast milk samples from Gothenburg and analysis of a wider range of PFAS (Nyberg *et al.*, 2018). The previously observed trends in concentrations of PFOS, PFOA and PFHxS continued with 2016 mean concentrations of 45, 46 and 7.3 ng/L, respectively. PFNA also followed the same trend, with a 2016 concentration of 15 ng/L. However, concentrations of several other PFASs, including perfluorohexanoic acid (PFHxA), PFDA, perfluorotetradecanoic acid (PFTeDA), perfluorotridecanoic acid (PTTrDA) and PFUnDA, appear to be increasing. These PFAS were rarely detected in samples before 1990 and, in some cases, before 2010.

China carried out the third National Human Milk Survey in 2017–2020, with 3 531 individual human milk samples combined into 100 pooled samples (Han *et al.*, 2023). Samples were analysed for a range of PFASs and overall results compared to those of the first National Human Milk Survey conducted in 2007. For 12 provinces that were common to both surveys, the mean of the sum of six PFASs (PFHxS, PFOS, PFOA, PFNA, PFDA, and PFUnDA) decreased from 220 ng/L to 173 ng/L. However, the mean concentration of PFOA showed a marginally significant increase over time (concentrations not reported), while mean PFOS concentrations increased non-significantly from 56.0 to 64.2 ng/L. The authors noted that selected PFAS had been added to the Stockholm Convention in 2019 and that decreases in production and use could be expected in the future.

Utilizing primiparous human breast milk samples collected as part of the Czech Human Biomonitoring (CZ-HBM) survey in Czechia, trends in exposure to PFASs were examined across the years 2006, 2010–2011, 2014 and 2017 (Černá *et al.*, 2020). Consistent with other European studies, breast milk concentrations of the shorter chain PFASs (PFOS and PFOA) decreased across this time period, while PFNA was only detected in the most recent collection (2017). However, it should be noted that the method limit of quantification (LOQ) for PFNA was lower in 2017. Results of this study are summarized in Table 35.

TABLE 35 **SUMMARY OF PERFLUOROALKYLATED SUBSTANCES IN HUMAN BREAST MILK, CZECHIA, 2006–2017**

| SUBSTANCE | GEOMETRIC MEAN CONCENTRATION (RANGE) , ng/L | | | |
|---|---|---|---|---|
| | 2006 | 2010–2011 | 2014 | 2017 |
| PFOS | 50 (16–162) | 31 (7–158) | 30 (3–212) | 22 (2–169) |
| PFOA | 78 (28–230) | 54 (16–159) | 34 (<6–159) | 24 (<0.003–160) |
| PFNA | ND | ND | ND | 7 (<3–29) |

*Notes:* PFOS: perfluorooctanesulfonic acid; PFOA: perfluorooctanoic acid; PFNA: perfluorononanoic acid; and ND: not detected.

*Source:* **Černá, M., Grafnetterová, A.P., Dvořáková, D., Pulkrabová, J., Malý, M., Janoš, T., Vodrážková, N., Tupá, Z. & Puklová, V.** 2020. Biomonitoring of PFOA, PFOS and PFNA in human milk from Czech Republic, time trends and estimation of infant's daily intake. *Environmental Research*, 188: 109763. https://doi.org/10.1016/j.envres.2020.109763

## 5.8 PHYTOESTROGENS

Phytoestrogens are plant compounds that can mimic the activity of the female sex hormone 17β-estradiol through similarities in chemical structure. The best known and characterized phytoestrogens are the soy isoflavones, daidzein and genistein.

Very little information was found on trends in population exposure to phytoestrogens. The NHANES in the United States included analysis of some phytoestrogens and their metabolites in urine over the period 2001–2010 (see Table 37) (CDC, 2024). An upward trend in urinary levels of daidzein and its metabolite, O-desmethylangolensin, was apparent, possibly reflecting increasing incorporation of soy products in processed foods.

Although it was outside the primary date range for the current report, a German study examined urinary concentrations of daidzein, genistein and equol (a metabolite of daidzein) during the period 1985 to 2000 (Degen *et al.*, 2011). Participants in the study were grouped into three year ranges, based on the date of provision of urine samples; 1985–1989, 1990–1994 and 1995–2000. While median concentration of all phytoestrogens increased between the first two periods and decreased again at the final period, no significant trends were observed.

## 5.9 NATIONAL BIOMONITORING PROGRAMMES

### 5.9.1 CANADA

The Canadian Health Measures Survey (CHMS) is conducted on a two-year cycle and began in 2007. The CHMS analyses a range of contaminants in blood, plasma or urine. After the first five cycles of the CHMS had been completed (2007–2017), data were analysed for trends in exposure to environmental contaminants (Pollock *et al.*, 2021). Across the period 2007–2017, statistically significant decreases in geometric mean concentration were identified for lead, cadmium and selenium (blood, decreases of 33, 22 and 16 percent, respectively), BPA, triclosan, methyl paraben and propyl paraben (urine, decreases of 32, 31, 32 and 36 percent, respectively), PFOA, PFOA and PFHxS (plasma, decreases of 61, 48 and 58 percent, respectively), phthalate metabolites (urine, decreases in the range 42–75 percent), and several other volatile organic compounds and organophosphate pesticide metabolites. It should be noted that not all analytes were included in all cycles of the CHMS, and the percentage decreases are from the first cycle in which the analyte was included to the most recent cycle in which it was included.

The CHMS is currently in its seventh cycle (2022–2024). Results for the first six cycles have been published (Health Canada, 2021). Geometric mean concentrations for all participants (total population) for endocrine disrupting chemicals are summarized in Table 36.

TABLE 36 **TRENDS IN POPULATION EXPOSURE TO ENDOCRINE DISRUPTING CHEMICALS IN CANADA, CANADIAN HEALTH MEASURES SURVEY**

| SUBSTANCE | MATRIX | UNITS | GEOMETRIC MEAN CONCENTRATION, TOTAL POPULATION | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 2007–2009 | 2009–2011 | 2012–2013 | 2014–2015 | 2016–2017 | 2018–2019 |
| Bisphenol A | Urine | mg/kg creatinine | - | 1.2 | 1.1 | 0.93 | 0.79 | 0.74 |
| Methyl paraben | Urine | mg/kg creatinine | - | - | 21 | 15 | 14 | 12 |
| Propyl paraben | Urine | mg/kg creatinine | - | - | 3.0 | 2.3 | 1.8 | - |
| PFOA | Plasma | µg/L | - | - | - | - | 1.3 | 1.2 |
| PFNA | Plasma | µg/L | - | - | - | - | 0.51 | 0.44 |
| PFDA | Plasma | µg/L | - | - | - | - | 0.18 | 0.12 |
| PFHxS | Plasma | µg/L | - | - | - | - | 0.90 | 0.76 |
| PFOS | Plasma | µg/L | - | - | - | - | 3.0 | 2.5 |
| MMP | Urine | mg/kg creatinine | - | - | - | - | 2.0 | 1.8 |
| MEP | Urine | mg/kg creatinine | - | 44 | - | - | 21 | 18 |
| MnBP | Urine | mg/kg creatinine | - | 20 | - | - | 12 | 13 |
| MiBP | Urine | mg/kg creatinine | - | 13 | - | - | 9.8 | 9.2 |
| MBzP | Urine | mg/kg creatinine | - | 7.4 | - | - | 3.7 | 2.8 |
| MEHHP | Urine | mg/kg creatinine | - | 12 | - | - | 5.0 | 5.1 |

*Notes:* PFOS: PFOA: perfluorooctanoic acid; PFNA: perfluorononanoic acid; PFDA: perfluorodecanoic acid; PFHxS: perfluorohexanesulfonic acid; PFOS: perfluorooctanesulfonic acid; MMP: mono-methyl phthalate; MEP: mono-ethyl phthalate; MiBP: mono-isobutyl phthalate; MnBP: mono-n-butyl phthalate; MBzP: mono-benzyl phthalate; and MEHHP: mono-(2ethyl-5-hydroxyhexyl) phthalate.

*Source:* **Health Canada.** 2021. *Sixth report on human biomonitoring of environmental chemicals in Canada.* Government of Canada. https://www.canada.ca/content/dam/hc-sc/documents/services/environmental-workplace-health/reports-publications/environmental-contaminants/sixth-report-human-biomonitoring/pub1-eng.pdf

### 5.9.2 UNITED STATES OF AMERICA

The National Health and Nutrition Examination Survey (NHANES) is a programme of studies designed to assess the health and nutritional status of adults and children in the United States. The survey examines a nationally representative sample of about 5 000 persons each year and includes collection of clinical samples (blood, urine) for laboratory analysis, including analysis of EDCs. Data can be viewed directly from the Centers for Disease Control and Prevention website (CDC, 2024) or as a component of published studies.

NHANES data for the total survey cohort (total population) for relevant EDCs are summarized in Table 37.

South Sudan - Emergency Seed distribution Campaign

TABLE 37 **TRENDS IN POPULATION EXPOSURE TO ENDOCRINE DISRUPTING CHEMICALS IN THE UNITED STATES OF AMERICA, NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY**

| SUBSTANCE | MATRIX | UNITS | TOTAL POPULATION GEOMETRIC MEAN | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 2001–2002 | 2003–2004 | 2005–2006 | 2007–2008 | 2009–2010 | 2011–2012 | 2013–2014 | 2015–2016 | 2017–2018 |
| PHENOLS | | | | | | | | | | | |
| Bisphenol A | Urine | mg/kg creatinine | | 2.58 | 1.86 | 2.10 | 1.91 | 1.72 | 1.28 | 1.12 | |
| Triclosan | Urine | mg/kg creatinine | | 12.7 | 18.0 | 15.5 | 15.1 | 13.4 | 9.8 | 5.9 | |
| Methyl paraben | Urine | mg/kg creatinine | | | 55 | 61 | 60 | 46 | 48 | 32 | |
| Propyl paraben | Urine | mg/kg creatinine | | | 7.7 | 7.7 | 7.3 | 6.2 | 5.7 | 4.3 | |
| Perchlorate | | | | | | | | | | | |
| Perchlorate | Urine | mg/kg creatinine | 3.7 | 3.3 | 3.5 | 4.0 | 3.6 | 3.4 | 3.0 | 2.9 | 2.5 |
| POLYFLUORINATED ALKYL SUBSTANCES | | | | | | | | | | | |
| PFOA | Serum | µg/L | - | 4.0 | 3.9 | 4.1 | 3.1 | 2.1 | 1.9 | 1.6 | 1.4 |
| PFOS | Serum | µg/L | - | 20.7 | 17.1 | 13.2 | 9.3 | 6.3 | 5.0 | 4.7 | 4.3 |
| PFHxS | Serum | µg/L | - | 1.9 | 1.7 | 2.0 | 1.7 | 1.3 | 1.4 | 1.2 | 1.1 |
| PHTHALATE METABOLITES | | | | | | | | | | | |
| MEP | Urine | mg/kg creatinine | 110 | 120 | 106 | 91 | 67 | 43 | 36 | 35 | 28 |
| MiBP | Urine | mg/kg creatinine | 2.5 | 3.6 | 5.1 | 7.2 | 8.0 | 6.8 | 7.1 | 8.7 | 7.3 |
| MnBP | Urine | mg/kg creatinine | 17.8 | 19.8 | 19.2 | 19.0 | 15.3 | 8.9 | 9.1 | 10.2 | 9.0 |
| MBzP | Urine | mg/kg creatinine | 10.2 | 9.3 | 8.1 | 7.3 | 6.7 | 5.2 | 4.5 | 4.6 | 3.4 |
| MEHHP | Urine | mg/kg creatinine | 18.8 | 20.4 | 24.8 | 22.2 | 13.5 | 9.0 | 6.5 | 5.9 | 4.8, |
| PHTHALATE SUBSTITUTE METABOLITES | | | | | | | | | | | |
| MECPTP | Urine | mg/kg creatinine | - | - | - | - | - | - | - | 20.4 | 27.1 |
| MEHHTP | Urine | mg/kg creatinine | - | - | - | - | - | - | - | 5.3 | 7.2 |

TABLE 37 **TRENDS IN POPULATION EXPOSURE TO ENDOCRINE DISRUPTING CHEMICALS IN THE UNITED STATES OF AMERICA, NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY** (cont.)

| SUBSTANCE | MATRIX | UNITS | TOTAL POPULATION GEOMETRIC MEAN | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 2001–2002 | 2003–2004 | 2005–2006 | 2007–2008 | 2009–2010 | 2011–2012 | 2013–2014 | 2015–2016 | 2017–2018 |
| PHYTOESTROGENS[a] | | | | | | | | | | | |
| Daidzein | Urine | mg/kg creatinine | 49 | 63 | 65 | 68 | 74 | - | - | - | - |
| Genistein | Urine | mg/kg creatinine | 31 | 29 | 28 | 31 | 35 | - | - | - | - |
| Enterodiol | Urine | mg/kg creatinine | 34 | 37 | 37 | 37 | 42 | - | - | - | - |
| Enterolactone | Urine | mg/kg creatinine | 240 | 280 | 280 | 240 | 230 | - | - | - | - |
| Equol | Urine | mg/kg creatinine | 8.6 | 7.5 | 8.2 | 7.3 | 8.4 | - | - | - | - |
| O-desmethylangolensin | Urine | mg/kg creatinine | 3.8 | 4.6 | 4.6 | 4.7 | 5.1 | - | - | - | - |

*Notes:* [a] Daidzein and genistein are the primary isoflavones present in soybean. Equol and O-desmethylangolensin are metabolites of daidzein. Enterodiol and enterolactone are metabolites of lignans. PFOA: perfluorooctanoic acid; PFOS: perfluorooctanesulfonic acid; PFHxS: perfluorohexanesulfonic acid; MEP: mono-ethyl phthalate; MiBP: mono-isobutyl phthalate; MnBP: mono-n-butyl phthalate; MBzP: mono-benzyl phthalate; MEHHP: mono-(2ethyl-5-hydroxyhexyl) phthalate; MECPTP: mono-(2-ethyl-5-carboxypentyl) terephthalate; and MEHHTP: mono-(2-thyl-5-hydroxyhexyl) terephthalate.

*Source:* **CDC (Centers for Disease Control and Prevention).** 2024. Biomonitoring data tables for environmental chemicals. In: *Centers for Disease Control and Prevention*. Atlanta, Georgia. [Cited 10 June 2024]. https://www.cdc.gov/exposurereport/data_tables.html

NHANES data were used to examine trends in exposure of children and adolescents (6–19 years) to BPA, BP-3 and triclosan during the period 2005–2016 (Li *et al.*, 2023). Urinary concentration of these EDCs were converted to estimated daily intakes (EDIs) and to hazard quotients (HQs) by dividing the EDI by a health-based guidance value (HBGV). While the remaining analyses were conducted on the HQs, for a single chemical, the HQ will be proportional to the EDI. While time-stratified data are not provided in this publication, the percentage change in HQ (and therefore EDI) per cycle (two years) were calculated at -6.3 percent for BPA, +1.9 percent for BP-3 and -9.2 percent for triclosan.

Budapest - Fresh meat on sale at a supermarket

# CHAPTER 6
# TRENDS IN EXPOSURE OF INDIGENOUS PEOPLES TO ENDOCRINE DISRUPTING CHEMICALS

Some Indigenous Peoples are heavily reliant on marine mammals for food (Adamou *et al.*, 2020; Dudarev *et al.*, 2010). These food sources can contain high concentrations of persistent organic pollutants (POPs), including POPs that are considered to be EDCs.

## 6.1 ARCTIC REGION

A number of Indigenous Peoples live in areas adjoining the Arctic, the circumpolar region. Levels of chemical contamination of this region have been monitored through the Arctic Monitoring and Assessment Programme with reports published in 1998, 2003, 2009 and 2015 (Abass *et al.*, 2018). Several aspects of this monitoring have recently been reviewed:

> Three child cohort studies, two in the Faroe Islands and one in Nunavik, Canada, carried out serum testing on the same group of children on 2 to 4 occasions between 2000 and 2013. The studies were consistent in demonstrating decreases in serum concentrations of DDT (p,p'-DDT and p,p'-DDE), PCBs (118, 138, 153 and 180), PFAS (PFOS and PFOA), HCB and β-HCH. The only exception was for HCB in the Faroe Islands Cohort 3, in which the mean HCB concentration decreased between ages 5 and 7.5 years but increased between 7.5 and 13.2 years.

> Four breast milk studies were summarized, three in Finland (Northern, Central and Southern) and one in Sweden. The Swedish study included annual cohorts of mothers over the period 1996 to 2012, while the Finnish studies included up to five time points between 1987 and 2010. The Swedish study demonstrated

consistent temporal declines in the breast milk concentrations of PBDE-47, HCB, p,p'-DDE, PCB-28, PCB-153 and total TEQ. PBDE-153 concentrations varied year-to-year, but no clear trend was apparent across the period 1996–2012. The sum of PBDEs and PCB-153 concentrations declined in the Finnish studies, except for PCB-153 in the Northern study, where concentrations were stable across the only two time points considered (2005 and 2010).

> Studies of persistent contaminants in maternal blood were carried out among the Yup'ik in Alaska (United States), in Nunavik (Canada), Reykjavik (Iceland), in all of Iceland, Chukotka (the Russian Federation) and Disko Bay (Greenland). The Nunavik study was the most extensive, with 11 time points between 1992 and 2013. Across all studies, decreases were seen in concentrations of DDT (p,p'-DDE and p,p'-DDT), HCB, β-HCH, PCBs (138, 153 and 180), mirex, oxychlordane, trans-nonachlor. The sole exception was a slight increase in oxychlordane concentrations across the two years of the all-Iceland study (1998 and 2004). In a more limited subset of the Yup'ik in Alaska and Nunavik studies (two time points), blood concentrations of PBDE-153 increased during the period 2004 to 2012 at both sites, while PFOA, PFNA and PFOS increased in blood samples from the Yup'ik, but PFOS decreased in blood samples from Nunavik.

> Two further studies examined PFAS in blood samples from nursing Swedish women (1996–2010) and northern Norwegian men (1979–2007). The Swedish study showed a steady decline in blood concentrations of PFOA and PFOS, but a stable or slightly increasing concentration of PFDA. In the Norwegian study, concentrations of all studied PFASs (PFOA, PFOS, PFHxS, PFNA and PFDA) increased during the period 1979 to 2001. While concentrations of PFOA, PFOS and PFHxS decreased from 2001 to 2007, concentrations of PFNA and PFDA continued to increase. These temporal patterns appear consistent with the adoption of voluntary and regulatory control measures in Europe and Scandinavia.

The Nunavik region of Canada is home to many Inuit people, whose exposure to environmental contaminants can differ markedly from the general population due to their consumption of "country" foods. Plasma samples from pregnant Inuit women were collected in 2004, 2007, 2011–2012 and 2016–2017 and the PFAS content of serum determined by LC-MS/MS (Caron-Beaudoin *et al.*, 2020). Decreases in the geometric mean serum concentrations of shorter chain (6–8 carbon) PFAS were apparent, while concentrations of 9–11 carbon PFAS increased between the two time points at which these compounds were determined. A summary of the findings is included in Table 38. Comparison with PFAS concentrations in plasma of the general Canadian population (2016–2017) shows no clear pattern, with Inuit women less exposed to some PFAS (PFHxS and PFOA) and more highly exposed to other PFAS (PFOS, PFNA and PFDA). The strongest associations between PFAS in the serum of Inuit women and food consumption frequencies was for consumption of meat and organs from marine mammals. These foods are unlikely to be consumed by the general Canadian population and may explain the differing pattern of serum PFAS

concentrations.

TABLE 38 **CONCENTRATIONS OF PERFLUOROALKYLATED SUBSTANCES IN SERUM OF PREGNANT INUIT WOMEN, NUNAVIK, CANADA, 2004–2017**

| SUBSTANCE | CARBON CHAIN LENGTH | GEOMETRIC MEAN CONCENTRATION, µg/L | | | | |
|---|---|---|---|---|---|---|
| | | 2004 | 2007 | 2011–2012 | 2016–2017 | 2016–2017 GENERAL CANADIAN POPULATION[a] |
| PFHxS | 6 | - | 0.53 | 0.35 | 0.27 | 0.76 |
| PFOA | 8 | - | 0.97 | 0.67 | 0.54 | 1.2 |
| PFOS | 8 | 9.8 | 5.3 | 3.8 | 3.3 | 2.5 |
| PFNA | 9 | - | - | 2.0 | 2.3 | 0.44 |
| PFDA | 10 | - | - | 0.45 | 0.51 | 0.12 |
| PFUnDA | 11 | - | - | 0.44 | 0.54 | - |

*Notes:* [a] **Health Canada.** 2021. *Sixth report on human biomonitoring of environmental chemicals in Canada.* Government of Canada. https://www.canada.ca/content/dam/hc-sc/documents/services/environmental-workplace-health/reports-publications/environmental-contaminants/sixth-report-human-biomonitoring/pub1-eng.pdf. PFHxS; perfluorohexane sulfonic acid; PFOA: perfluorooctanoic acid; PFOS: perfluorooctanesulfonic acid; PFNA: perfluorononanoic acid; PFDA: perfluorodecanoic acid; and PFUnDA: perfluoroundecanoic acid.

*Source:* **Caron-Beaudoin, É., Ayotte, P., Blanchette, C., Muckle, G., Avard, E., Ricard, S. & Lemire, M.** 2020. Perfluoroalkyl acids in pregnant women from Nunavik (Quebec, Canada): Trends in exposure and associations with country foods consumption. *Environment International*, 145: 106169. https://doi.org/10.1016/j.envint.2020.106169

Pregnant women from 14 Inuit villages in the Nunavik region participated in biomonitoring projects during 1992 to 2017, with a total of 559 women participating (Adamou *et al.*, 2020). Analyses for PCBs were carried out on plasma before 2010 and in serum thereafter. Concentrations from both media were considered to be equivalent. The six most prevalent PCBs (99, 118, 138, 153, 180, 187) were included in all sub-studies. Geometric mean concentrations of the marker PCB, PCB153, and the sum of the six PCBs decreased by 82 and 84 percent, respectively, across the 25-year time line of the study. The sum of PCBs decreased from 1 480 µg/kg lipid in 1992 to 231 µg/kg lipid in 2017. The decrease was thought to be at least partly due to a decrease in the consumption of marine foods.

Analyses of organochlorine compounds were carried out on randomly selected blood samples collected as part of health surveys conducted in Greenland during 1993–1995, 1999–2001 and 2005–2009 (Bjerregaard *et al.*, 2013). The population of Greenland is 90 percent Inuit. PCBs and OCPs were determined by GC-MS. All contaminants showed significant decreases from 1993–1995 to 2005–2009, ranging from 46 to 60 percent after adjustment for age, sex and smoking status. Despite decreases, serum concentrations of organochlorine compounds appeared high in 2005–2009. For example, the geometric mean concentration of PCB-153 was 353 µg/kg lipid, compared to a mean of 30 µg/kg lipid in a cohort of adult males in Guinea-Bissau (Linderholm *et al.*, 2010). Similarly, the geometric mean serum concentration of 727 µg/kg lipid was about 2 to 3-fold higher than mean concentrations in the United States (Li *et al.*, 2022) and Australia (Thomas *et al.*, 2017), but less than in Guinea-Bissau (Linderholm *et al.*, 2010).

Trends in the PCB, OCP and PFAS content of blood from the Inuit in Greenland was examined over the period 1994 to 2015 (Long *et al.*, 2021). Participants were

predominantly female (1 693 of 2 131), with approximately equal numbers of pregnant and non-pregnant females. Mean concentrations of marker organochlorine compounds (PCB-153, p,p'-DDE and oxychlordane) appeared to reach a peak of about 2 000 to 2 002 before decreasing steadily across the duration of the study. Rates of decrease for the entire period 1994–2015 were in the range 4.5 to 10.3 percent per year. Consistent with the study of Caron-Beaudoin *et al.* (2020), concentrations of shorter chain PFAS (PFHxS, PFOA and PFOS) decreased over the study period, while concentrations of the longer chain PFAS (PFNA, PFDA, PFUnDA) increased.

A study among the Indigenous Peoples of coastal Chukotka, on the Russian side of the Bering Strait, examined serum levels of OCPs and PCBs in a cohort of pregnant women ($n$ = 17) in 2001–2002 and re-examined the same women in 2007 (Dudarev *et al.*, 2010). The method of analysis was not reported, but the laboratory carrying out the analyses was reported to be accredited. Geometric mean concentrations of OCPs (HCB, HCH, p,p-DDT, p,p'-DDT, oxychlordane, trans-nonachlor and mirex) and the sum of PCBs decreased over the period 2001–2002 to 2007 by 19 to 73 percent, with the lowest percentage decrease for HCB and the highest for oxychlordane. The study also attempted to determine trends in child exposure by comparing concentrations in cord blood in 2001–2002 to serum concentrations in the offspring in 2007. This component of the study showed a mixture of increases and decreases and is somewhat difficult to interpret.

# CHAPTER 7
# TRENDS IN ANIMAL EXPOSURE TO ENDOCRINE DISRUPTING CHEMICALS

## 7.1 FISH AND SHELLFISH

Exposure to estrogenic compounds can have a feminizing effect on male fish, including the production of the female-specific yolk precursor protein vitellogenin (VTG). During the period 1996 to 2001, male flounder (*Platichthys flesus*) were collected from six river estuaries in the United Kingdom of Great Britain and Northern Ireland and analyses for plasma VTG concentrations (Kirby *et al.*, 2004). A decrease in mean flounder VTG concentrations over the course of the study was apparent, particularly at sites in the River Tyne and the Mersey River. For example, the mean VTG concentration in male flounder at Hebburn in the River Tyne estuary decreased from 113 µg/mL and 1996 and 448 µg/mL in 1997 to 0.9 µg/mL in 2001. One of the sites (Howden) is adjacent to a sewage treatment plant. It was demonstrated that as the concentration of estradiol, estrone and ethynyl-estradiol in discharge effluent decreased from 21, 96 and 15 ng/L, respectively, to <1, 5.0 and <1 ng/L, respectively, mean VTG concentrations in male flounder from the environs decreased from 240 µg/mL to approximately 2 µg/mL.

A Danish study examined VTG concentrations in male brown trout (*Salmo trutta*) in streams receiving sewage effluent from non-central wastewater treatment plants, including on-site facilities (Morthorst *et al.*, 2018). During the period 2000 to 2004, 79 percent of juvenile male brown trout had VTG concentration greater than 50 ng/mL. Following a national effort to improve on-site wastewater treatment in dispersed communities, the survey was repeated in 2010 to 2016, with only 0.7 perecent of juvenile males having VTG concentration greater than 50 ng/mL.

As part of the Japanese total diet study, composite samples of fish and shellfish were analysed for total dioxins (PCDD/F and DL-PCB) over the period 1998 to 2016 (Tsutsumi *et al.*, 2018). During this period, dietary exposure to dioxins from this food group decreased from 61 pg TEQ/kg bw per day to 24 pg TEQ/kg bw per day. During the period 1998–2016, consumption of foods in this group decreased in Japan by about 26 percent. However, the decrease in dietary exposure from this food group would have included substantial decreases in dioxin concentrations.

Concentrations of PCDD/F, PCBs and PBDEs were determined in the muscle meat of Baltic herring (*Clupea harengus*) from the Gulfs of Finland and Bothnia over the period 1978–2009 (Airaksinen *et al.*, 2014). PCDD/F and PCB concentrations, expressed as 2005 WHO TEQ, decreased by about 80 percent over the 31-year period, from approximately 20 to 5 ng TEQ/kg fresh weight. PBDE concentrations, expressed as the sum of 14 PBDE, increased from 1978 to approximately 1990–1995 before decreasing to similar concentrations in 2009 to those in 1978.

PBDEs were analysed in various fish species from the Great Lakes in the United States in 2006–2007 and in 2012 (Gandhi *et al.*, 2017). While there were distinct geographical variations in the trends of fillet concentrations of different PBDE congeners, the only trends that reached statistical significance ($p<0.05$) were for decreases in congener concentrations of coho salmon and rainbow trout. No statistically significant increases were observed for any congener in any monitored species.

Pooled samples of blue mussel (*Mytilus edulis*) tissue and eelpout (*Zoarces viviparus*) fillets, collected from the Baltic Sea in each year during 1994–2017, were analysed for a range of lipophilic organic contaminants by gas chromatography with high resolution quantitative time-of-flight mass spectrometric detection (GC-QTOF-MS) (Rebryk, Koschorreck and Haglund, 2023). Results from this study were only reported in terms of annual percentage change. PCB concentrations in both species decreased across the study period at rates of 3–6 percent per year, although most of the trends were not statistically significant ($p<0.05$). Concentrations of PBDE congeners decreased at rates of 5–13 percent per year in both species. However, decreases were only significant for BDE-47 (both species) and BDE-182 (blue mussel). Decreases in concentrations of DDT and metabolites and other OCPs were in the range 3–12 percent per year, with the majority of decreases being statistically significant. Trends were reported for two phthalates (DEHP and di-n-hexyl phthalate). Trends were only reported for the fish species (eelpout), with concentrations increasing significantly or near significantly over the study period.

The BPA concentration of non-canned retail fish samples collected in France in 2007–2009 and in 2015 were compared (Gorecki *et al.*, 2017). Substantial decreases were apparent in the mean concentrations of BPA in cooked pollack or coley (16.7 to 2.1 µg/kg), smoked salmon (1.1 to 0.47 µg/kg), steamed salmon (13.8 to 3.7 µg/kg), oven-based salmon (4.0 to 1.5 µg/kg) and cooked shrimp (12.0 to 0.28 µg/kg).

The Canadian total diet study analysed composite food samples for BPA during 2008–2012 and 2016 (Government of Canada, n.d.). Of the foods from

food-producing animals, BPA was only consistently detected in fresh fish composites. The mean concentration of the two composites analysed each survey year increased from 0.95 µg/kg in 2009, to 3.95 µg/kg in 2011, before reducing to below the LOD in both composites analysed in 2016.

Banked samples of rainbow trout (*Oncorhynchus mykiss*) from farms on Sweden's Baltic coast, collected during 1999–2010, were analysed individually for PFAS by LC-MS/MS (Johansson *et al.*, 2014). PFOS was the most frequently detected compound. Concentrations of PFOS in rainbow trout cutlets decreased from a mean (range) of 436 (179–795) ng/kg fresh weight in 1999 to 87 (60–121) ng/kg fresh weight in 2005 and 59 ng/kg fresh weight in the sole sample taken in 2010.

Concentrations of PFAS were determined in the livers of Baltic cod (*Gadus morhua*), sampled near southeast Gotland during 1981 to 2013 (Schultes *et al.*, 2020). The main PFAS detected was PFOS, which accounted for more than 50 percent of the sum of PFAS at all time points. Statistical analysis of time trends indicated a significant increase in PFOS concentration of 3.4 percent per year over the whole study period but not for the period 2000–2013. No significant trend in PFOA concentrations was found for either the complete study period or the later portion of the study period. PFHxS and the longer chain PFAS (PFNA, PFDA, PFUnDA, and PFDoDA) concentrations in cod liver increased significantly across the entire study period and the later portion of the study period. Representative concentrations are summarized in Table 39.

TABLE 39 **PERFLUOROALKYLATED SUBSTANCES CONCENTRATIONS IN LIVERS OF BALTIC COD (*GADUS MORHUA*), 1981–2013**

| SUBSTANCE | GEOMETRIC MEAN CONCENTRATION, µg/kg WET WEIGHT | | | | | RATE OF CHANGE, 1981–2013 (%) |
|---|---|---|---|---|---|---|
| | 1981 | 1990 | 2000 | 2006 | 2013 | |
| PFHxS | 0.04 | 0.03 | 0.07 | 0.06 | 0.08 | +3.0 |
| ΣPFOS | 3.2 | 2.5 | 7.1 | 5.6 | 6.5 | +3.4 |
| PFOA | 0.15 | 0.52 | 0.12 | 0.10 | 0.26 | NS |
| PFNA | 0.28 | 1.24 | 0.70 | 0.86 | 1.52 | +3.9 |
| PFDA | 0.08 | 0.19 | 0.23 | 0.42 | 0.73 | +5.9 |
| PFUnDA | 0.09 | 0.19 | 0.37 | 0.89 | 1.07 | +7.2 |
| PFDoDA | 0.05 | <0.05 | 0.04 | 0.11 | 0.08 | +7.3 |

*Notes*: PFHxS: perfluorohexanesulfonic acid; ΣPFOS: perfluorooctanesulfonic acid, sum of linear and branched isomers; PFOA: perfluorooctanoic acid; PFNA: perfluorononanoic acid; PFDA: perfluorodecanoic acid; PFUnDA: perfluoroundecanoic acid; PFDoDA: perfluorododecanoic acid; and NS: not significant.

*Source:* **Schultes, L., Sandblom, O., Broeg, K., Bignert, A. & Benskin, J.P.** 2020. Temporal trends (1981–2013) of per- and polyfluoroalkyl substances and total fluorine in Baltic cod (*Gadus morhua*). *Environmental Toxicology and Chemistry*, 39(2): 300–309. https://doi.org/10.1002/etc.4615

## 7.2 BOVINES AND MILK

Bovine milk samples ($n$ = 30) were collected from farms near a known source of dioxin contamination, a rural/alpine area and from tanks at a large processing plant (Schmid *et al.*, 2003). Samples were analysed for polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/F). The results were compared to those of samples taken at the same sites in 1984 and 1990/91. A general downward trend in PCDD/F concentrations was apparent, with the overall mean concentration, expressed as international toxic equivalents (I-TEQ), for milk from processing plants decreasing from 1.9 ng I-TEQ/kg lipid basis in 1984 to 1.3 ng I-TEQ/kg lipid basis in 1990–91 and 0.51 ng I-TEQ/kg lipid basis in 2001. A similar rate of decrease was seen for milk collected from sites near known point sources, with a mean decrease from 8.5 to 3.0 to 0.63 ng I-TEQ/kg lipid basis in 1984, 1990–91 and 2001, respectively. The decrease in PCDD/F content of milk from rural/alpine environments was very similar to that seen for processing plants. The changes were reported to be "paralleled by and correlated to the remediation of known PCDD/F emitting industries, as enforced by federal authorities".

Between 1991 and 2004, adipose tissue was randomly sampled from bovines in major slaughter facilities in Sweden (Glynn *et al.*, 2009). Samples were analysed for a range of organochlorine compounds by gas chromatography-electron capture detection (GC-ECD). Only three compounds were detected above the LOQ frequently enough for trend analysis: PCB-153, HCB and p,p'-DDE. While there was substantial year-to-year variability, across the complete 14-year period, the mean concentrations of the three compounds decreased from 3.1 to 1.8 µg/kg lipid (PCB-153), 3.9 to 2.7 µg/kg lipid (HCB) and 3.3 to 2.4 µg/kg lipid (p,p'-DDE).

Adipose tissue samples were collected from beef cattle (steers and heifers) at slaughter during 2012–2013 and analysed for PBDE by GC-HRMS (Lupton and Hakk, 2017). Results were compared to those from an equivalent survey conducted in 2007–2008. Results were expressed as the sum of BDEs 28, 47, 99, 100, 153, 154 and 183. The median concentration of ΣPBDE decreased from 0.14 to 0.10 µg/kg lipid, however, this decrease was not statistically significant.

The BPA concentration of non-canned retail beef and veal samples collected in France in 2007–2009 and in 2015 were compared (Gorecki *et al.*, 2017). Decreases were apparent in the mean concentrations of BPA in beef steak (3.4 to 2.9 µg/kg), and veal (34.4 to 1.2 µg/kg).

Banked samples of milk collected from milk transport vehicles, collected during the period 1999–2010, were combined into three annual pools and analysed for PFAS by LC-MS/MS (Johansson *et al.*, 2014). PFOS was the only PFAS detected frequently enough to allow analysis of temporal trends. No temporal trends were observed, with concentrations in the range <3.5 to 7.3 ng/kg fresh weight across the course of the study.

## 7.3 OTHER MEAT-PRODUCING ANIMALS

Between 1991 and 2004, adipose tissue was randomly sampled from pigs in major slaughter facilities in Sweden (Glynn *et al.*, 2009). Samples were analysed for a range of organochlorine compounds by GC-ECD. Only two compounds were detected above the LOQ frequently enough for trend analysis: PCB-153 and p,p'-DDE. While there was substantial year-to-year variability, across the complete 14-year period, the mean concentrations of the two compounds decreased in pig tissues, with decreases of 1.9 to 0.5 µg/kg lipid (PCB-153) and 4.4 to 0.5 µg/kg lipid (p,p'-DDE).

Adipose tissue samples were collected from market hogs (pigs) at slaughter during 2012–2013 and analysed for PBDE by GC-HRMS (Lupton and Hakk, 2017). Results were compared to those from an equivalent survey conducted in 2007–2008. Results were expressed as the sum of BDEs 28, 47, 99, 100, 153, 154 and 183. The median concentration of ΣPBDE decreased from 0.27 to 0.20 µg/kg lipid. This decrease was statistically significant ($p<0.05$).

The BPA concentration of non-canned retail meat samples collected in France in 2007–2009 and in 2015 were compared (Gorecki *et al.*, 2017). Decreases were apparent in the mean concentrations of BPA in mutton (7.8 to 3.2 µg/kg), pork chop (17.0 to 1.6 µg/kg), roast pork (12.4 to 3.5 µg/kg), raw ham (2.7 to 1.1 µg/kg), and cooked ham (1.2 to 0.09 µg/kg).

## 7.4 POULTRY AND EGGS

Adipose tissue samples were collected from chickens and turkeys at slaughter during 2012–2013 and analysed for PBDE by GC-HRMS (Lupton and Hakk, 2017). Results were compared to those from an equivalent survey conducted in 2007–2008. Results were expressed as the sum of BDEs 28, 47, 99, 100, 153, 154 and 183. The median concentration of ΣPBDE in chicken fat decreased from 0.40 to 0.12 µg/kg lipid, while median concentrations in turkey fat decreased from 1.36 to 0.53 µg/kg lipid. Both decreases were statistically significant ($p<0.001$).

The BPA concentration of non-canned retail poultry meat samples collected in France in 2007–2009 and in 2015 were compared (Gorecki *et al.*, 2017). Decreases were apparent in the mean concentrations of BPA in sauteed turkey breast (6.8 to 4.4 µg/kg) and roast turkey (4.1 to 0.09 µg/kg), but an increase in the BPA content of chicken (2.6 to 3.9 µg/kg).

Banked samples of hens' eggs from the largest Swedish packaging plants, collected during the period 1999 to 2010, were combined into three annual pools and analysed for PFAS by LC-MS/MS (Johansson *et al.*, 2014). PFOS was the most frequently detected compound. Concentrations of PFOS in hens' eggs decreased from a mean (range) of 3 500 (1 890–6 480) ng/kg fresh weight in 1999 to 1 210 (370–2 890) ng/kg fresh weight in 2005 and 190 (<26-432) ng/kg fresh weight in 2010. To calculate the mean for the 2010 samples, the result below the LOD was set equal to the LOD.

Uganda - A farmer clearing weeds in a rice farm

# CHAPTER 8
# CONCLUSIONS

This report summarizes evidence for temporal trends in human exposure to selected EDCs and evidence for trends in animals that are food sources for humans. A study commissioned by the World Health Organization study presented the state of the science with respect to EDCs in 2002 (Damstra *et al.*, eds., 2002) and this study has only summarized evidence that extends beyond 2002. An enormous number of chemicals have been reported to have endocrine disrupting activity and this report does not attempt to address trends in human exposure to every one of those chemicals. Instead, this report has focused on chemicals or groups of chemicals that have repeatedly been implicated as EDCs. There is a considerable overlap between chemicals considered to be EDCs and chemicals classified as POPs, and the inclusion of chemicals in the Stockholm Convention (UNEP, 2019) has been the impetus for much of the information on human exposures that is currently available.

In general, there has been a downward trend in human exposure to chemicals where there are specific regulatory measures placed on the manufacture and use of the chemical, where public health concerns have led to voluntary control measures by the manufacturing or using industries, or where publicly available information has raised concerns in the general population. While all these mechanisms have been effective in reducing exposure to EDCs, they have not eliminated exposure. Exposure to many EDCs will continue for some time due to the incomplete application of control measures and the extreme environmental persistence of some EDCs. For example, although manufacture and use of PBDEs has largely ceased, the items that these flame retardants were used in may continue to be used for some time or may be inappropriately disposed of (O'Driscoll *et al.*, 2016).

It should be noted that the available studies summarized in this report do not cover all geographical areas, with information from Africa and Latin America being particularly sparse. However, the well-standardized studies of POPs in breast milk have indicated that, in most cases, levels of exposure to PCDD/F and DL-PCBs (Malisch *et al.*, 2023a), OCPs (Malisch *et al.*, 2023c), PBDEs (Schächtele *et al.*, 2023) and PFAS (Malisch *et al.*, 2023d), are no greater in these regions than in Europe and Northern America and that similar downward trends in exposure are occurring.

Conclusions for specific chemicals or classes of chemicals are given below.

**Organochlorine compounds.** The manufacture and use of many OCPs ceased in the 1980s and all studies summarized in this report have shown continuing decreases in the OCP content of food-producing animals and human exposure. The peak in human exposure to DDT before the ongoing decline may have occurred later in some African countries (Linderholm *et al.*, 2010), where the use of DDT for vector control was allowed under an exemption to the Stockholm Convention (UNEP, 2019).

Animal concentrations and human exposure to PCDD/F and DL-PCBs have similarly declined through the period considered in this study, with the exception of northern China. There is evidence from two studies (Lu *et al.*, 2015; Sun *et al.*, 2011) that exposure to the sum of PCDD/F and DL-PCBs was increasing through the late 2000s/early 2010s. Neither of the studies provided an explanation for this divergent trend.

**Polybrominated diphenyl ether.** Trends in concentrations of PBDE congeners in animals and humans are complicated by the presence of multiple industrial formulations and the mixture of voluntary industry control and regulatory measures. Penta- and octa-BDE products were phased out the earliest and this is reflected in the largely uniform decreases in congeners BDE-47, -99 and -100. While more recent studies show decreases in BDE-153 and -209 and HBCDDs, such trends are not always apparent in earlier studies. BDE-209 is the main congener in deca-BDE formulations, which were still in use at a later date than the penta- and octa-BDE formulations. Similarly, the use of HBCDDs continued in some regions to a more recent time.

**Phthalates.** While there is variation from study to study, overall, there is good evidence to show that human exposure to low molecular weight phthalates decreased across the period considered by this report. However, in some studies, decreases in exposure were not apparent until after regulatory action in Europe in 2013. While not always included in studies, there is less evidence of decreases in exposure to the high molecular weight phthalates that are not included in the European regulatory action. Several studies have shown that human exposure to phthalate substitutes, such as DINCH, is increasing.

**Bisphenols.** Decreases in exposure to BPA appear to have occurred at an earlier time in Asia than in Europe and Northern America. While most studies have demonstrated decreases in BPA exposure, the decreases are often not substantial. While there is some evidence that the substitution of BPA by other bisphenols may have occurred to some extent, no sustained trends in exposure to other bisphenols was apparent.

**Parabens, triclosan and benzophenone.** While use levels of these chemicals in cosmetic and consumer products are regulated in some countries, their use has not been banned and decreases seen in exposure, particularly for parabens and triclosan, are likely to be the result of public pressure and manufacturers responses to that pressure. There is moderately consistent evidence for decreasing exposure to

parabens and triclosan, particularly for methyl and propyl paraben. Unsurprisingly, most studies that have estimated trends in exposure to BP-3 have reported increases. BP-3 is an active ingredient in sunscreen formulations and many countries have had active programmes encouraging the use of sunscreens.

**Alkyl phenols.** Only two studies were identified that considered trends in human exposure to alkyl phenols (Ringbeck *et al.*, 2022b; Ringbeck *et al.*, 2022a). The two studies, one in Germany and one in Japan, indicated decreases in human exposure to alkyl phenols after 2012.

**Perfluorinated alkyl substance.** Human exposure to the shorter chain PFAS (PFOA, PFOS, PFHxS) appears to have decreased from about 2000 to 2008, with the peak of exposure varying between countries. There is limited evidence for decreased exposure to the longer chain PFAS and some indications of increases in exposure. There are relatively few studies on trends in the PFAS exposure of food-producing animals and the available studies give inconsistent indications of whether exposure is increasing or decreasing.

**Phytoestrogens.** Only two sources of information were found on trends in exposure to phytoestrogens, particularly the soy isoflavones, daidzein and genistein. There is little evidence of trends in exposure to these chemicals. Data from the NHANES are suggestive of increased exposure to daidzein. This may be due to increased use of soy products in processed foods.

Mazar-e Sharif - A view of a wheat field.

# REFERENCES


**'t Mannetje, A., Coakley, J., Bridgen, P., Brooks, C., Harrad, S., Smith, A.H., Pearce, N. & Douwes, J.** 2013. Current concentrations, temporal trends and determinants of persistent organic pollutants in breast milk of New Zealand women. *Science of the Total Environment*, 458: 399–407. https://doi.org/10.1016/j.scitotenv.2013.04.055

**Abass, K., Emelyanova, A. & Rautio, A.** 2018. Temporal trends of contaminants in Arctic human populations. *Environmental Science and Pollution Research*, 25(29): 28834–28850. https://doi.org/10.1007/s11356-018-2936-8

**Adamou, T.Y., Riva, M., Muckle, G., Laouan Sidi, E.A., Lemire, M. & Ayotte, P.** 2020. Blood mercury and plasma polychlorinated biphenyls concentrations in pregnant Inuit women from Nunavik: Temporal trends, 1992–2017. *Science of the Total Environment*, 743: 140495. https://doi.org/10.1016/j.scitotenv.2020.140495

**Ae, R., Nakamura, Y., Tada, H., Kono, Y., Matsui, E., Itabashi, K., Ogawa, M. *et al.*** 2018. An 18-Year Follow-up Survey of Dioxin Levels in Human Milk in Japan. *Journal of Epidemiology*, 28(6): 300–306. https://doi.org/10.2188/jea.JE20170032

**Airaksinen, R., Hallikainen, A., Rantakokko, P., Ruokojärvi, P., Vuorinen, P.J., Parmanne, R., Verta, M., Mannio, J. & Kiviranta, H.** 2014. Time trends and congener profiles of PCDD/Fs, PCBs, and PBDEs in Baltic herring off the coast of Finland during 1978–2009. *Chemosphere*, 114: 165–171. https://doi.org/10.1016/j.Chemosphere.2014.03.097

**Alivernini, S., Battistelli, C.L. & Turrio-Baldassarri, L.** 2011. Human Milk as a Vector and an Indicator of Exposure to PCBs and PBDEs: Temporal Trend of Samples Collected in Rome. *Bulletin of Environmental Contamination and Toxicology*, 87(1): 21–25. https://doi.org/10.1007/s00128-011-0262-7

**Ashrap, P., Watkins, D.J., Calafat, A.M., Ye, X., Rosario, Z., Brown, P., Vélez-Vega, C.M., Alshawabkeh, A., Cordero, J.F. & Meeker, J.D.** 2018. Elevated concentrations of urinary triclocarban, phenol and paraben among pregnant women in Northern Puerto Rico: Predictors and trends. *Environment International*, 121: 990–1002. https://doi.org/10.1016/j.envint.2018.08.020

**Bates, M.N., Hannah, D.J., Buckland, S.J., Taucher, J.A. & Van Maanen, T.** 1994. Chlorinated organic contaminants in breast milk of New Zealand women. *Environmental Health Perspectives*, 102: 211–217. https://doi.org/10.1289/ehp.94102s1211

**Bates, M., Thomson, B. & Garrett, N.** 2002. Reduction in organochlorine levels in milk of New Zealand women. *Archives of Environmental Health*,57: 591–597. https://doi.org/10.1080/00039890209602093

**Bjerregaard, P., Pedersen, H.S., Nielsen, N.O. & Dewailly, E.** 2013. Population surveys in Greenland 1993–2009: Temporal trend of PCBs and pesticides in the general Inuit population by age and urbanisation. *Science of the Total Environment*, 454–455: 283–288. https://doi.org/10.1016/j.scitotenv.2013.03.031

**Boon, P.E., Van der Voet, H., Van Raaij, M.T.M. & Van Klaveren, J.D.** 2008. Cumulative risk assessment of the exposure to organophosphorus and carbamate insecticides in the Dutch diet. *Food and Chemical Toxicology*, 46(9): 3090–3098. https://doi.org/10.1016/j.fct.2008.06.083

**Caron-Beaudoin, É., Ayotte, P., Blanchette, C., Muckle, G., Avard, E., Ricard, S. & Lemire, M.** 2020. Perfluoroalkyl acids in pregnant women from Nunavik (Quebec, Canada): Trends in exposure and associations with country foods consumption. *Environment International*, 145: 106169. https://doi.org/10.1016/j.envint.2020.106169

**CDC (Centers for Disease Control and Prevention).** 2024. Biomonitoring data tables for environmental chemicals. In: *CDC*. [Cited 10 June 2024]. https://www.cdc.gov/exposurereport/data_tables.html

**Černá, M., Grafnetterová, A.P., Dvořáková, D., Pulkrabová, J., Malý, M., Janoš, T., Vodrážková, N., Tupá, Z. & Puklová, V.** 2020. Biomonitoring of PFOA, PFOS and PFNA in human milk from Czech Republic, time trends and estimation of infant's daily intake. *Environmental Research*, 188: 109763. https://doi.org/10.1016/j.envres.2020.109763

**Chen, T., Huang, M.H., Li, J., Li, J. & Shi, Z.** 2019. Polybrominated diphenyl ethers and novel brominated flame retardants in human milk from the general population in Beijing, China: Occurrence, temporal trends, nursing infants' exposure and risk assessment. *Science of the Total Environment*, 689: 278–286. https://doi.org/10.1016/j.scitotenv.2019.06.442

**Cowell, W.J., Sjodin, A., Jönes, R., Wang, Y., Wang, S. & Herbstman, J.B.** 2019. Temporal trends and developmental patterns of plasma polybrominated diphenyl ether concentrations over a 15-year period between 1998 and 2013. *Journal of Exposure Science and Environmental Epidemiology*, 29(1): 49–60. https://doi.org/10.1038/s41370-018-0031-3

**Damstra, T., Barlow, S., Bergman, A., Kavlock, R. & Van Der Kraak, G., eds.** 2002. *Global Assessment of the State-of-the-Science of Endocrine Disruptors*. Geneva, Switzerland, WHO. https://www.who.int/publications/i/item/WHO-PSC-EDC-02.2

**Darnerud, P.O., Lignell, S., Aune, M., Isaksson, M., Cantillana, T., Redeby, J. & Glynn, A.** 2015. Time trends of polybrominated diphenylether (PBDE) congeners in serum of Swedish mothers and comparisons to breast milk data. *Environmental Research*, 138: 352–360. https://doi.org/10.1016/j.envres.2015.02.031

**Degen, G.H., Blaszkewicz, M., Shi, L.J., Buyken, A.E. & Remer, T.** 2011. Urinary isoflavone phytoestrogens in German children and adolescents - A longitudinal examination in the DONALD cohort. *Molecular Nutrition & Food Research*, 55(3): 359–367. https://doi.org/10.1002/mnfr.201000325

**Demeneix, B. & Slama, R.** 2019. *Endocrine disruptors: from scientific evidence to human health protection.* Brussels, European Parliament. https://www.europarl.europa.eu/RegData/etudes/STUD/2019/608866/IPOL_STU(2019)608866_EN.pdf

**DeVito, M., Bokkers, B., van Duursen, M.B.M., van Ede, K., Feeley, M., Gáspár, E.A.F., Haws, L. *et al.*** 2024. The 2022 World Health Organization reevaluation of human and mammalian toxic equivalency factors for polychlorinated dioxins, dibenzofurans and biphenyls. *Regulatory Toxicology and Pharmacology*, 146: 105525. https://doi.org/10.1016/j.yrtph.2023.105525

**Domingo, J.L., Martí-Cid, R., Castell, V. & Llobet, J.M.** 2008. Human exposure to PBDEs through the diet in Catalonia, Spain: Temporal trend: A review of recent literature on dietary PBDE intake. *Toxicology,* 248(1): 25-32. https://doi.org/10.1016/j.tox.2008.03.006

**Dong, Z., Wang, H., Yu, Y.Y., Li, Y.B., Naidu, R. & Liu, Y.** 2019. Using 2003–2014 U.S. NHANES data to determine the associations between per- and polyfluoroalkyl substances and cholesterol: Trend and implications. *Ecotoxicology and Environmental Safety*, 173: 461–468. https://doi.org/10.1016/j.ecoenv.2019.02.061

**Drage, D.S., Mueller, J.F., Hobson, P., Harden, F.A. & Toms, L-M.L.** 2017. Demographic and temporal trends of hexabromocyclododecanes (HBCDD) in an Australian population. *Environmental Research*, 152: 192–198. https://doi.org/10.1016/j.envres.2016.10.015

**Dudarev, A.A., Chupakhin, V.S., Odland, J.O., Reiersen, L.O. & Chashchin, V.P.** 2010. A follow-up study of blood levels of persistent toxic substances (PTS) among indigenous peoples of coastal Chukotka, Russia, 2001–2007. *International Journal of Circumpolar Health*, 69: 263–268. https://doi.org/10.3402/ijch.v63i0.17895

**ECHA (European Chemicals Agency).** 2023. New hazard classes 2023. In: *ECHA*. [Cited 27 June 2024]. https://echa.europa.eu/new-hazard-classes-2023#:~:text=The%20new%20hazard%20classes%20are,(very%20persistent%2C%20very%20bioaccumulative)

**EFSA (European Food Safety Authority).** 2011. Scientific Opinion on Polybrominated Diphenyl Ethers (PBDEs) in Food. EFSA Panel on Contaminants in the Food Chain (CONTAM). *EFSA Journal*, 9(5): 2156. https://doi.org/10.2903/j.efsa.2011.2156

**EFSA.** 2015. Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). *EFSA Journal*, 13(1): 3978. https://doi.org/10.2903/j.efsa.2015.3978

**EFSA.** 2018. Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food. *EFSA Journal*, 16(11): 5333. https://doi.org/10.2903/j.efsa.2018.5333

**EFSA.** 2019. Update of the risk assessment of di-butylphthalate (DBP), butyl-benzyl-phthalate (BBP), bis(2-ethylhexyl)phthalate (DEHP), di-isononylphthalate (DINP) and diisodecylphthalate (DIDP) for use in food contact materials. *EFSA Journal*, 17(12): 5838. https://doi.org/10.2903/j.efsa.2019.5838

**EFSA.** 2024. Update of the risk assessment of polybrominated diphenyl ethers (PBDEs) in food. *EFSA Journal*, 22(1): e8497. https://doi.org/10.2903/j.efsa.2024.8497

**Endocrine Society.** 2022. Hormone and endocrine disrupting chemicals. What you need to know. In. *Endocrine Society.* [Cited 16 May 2024]. https://www.endocrine.org/-/media/endocrine/files/patient-engagement/hormones-and-series/hormones_and_edcs_what_you_need_to_know.pdf

**Evans, D.H.** 1987. The fish gill: Site of action and model for toxic effects of environment pollutants. *Environmental Health Perspectives*, 71: 47–58. https://doi.org/10.1289%2Fehp.877147

**Fång, J., Nyberg, E., Bignert, A. & Bergman, Å.** 2013. Temporal trends of polychlorinated dibenzo-p-dioxins and dibenzofurans and dioxin-like polychlorinated biphenyls in mothers' milk from Sweden, 1972–2011. *Environment International*, 60: 224–231. https://doi.org/10.1016/j.envint.2013.08.019

**Fängström, B., Athanassiadis, I., Odsjö, T., Norén, K. & Bergman, Å.** 2008. Temporal trends of polybrominated diphenyl ethers and hexabromocyclododecane in milk from Stockholm mothers, 1980–2004. *Molecular Nutrition & Food Research*, 52(2): 187–193. https://doi.org/10.1002/mnfr.200700182

**FAO (Food and Agriculture Organization of the United Nations) & WHO (World Health Organization).** 2019. *FAO/WHO Expert Consultation on Dietary risk assessment of chemical mixtures (Risk assessment of combined exposure to multiple chemicals). WHO, Geneva, 16-18 April 2019.* Rome, FAO and Geneva, Switzerland, WHO. https://openknowledge.fao.org/server/api/core/bitstreams/0e2581f3-03e5-44c8-9726-4445d5dba19a/content

**FAO & WHO.** 2009. *Principles and methods for the risk assessment of chemicals in food.* Geneva, Switzerland, WHO. https://www.who.int/publications/i/item/9789241572408

**Fiedler, H., Sadia, M., Krauss, T., Baabish, A. & Yeung, L.W.Y.** 2022. Perfluoroalkane acids in human milk under the global monitoring plan of the Stockholm Convention on Persistent Organic Pollutants (2008–2019). *Frontiers of Environmental Science & Engineering*, 16(10): 132. https://doi.org/10.1007/s11783-022-1541-8

**Fromme, H., Fuchs, V., Albrecht, M., Aschenbrenner, B., Röhl, C., Janitzki, N., Herber-Jonat, S. *et al.*** 2022. Polychlorinated dioxins and dibenzofurans (PCDD/F), polybrominated dioxins and dibenzofurans (PBDD/F), polychlorinated biphenyls (PCB), polybrominated diphenyl ethers (PBDE), and per- and polyfluoroalkyl substances (PFAS) in German breast milk samples (LUPE 8). *Science of the Total Environment*, 825: 154066. https://doi.org/10.1016/j.scitotenv.2022.154066

**Fromme, H., Körner, W., Shahin, N., Wanner, A., Albrecht, M., Boehmer, S., Parlar, H., Mayer, R., Liebl, B. & Bolte, G.** 2009. Human exposure to polybrominated diphenyl ethers (PBDE), as evidenced by data from a duplicate diet study, indoor air, house dust, and biomonitoring in Germany. *Environment International*, 35(8): 1125–1135. https://doi.org/10.1016/j.envint.2009.07.003

**Gandhi, N., Gewurtz, S.B., Drouillard, K.G., Kolic, T., MacPherson, K., Reiner, E.J. & Bhavsar, S.P.** 2017. Polybrominated diphenyl ethers (PBDEs) in Great Lakes fish: Levels, patterns, trends and implications for human exposure. *Science of the Total Environment*, 576: 907–916. https://doi.org/10.1016/j.scitotenv.2016.10.043

**Gebbink, W.A., Glynn, A., Darnerud, P.O. & Berger, U.** 2015. Perfluoroalkyl acids and their precursors in Swedish food: The relative importance of direct and indirect dietary exposure. *Environmental Pollution*, 198: 108–115. http://dx.doi.org/10.1016/j.envpol.2014.12.022

**Glynn, A., Aune, M., Nilsson, I., Darnerud, P.O., Ankarberg, E.H., Bignert, A. & Nordlander, I.** 2009. Declining levels of PCB, HCB and p,p′-DDE in adipose tissue from food producing bovines and swine in Sweden 1991–2004. *Chemosphere*, 74(11): 1457–1462. https://doi.org/10.1016/j.Chemosphere.2008.11.056

**Nøst B., Weber, T., Rüdel, H., Bücking, M. & Kolossa-Gehring, M.** 2020. Human biomonitoring of per- and polyfluoroalkyl substances in German blood plasma samples from 1982 to 2019. *Environment International*, 145: 106123. https://doi.org/10.1016/j.envint.2020.106123

**Gorecki, S., Bemrah, N., Roudot, A-C., Marchioni, E., Le Bizec, B., Faivre, F., Kadawathagedara, M., Botton, J. & Rivière, G.** 2017. Human health risks related to the consumption of foodstuffs of animal origin contaminated by bisphenol A. *Food and Chemical Toxicology,* 110: 333–339. https://doi.org/10.1016/j.fct.2017.10.045

**Government of Canada.** n.d. Concentration of Contaminants and Other Chemicals in Food Composites. In: *Government of Canada.* [Cited 29 May 2024]. https://www.canada.ca/en/health-canada/services/food-nutrition/food-nutrition-surveillance/canadian-total-diet-study/concentration-contaminants-other-chemicals-food-composites.html#a1

**Gyllenhammar, I., Aune, M., Fridén, U., Cantillana, T., Bignert, A., Lignell, S. & Glynn, A.** 2021. Are temporal trends of some persistent organochlorine and organobromine compounds in Swedish breast milk slowing down? *Environmental Research*, 197: 111117. https://doi.org/10.1016/j.envres.2021.111117

**Gyllenhammar, I., Glynn, A., Jönsson, B.A.G., Lindh, C.H., Darnerud, P.O., Svensson, K. & Lignell, S.** 2017. Diverging temporal trends of human exposure to bisphenols and plastizisers, such as phthalates, caused by substitution of legacy EDCs? *Environmental Research*, 153: 48–54. https://doi.org/10.1016/j.envres.2016.11.012

**Gys, C., Ait Bamai, Y., Araki, A., Bastiaensen, M., Caballero-Casero, N., Kishi, R. & Covaci, A.** 2020. Biomonitoring and temporal trends of bisphenols exposure in Japanese school children. *Environmental Research*, 191: 110172. https://doi.org/10.1016/j.envres.2020.110172

**Han, C., Lim, Y-H. & Hong, Y-C.** 2016. Ten-year trends in urinary concentrations of triclosan and benzophenone-3 in the general U.S. population from 2003 to 2012. *Environmental Pollution*, 208: 803–810. https://doi.org/10.1016/j.envpol.2015.11.002

**Han, F., Wang, Y., Li, J., Lyu, B., Liu, J., Zhang, J., Zhao, Y. & Wu, Y.** 2023. Occurrences of legacy and emerging per- and polyfluoroalkyl substances in human milk in China: Results of the third National Human Milk Survey (2017–2020). *Journal of Hazardous Materials*, 443: 130163. https://doi.org/10.1016/j.jhazmat.2022.130163

**Hardell, E., Carlberg, M., Nordström, M. & van Bavel, B.** 2010. Time trends of persistent organic pollutants in Sweden during 1993–2007 and relation to age, gender, body mass index, breast-feeding and parity. *Science of the Total Environment*, 408(20): 4412–4419. https://doi.org/10.1016/j.scitotenv.2010.06.029

**Health Canada.** 2021. *Sixth report on human biomonitoring of environmental chemicals in Canada. Government of Canada.* https://www.canada.ca/content/dam/hc-sc/documents/services/environmental-workplace-health/reports-publications/environmental-contaminants/sixth-report-human-biomonitoring/pub1-eng.pdf

**Ingelido, A.M., Ballard, T., Dellatte, E., di Domenico, A., Ferri, F., Fulgenzi, A.R., Herrmann, T. *et al.*** 2007. Polychlorinated biphenyls (PCBs) and polybrominated diphenyl

ethers (PBDEs) in milk from Italian women living in Rome and Venice. *Chemosphere*, 67(9): S301–S306. https://doi.org/10.1016/j.Chemosphere.2006.05.111

**IPCS (International Programme on Chemical Safety) & WHO.** 2009. *Assessment of combined exposures to multiple chemicals: report of a WHO/IPCS international workshop on aggregate/cumulative risk assessment.* Geneva, Switzerland, WHO. https://www.who.int/publications/i/item/9789241563833

**Iribarne-Durán, L.M., Peinado, F.M., Freire, C., Castillero-Rosales, I., Artacho-Cordón, F. & Olea, N.** 2022. Concentrations of bisphenols, parabens, and benzophenones in human breast milk: A systematic review and meta-analysis. *Science of the Total Environment*, 806: 150437. https://doi.org/10.1016/j.scitotenv.2021.150437

**Jardim, A.N.O., Brito, A.P., van Donkersgoed, G., Boon, P.E. & Caldas, E.D.** 2018. Dietary cumulative acute risk assessment of organophosphorus, carbamates and pyrethroids insecticides for the Brazilian population. *Food and Chemical Toxicology*, 112: 108–117. https://doi.org/10.1016/j.fct.2017.12.010

**Jiang, V.S., Calafat, A.M., Williams, P.L., Chavarro, J.E., Ford, J.B., Souter, I., Hauser, R. & Mínguez-Alarcón, L.** 2023. Temporal trends in urinary concentrations of phenols, phthalate metabolites and phthalate replacements between 2000 and 2017 in Boston, MA. *Science of the Total Environment*, 898: 165353. https://doi.org/10.1016/j.scitotenv.2023.165353

**Johansson, J.H., Berger, U., Vestergren, R., Cousins, I.T., Bignert, A., Glynn, A. & Darnerud, P.O.** 2014. Temporal trends (1999–2010) of perfluoroalkyl acids in commonly consumed food items. *Environmental Pollution*, 188: 102–108. https://doi.org/10.1016/j.envpol.2014.01.026

**Kakimoto, K., Akutsu, K., Konishi, Y. & Tanaka, Y.** 2008. Time trend of hexabromocyclododecane in the breast milk of Japanese women. *Chemosphere*, 71(6): 1110–1114. https://doi.org/10.1016/j.Chemosphere.2007.10.035

**Kim, S-K., Kim, K-S. & Sang, H.H.** 2016. Overview on relative importance of house dust ingestion in human exposure to polybrominated diphenyl ethers (PBDEs): International comparison and Korea as a case. *Science of the Total Environment*, 571: 82–91. https://doi.org/10.1016/j.scitotenv.2016.07.068

**Kim, K., Shin, H.M., Busgang, S.A., Barr, D.B., Panuwet, P., Schmidt, R.J., Hertz-Picciotto, I. & Bennett, D.H.** 2021. Temporal trends of phenol, paraben, and triclocarban exposure in California pregnant women during 2007–2014. *Environmental Science & Technology*, 55(16): 11155–11165. https://doi.org/10.1021/acs.est.1c01564

**Kirby, M.F., Allen, Y.T., Dyer, R.A., Feist, S.W., Katsiadaki, I., Matthiessen, P., Scott, A.P. et al. 2004.** Surveys of plasma vitellogenin and intersex in male flounder (*Platichthys flesus*) as measures of endocrine disruption by estrogenic contamination in United Kingdom estuaries: Temporal trends, 1996 to 2001. *Environmental Toxicology and Chemistry*, 23(3): 748–758. https://doi.org/10.1897/03-166

**Koch, H.M., Kolossa-Gehring, M., Schröter-Kermani, C., Angerer, J. & Brüning, T.** 2012. Bisphenol A in 24 h urine and plasma samples of the German Environmental Specimen Bank from 1995 to 2009: A retrospective exposure evaluation. *Journal of Exposure Science & Environmental Epidemiology*, 22(6): 610–616. https://doi.org/10.1038/jes.2012.39

**Koch, H.M., Rüther, M., Schütze, A., Conrad, A., Pälmke, C., Apel, P., Brüning, T. & Kolossa-Gehring, M.** 2017. Phthalate metabolites in 24-h urine samples of the German Environmental Specimen Bank (ESB) from 1988 to 2015 and a comparison with US NHANES data from 1999 to 2012. *International Journal of Hygiene and Environmental Health*, 220(2, Part A): 130–141. https://doi.org/10.1016/j.ijheh.2016.11.003

**La Merrill, M.A., Vandenberg, L.N., Smith, M.T., Goodson, W., Browne, P., Patisaul, H.B., Guyton, K.Z. *et al.*** 2020. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. *Nature Reviews Endocrinology*, 16(1): 45–57. https://doi.org/10.1038/s41574-019-0273-8

**Larsen, B.R., Turriobaldassarri, L., Nilsson, T., Iacovella, N., Didomenico, A., Montagna, M. & Facchetti, S.** 1994. Toxic PCB congeners and organochlorine pesticides in Italian human milk. *Ecotoxicology and Environmental Safety*, 28(1): 1–13. https://doi.org/10.1006/eesa.1994.1029

**Li, C.L., Zhao, Z.H., Lei, B.L., An, J., Zhang, X.Y. & Yu, Y.X.** 2015. Polybrominated diphenyl ethers in the air and comparison of the daily intake and uptake through inhalation by Shanghai residents with those through other matrices and routes. *Environmental Science and Pollution Research*, 22(3): 1750–1759. https://doi.org/10.1007/s11356-014-3264-2

**Li, M.M., Wang, R., Su, C., Li, J.W. & Wu, Z.Y.** 2022. Temporal Trends of Exposure to Organochlorine Pesticides in the United States: A Population Study from 2005 to 2016. *International Journal of Environmental Research and Public Health*, 19(7): 3862. https://doi.org/10.3390/ijerph19073862

**Li, R., Zhan, W., Ren, J., Zhang, F., Huang, X. & Ma, Y.** 2023. Temporal trends in risk of bisphenol A, benzophenone-3 and triclosan exposure among U.S. children and adolescents aged 6–19 years: Findings from the National Health and Nutrition Examination Survey 2005–2016. *Environmental Research*, 216: 114474. https://doi.org/10.1016/j.envres.2022.114474

**Lignell, S., Aune, M., Darnerud, P.O., Cnattingius, S. & Glynn, A.** 2009. Persistent organochlorine and organobromine compounds in mother's milk from Sweden 1996–2006: Compound-specific temporal trends. *Environmental Research*, 109(6): 760–767. https://doi.org/10.1016/j.envres.2009.04.011

**Linderholm, L., Biague, A., Månsson, F., Norrgren, H., Bergman, Å. & Jakobsson, K.** 2010. Human exposure to persistent organic pollutants in West Africa — A temporal trend study from Guinea-Bissau. *Environment International*, 36(7): 675–682. https://doi.org/10.1016/j.envint.2010.04.020

**Link, B., Gabrio, T., Mann, V., Schilling, B., Maisner, V., König, M., Flicker-Klein, A., Zöllner, I. & Fischer, G.** 2012. Polybrominated diphenyl ethers (PBDE) in blood of children in Baden-Württemberg between 2002/03 and 2008/09. *International Journal of Hygiene and Environmental Health*, 215(2): 224–228. https://doi.org/10.1016/j.ijheh.2011.10.018

**Lo, S-L., Wang, R-D., Chen, Y-J., Hsu, Y-C., Luo, Y-S. & Wang, G-S.** 2023. Human health risk assessment from exposure to multiple sources of Hexabromocyclododecanes (HBCDs) in Taiwan. *Sustainable Environment Research*, 33(1): 10. https://doi.org/10.1186/s42834-023-00172-z

**Long, M., Wielsøe, M. & Bonefeld-Jørgensen, E.C.** 2021. Time Trend of Persistent Organic Pollutants and Metals in Greenlandic Inuit during 1994–2015. *International Journal of Environmental Research and Public Health*, 18(5): 2774. https://doi.org/10.3390/ijerph18052774

**Lu, D., Lin, Y., Feng, C., Wang, D., She, J., Shen, H., Wang, G. & Zhou, Z.** 2015. Levels of polychlorinated dibenzo-p-dioxins/furans (PCDD/Fs) and dioxin-like polychlorinated biphenyls (DL-PCBs) in breast milk in Shanghai, China: A temporal upward trend. *Chemosphere*, 137: 14–24. https://doi.org/10.1016/j.Chemosphere.2015.04.043

**Lupton, S.J. & Hakk, H.** 2017. Polybrominated diphenyl ethers (PBDEs) in US meat and poultry: 2012–13 levels, trends and estimated consumer exposures. *Food Additives & Contaminants: Part A*, 34(9): 1584–1595. https://doi.org/10.1080/19440049.2017.1340675

**Lyu, Z., Harada, K.H., Kim, S., Fujitani, T., Cao, Y., Hitomi, T., Fujii, Y., Kho, Y. & Choi, K.** 2022. Exposure to phthalate esters in Japanese females in Kyoto, Japan from 1993 to 2016: Temporal trends and associated health risks. *Environment International*, 165: 107288. https://doi.org/10.1016/j.envint.2022.107288

**Lyu, Z., Harada, K.H., Kim, S., Fujitani, T., Hitomi, T., Pan, R., Park, N., Fujii, Y., Kho, Y. & Choi, K.** 2023. Temporal trends in bisphenol exposures and associated health risk among Japanese women living in the Kyoto area from 1993 to 2016. *Chemosphere*, 316: 137867. https://doi.org/10.1016/j.Chemosphere.2023.137867

**Ma, Y., Li, P., Jin, J., Wang, Y. & Wang, Q.** 2017. Current halogenated flame retardant concentrations in serum from residents of Shandong Province, China, and temporal changes in the concentrations. *Environmental Research*, 155: 116–122. https://doi.org/10.1016/j.envres.2017.02.010

**Ma, Y., Stubbings, W.A., Abdallah, M.A-E., Cline-Cole, R. & Harrad, S.** 2023. Temporal trends in concentrations of brominated flame retardants in UK foodstuffs suggest active impacts of global phase-out of PBDEs and HBCDD. *Science of the Total Environment*, 863: 160956. https://doi.org/10.1016/j.scitotenv.2022.160956

**Malisch, R., Kypke, K., Dambacher, B., Hardebusche, B., Lippold, R., van Leeuwen, F.X.R., Moy, G. & Tritscher, A.** 2023a. WHO-and UNEP-coordinated exposure studies 2000–2019: Findings of organochlorine pesticides and industrial chemicals. In: R. Malisch, P. Fürst & K. Šebková, eds. *Persisent Organic Pollutants in Human Milk*, pp. 249–298. Cham, Switzerland, Springer.

**Malisch, R., Schächtele, A., van Leeuwen, F.X.R., Moy, G., Tritscher, A., Šebková, K., Klánová, J. & Kalina, J.** 2023b. Time trends in human milk derived from WHO-and UNEP-Coordinated exposure studies, Chapter 1: Polychlorinated Biphenyls, Polychlorinated Dibenzo-p-Dioxins and Polychlorinated Dibenzofurans. In: R. Malisch, P. Fürst & K. Šebková, eds. Persisent Organic Pollutants in Human Milk, pp. 417–484. Cham, Switzerland, Springer.

**Malisch, R., Hardebusche, B., Lippold, R., van Leeuwen, F.X.R., Moy, G., Tritscher, A., Šebková, K., Klánová, J. & Kalina, J.** 2023c. Time trends in human milk derived from WHO-and UNEP-Coordinated exposure studies, Chapter 2: DDT, beta-HCH and HCB. In: R. Malisch, P. Fürst & K. Šebková, eds. *Persisent Organic Pollutants in Human Milk*, pp. 485–542. Cham, Switzerland, Springer.

**Malisch, R., Fürst, P., Šebková, K., Sapunova, D. & Kalina, J.** 2023d. Time trends in human milk derived from WHO-and UNEP-Coordinated exposure studies, Chapter 3: Perfluoroalkyl substances (PFAS). In: R. Malisch, P. Fürst & K. Šebková, eds. *Persisent Organic Pollutants in Human Milk*, pp. 543–600. Cham, Switzerland, Springer.

**Malisch, R., Malisch, K., van Leeuwen, F.X.R., Moy, G., Tritscher, A., Witt, A. & Alvarez, J.** 2023e. Overview of WHO- and UNEP-coordinated human milk studies and their link to the Stockholm Convention on persistent organic pollutants. In: R. Malisch, P. Fürst & K. Šebková, eds. *Persisent Organic Pollutants in Human Milk*, pp. 29–62. Cham, Switzerland, Springer.

**Meng, T., Cheng, J., Tang, Z., Yin, H. & Zhang, M.** 2021. Global distribution and trends of polybrominated diphenyl ethers in human blood and breast milk: A quantitative meta-analysis of studies published in the period 2000–2019. Journal of Environmental Management, 280: 111696. https://doi.org/10.1016/j.jenvman.2020.111696

**Moos, R.K., Koch, H.M., Angerer, J., Apel, P., Schröter-Kermani, C., Brüning, T. & Kolossa-Gehring, M.** 2015. Parabens in 24h urine samples of the German Environmental Specimen Bank from 1995 to 2012. *International Journal of Hygiene and Environmental Health*, 218(7): 666–674. https://doi.org/10.1016/j.ijheh.2015.07.005

**Morthorst, J.E., Mathiesen, K.K., Holbech, H., Pedersen, K.L. & Bjerregaard, P.** 2018. Vitellogenin concentrations in feral Danish brown trout have decreased: An effect of improved sewage treatment in rural areas? *Environmental Toxicology and Chemistry*, 37(3): 839–845. https://doi.org/10.1002/etc.4016

**Mustieles, V., Balogh, R.K., Axelstad, M., Montazeri, P., Márquez, S., Vrijheid, M., Draskau, M.K. *et al.*** 2023. Benzophenone-3: Comprehensive review of the toxicological and human evidence with meta-analysis of human biomonitoring studies. *Environment International*, 173: 107739. https://doi.org/10.1016/j.envint.2023.107739

**NIEHS (National institute of Environmental Health Sciences).** 2023. Endocrine disruptors and your health. Fact sheet. NIEHS. https://www.niehs.nih.gov/sites/default/files/health/materials/endocrine_disruptors_508.pdf

**Nøst, T.H., Vestergren, R., Berg, V., Nieboer, E., Odland, J.Ø. & Sandanger, T.M.** 2014. 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. *Environment International*, 67: 43–53. https://doi.org/10.1016/j.envint.2014.02.011

**Nyberg, E., Awad, R., Bignert, A., Ek, C., Sallsten, G. & Benskin, J.P.** 2018. Inter-individual, inter-city, and temporal trends of per- and polyfluoroalkyl substances in human milk from Swedish mothers between 1972 and 2016. Environmental Science-Processes & Impacts, 20(8): 1136–1147. https://doi.org/10.1039/c8em00174j

**O'Driscoll, K., Robinson, J., Chiang, W.S., Chen, Y.Y., Kao, R.C. & Doherty, R.** 2016. The environmental fate of polybrominated diphenyl ethers (PBDEs) in western Taiwan and coastal waters: evaluation with a fugacity-based model. *Environmental Science and Pollution Research*, 23(13): 13222–13234. https://doi.org/10.1007/s11356-016-6428-4

**Pearson, A., Gibbs, M., Lau, K., Edmonds, J., Alexander, D. & Nicolas, J.** 2018. *2016 New Zealand Total Diet Study.* Wellington, New Zealand, Ministry for Primary Industries. https://www.mpi.govt.nz/dmsdocument/43177-2016-NZ-Total-Diet-Study-with-Appendices-report-

**Pirard, C. & Charlier, C.** 2022. Urinary levels of parabens, phthalate metabolites, bisphenol A and plasticizer alternatives in a Belgian population: Time trend or impact of an awareness campaign? *Environmental Research*, 214: 113852. https://doi.org/10.1016/j.envres.2022.113852

**Pollock, T., Karthikeyan, S., Walker, M., Werry, K. & St-Amand, A.** 2021. Trends in environmental chemical concentrations in the Canadian population: Biomonitoring data from the Canadian Health Measures Survey 2007–2017. *Environment International*, 155: 106678. https://doi.org/10.1016/j.envint.2021.106678

**Qu, J., Xia, W., Qian, X., Wu, Y., Li, J., Wen, S. & Xu, S.** 2022. Geographic distribution and time trend of human exposure of Di(2-ethylhexyl) phthalate among different age groups based on global biomonitoring data. *Chemosphere*, 287: 132115. https://doi.org/10.1016/j.Chemosphere.2021.132115

**Rebryk, A., Koschorreck, J. & Haglund, P.** 2023. Temporal trends of lipophilic organic contaminants in blue mussel (1994–2017) and eelpout (1994–2017) from the southern Baltic Sea. *Science of the Total Environment*, 897: 166282. https://doi.org/10.1016/j.scitotenv.2023.166282

**Ringbeck, B., Weber, T., Bury, D., Kasper-Sonnenberg, M., Pälmke, C., Brüning, T., Koch, H.M. & Kolossa-Gehring, M.** 2022a. Nonylphenol (NP) exposure in Germany between 1991 and 2021: Urinary biomarker analyses in the German Environmental Specimen Bank (ESB). *International Journal of Hygiene and Environmental Health*, 245: 114010. https://doi.org/10.1016/j.ijheh.2022.114010

**Ringbeck, B., Bury, D., Ikeda-Araki, A., Ait Bamai, Y., Ketema, R.M., Miyashita, C., Brüning, T., Kishi, R. & Koch, H.M.** 2022b. Nonylphenol exposure in 7-year-old Japanese children between 2012 and 2017– Estimation of daily intakes based on novel urinary metabolites. *Environment International*, 161: 107145. https://doi.org/10.1016/j.envint.2022.107145

**Rodriguez Martin, L., Gilles, L., Helte, E., Åkesson, A., Tägt, J., Covaci, A., Sakhi, A.K. *et al.*** 2023. Time Patterns in Internal Human Exposure Data to Bisphenols, Phthalates, DINCH, Organophosphate Flame Retardants, Cadmium and Polyaromatic Hydrocarbons in Europe. *Toxics*, 11(10): 819. https://doi.org/10.3390/toxics11100819

**Ryan, J.J. & Rawn, D.F.K.** 2014. The brominated flame retardants, PBDEs and HBCD, in Canadian human milk samples collected from 1992 to 2005; concentrations and trends. *Environment International*, 70: 1–8. https://doi.org/10.1016/j.envint.2014.04.020

**Schächtele, A., Malisch, R., Hardebusche, B., van Leeuwen, F.X.R., Moy, G., Tritscher, A., van Duursen, M. *et al.*** 2023. WHO-and UNEP-coordinated exposure studies 2000–2019: Findings of polybrominated substances (PBDE, HBCDD, PBB 153, PBDD/PBDF). In: R. Malisch, P. Fürst & K. Šebková, eds. *Persisent Organic Pollutants in Human Milk*, pp. 299–342. Cham, Switzerland, Springer.

**Schmid, P., Gujer, E., Zennegg, M. & Studer, C.** 2003. Temporal and local trends of PCDD/F levels in cow's milk in Switzerland. *Chemosphere*, 53(2): 129–136. https://doi.org/10.1016/S0045-6535(03)00439-9

**Schuhmacher, M., Kiviranta, H., Ruokojärvi, P., Nadal, M. & Domingo, J.L.** 2013. Levels of PCDD/Fs, PCBs and PBDEs in breast milk of women living in the vicinity of a hazardous waste incinerator: Assessment of the temporal trend. *Chemosphere*, 93(8): 1533–1540. https://doi.org/10.1016/j.Chemosphere.2013.07.071

**Schultes, L., Sandblom, O., Broeg, K., Bignert, A. & Benskin, J.P.** 2020. Temporal trends (1981–2013) of per- and polyfluoroalkyl substances and total fluorine in Baltic cod (*Gadus morhua*). *Environmental Toxicology and Chemistry*, 39(2): 300–309. https://doi.org/10.1002/etc.4615

**Shu, H., Jönsson, B.A.G., Gennings, C., Svensson, Å., Nånberg, E., Lindh, C.H., Knutz, M., Takaro, T.K. & Bornehag, C-G.** 2018. Temporal trends of phthalate exposures during 2007–2010 in Swedish pregnant women. *Journal of Exposure Science & Environmental Epidemiology*, 28(5): 437–447. https://doi.org/10.1038/s41370-018-0020-6

**Sun, S-J., Kayama, F., Zhao, J-H., Ge, J., Yang, Y-X., Fukatsu, H., Iida, T., Terada, M. & Liu, D-W.** 2011. Longitudinal increases in PCDD/F and dl-PCB concentrations in human milk in northern China. *Chemosphere*, 85(3): 448–453. https://doi.org/10.1016/j.Chemosphere.2011.07.073

**Sundström, M., Ehresman, D.J., Bignert, A., Butenhoff, J.L., Olsen, G.W., Chang, S-C. & Bergman, Å.** 2011. A temporal trend study (1972–2008) of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in pooled human milk samples from Stockholm, Sweden. *Environment International*, 37(1): 178–183. https://doi.org/10.1016/j.envint.2010.08.014

**Tarkowski, S. & Yrjänheikki, E.** 1989. WHO coordinated intercountry studies on levels of PCDDs and PCDFs in human milk. *Chemosphere*, 19(1): 995–1000. https://doi.org/10.1016/0045-6535(89)90447-5

**Thépaut, E., Dirven, H.A.A.M., Haug, L.S., Lindeman, B., Poothong, S., Andreassen, M., Hjertholm, H. & Husøy, T.** 2021. Per- and polyfluoroalkyl substances in serum and associations with food consumption and use of personal care products in the Norwegian biomonitoring study from the EU project EuroMix. *Environmental Research*, 195: 110795. https://doi.org/10.1016/j.envres.2021.110795

**Thomas, A., Toms, L-M.L., Harden, F.A., Hobson, P., White, N.M., Mengersen, K.L. & Mueller, J.F.** 2017. Concentrations of organochlorine pesticides in pooled human serum by age and gender. *Environmental Research*, 154: 10–18. https://doi.org/10.1016/j.envres.2016.12.009

**Tirsina, A., Sircu, R., Pinzaru, I. & Bahnarel, I.** 2017. Changes over time in persistent organic pollutants (POP) concentrations in human milk in the Republic of Moldova. *Toxicological & Environmental Chemistry*, 99(5–6): 1007–1019. https://doi.org/10.1080/02772248.2017.1287469

**Toms, L-M.L., Guerra, P., Eljarrat, E., Barceló, D., Harden, F.A., Hobson, P., Sjodin, A., Ryan, E. & Mueller, J.F.** 2012. Brominated flame retardants in the Australian population: 1993–2009. *Chemosphere*, 89(4): 398–403. https://doi.org/10.1016/j.Chemosphere.2012.05.053

**Toms, L-M.L., Sjödin, A., Hobson, P., Harden, F.A., Aylward, L.L. & Mueller, J.F.** 2018. Temporal trends in serum polybrominated diphenyl ether concentrations in the Australian population, 2002–2013. *Environment International*, 121: 357–364. https://doi.org/10.1016/j.envint.2018.09.014

**Toms, L-M.L., Thompson, J., Rotander, A., Hobson, P., Calafat, A.M., Kato, K., Ye, X., Broomhall, S., Harden, F. & Mueller, J.F.** 2014. Decline in perfluorooctane sulfonate and perfluorooctanoate serum concentrations in an Australian population from 2002 to 2011. *Environment International*, 71: 74–80. https://doi.org/10.1016/j.envint.2014.05.019

**Tranfo, G., Caporossi, L., Pigini, D., Capanna, S., Papaleo, B. & Paci, E.** 2018. Temporal Trends of Urinary Phthalate Concentrations in Two Populations: Effects of REACH Authorization after Five Years. *International Journal of Environmental Research and Public Health*, 15(9): 1950. https://doi.org/10.3390/ijerph15091950

**Tsutsumi, T., Matsuda, R., Yanagi, T., Iizuka, S., Isagawa, S., Takatsuki, S., Watanabe, T., Teshima, R. & Akiyama, H.** 2018. Dietary intake of dioxins in Japan in 2016 with time trends since 1998. *Food Additives & Contaminants: Part A*, 35(8): 1553–1564. https://doi.org/10.1080/19440049.2018.1469052

**UNEP (United Nations Environment Programme).** 2017. Endocrine disrupting chemical - chemical factsheets. In: *UNEP*. [Cited 16 May 2024]. https://wedocs.unep.org/bitstream/handle/20.500.11822/25635/edc_report2_factsheet.pdf?sequence=1&isAllowed=y

**UNEP.** 2019. *Stockholm Convention on persistent organic pollutants (POPs).* Nairobi, UNEP. https://www.pops.int/TheConvention/Overview/TextoftheConvention/tabid/2232/Default.aspx

**Van den Berg, M., Birnbaum, L.S., Denison, M., De Vito, M., Farland, W., Feeley, M., Fiedler, H. *et al.*** 2006. The 2005 World Health Organization reevaluation of human and mammalian toxic equivalency factors for dioxins and dioxin-like compounds. *Toxicological Sciences*, 93(2): 223–241. https://doi.org/10.1093/toxsci/kfl055

**van der Meer, T.P., Chung, M.K., van Faassen, M., Makris, K.C., van Beek, A.P., Kema, I.P., Wolffenbuttel, B.H.R., van Vliet-Ostaptchouk, J.V. & Patel, C.J.** 2021. Temporal exposure and consistency of endocrine disrupting chemicals in a longitudinal study of individuals with impaired fasting glucose. *Environmental Research*, 197: 110901. https://doi.org/10.1016/j.envres.2021.110901

**van der Schyff, V., Kalina, J., Abballe, A., Iamiceli, A.L., Govarts, E. & Melymuk, L.** 2023. Has Regulatory Action Reduced Human Exposure to Flame Retardants? *Environmental Science & Technology*, 57(48): 19106–19124. https://doi.org/10.1021/acs.est.3c02896

**Wemken, N., Drage, D.S., Cellarius, C., Cleere, K., Morrison, J.J., Daly, S., Abdallah, M.A-E., Tlustos, C., Harrad, S. & Coggins, M.A.** 2020. Emerging and legacy brominated flame retardants in the breast milk of first time Irish mothers suggest positive response to restrictions on use of HBCDD and Penta- and Octa-BDE formulations. *Environmental Research*, 180: 108805. https://doi.org/10.1016/j.envres.2019.108805

**Wu, Y., Song, Z., Little, J.C., Zhong, M., Li, H. & Xu, Y.** 2021. An integrated exposure and pharmacokinetic modeling framework for assessing population-scale risks of phthalates and their substitutes. *Environment International*, 156: 106748. https://doi.org/10.1016/j.envint.2021.106748

**Xu, S.S., Hansen, S., Rautio, A., Järvelin, M.R., Abass, K., Rysä, J., Palaniswamy, S. *et al.*** 2022. Monitoring temporal trends of dioxins, organochlorine pesticides and chlorinated paraffins in pooled serum samples collected from Northern Norwegian women: The MISA cohort study. *Environmental Research*, 204: 111980. https://doi.org/10.1016/j.envres.2021.111980

**Yu, Y., Li, C., Zhang, X., Zhang, X., Pang, Y., Zhang, S. & Fu, J.** 2012. Route-specific daily uptake of organochlorine pesticides in food, dust, and air by Shanghai residents, China. *Environment International*, 50: 31–37. https://doi.org/10.1016/j.envint.2012.09.007

**Zhang, X., Fu, M., Li, K., Cheng, X., Zhang, X., Shen, X., Lei, B. & Yu, Y.** 2024. Bisphenol chemicals in colostrum from Shanghai, China during 2006–2019: Concentration, temporal variation, and potential influence on birth parameters. *Food and Chemical Toxicology,* 185: 114485. https://doi.org/10.1016/j.fct.2024.114485

**Zhao, X. & Shi, Z.** 2021. Legacy brominated flame retardants in human milk from the general population in Beijing, China: Biomonitoring, temporal trends from 2011 to 2018, and nursing infant's exposure assessment. *Chemosphere*, 285: 131533. https://doi.org/10.1016/j.Chemosphere.2021.131533

## REFERENCES TABLE 1

**Bergman, A., Heindel, J.J., Jobling, S., Kidd, K.A. & Zoeller, R.T.** 2013. *State of the Science of Endocrine Disrupting Chemicals – 2012*. WHO, Geneva. https://www.who.int/publications/i/item/9789241505031

**Endocrine Society.** 2022. Hormone and endocrine disrupting chemicals. What you need to know. In. *Endocrine Society*. [Cited 16 May 2024]. https://www.endocrine.org/-/media/endocrine/files/patient-engagement/hormones-and-series/hormones_and_edcs_what_you_need_to_know.pdf

**Demeneix, B. & Slama, R.** 2019. *Endocrine disruptors: from scientific evidence to human health protection.* Brussels, European Parliament. https://www.europarl.europa.eu/RegData/etudes/STUD/2019/608866/IPOL_STU(2019)608866_EN.pdf

**La Merrill, M.A., Vandenberg, L.N., Smith, M.T., Goodson, W., Browne, P., Patisaul, H.B., Guyton, K.Z. *et al.*** 2020. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. *Nature Reviews Endocrinology*, 16(1): 45–57. https://doi.org/10.1038/s41574-019-0273-8

**NIEHS.** 2023. *Endocrine disruptors and your health.* Fact sheet. NIEHS. https://www.niehs.nih.gov/sites/default/files/health/materials/endocrine_disruptors_508.pdf

**UNEP.** 2017. Endocrine disrupting chemical - chemical factsheets. In: *UNEP*. [Cited 16 May 2024]. https://wedocs.unep.org/bitstream/handle/20.500.11822/25635/edc_report2_factsheet.pdf?sequence=1&isAllowed=y

## REFERENCES TABLE 5

**Malisch, R., Kypke, K., Dambacher, B., Hardebusche, B., Lippold, R., van Leeuwen, F.X.R., Moy, G. & Tritscher, A.** 2023a. WHO-and UNEP-coordinated exposure studies 2000–2019: Findings of organochlorine pesticides and industrial chemicals. In: R. Malisch, P. Fürst & K. Šebková, eds. *Persisent Organic Pollutants in Human Milk*, pp. 249–298. Cham, Switzerland, Springer.

**Malisch, R., Schächtele, A., van Leeuwen, F.X.R., Moy, G., Tritscher, A., Šebková, K., Klánová, J. & Kalina, J.** 2023b. Time trends in human milk derived from WHO-and UNEP-Coordinated exposure studies, Chapter 1: Polychlorinated Biphenyls, Polychlorinated Dibenzo-p-Dioxins and Polychlorinated Dibenzofurans. In: R. Malisch, P. Fürst & K. Šebková, eds. *Persisent Organic Pollutants in Human Milk*, pp. 417–484. Cham, Switzerland, Springer.

**Malisch, R., Hardebusche, B., Lippold, R., van Leeuwen, F.X.R., Moy, G., Tritscher, A., Šebková, K., Klánová, J. & Kalina, J.** 2023c. Time trends in human milk derived from WHO-and UNEP-Coordinated exposure studies, Chapter 2: DDT, beta-HCH and HCB. In: R. Malisch, P. Fürst & K. Šebková, eds. *Persisent Organic Pollutants in Human Milk*, pp. 485–542. Cham, Switzerland, Springer.

**Malisch, R., Fürst, P., Šebková, K., Sapunova, D. & Kalina, J.** 2023d. Time trends in human milk derived from WHO-and UNEP-Coordinated exposure studies, Chapter 3: Perfluoroalkyl substances (PFAS). In: R. Malisch, P. Fürst & K. Šebková, eds. *Persisent Organic Pollutants in Human Milk*, pp. 543–600. Cham, Switzerland, Springer.

**Schächtele, A., Malisch, R., Hardebusche, B., van Leeuwen, F.X.R., Moy, G., Tritscher, A., van Duursen, M. *et al.*** 2023. WHO-and UNEP-coordinated exposure studies 2000–2019: Findings of polybrominated substances (PBDE, HBCDD, PBB 153, PBDD/PBDF). In: R. Malisch, P. Fürst & K. Šebková, eds. *Persisent Organic Pollutants in Human Milk*, pp. 299–342. Cham, Switzerland, Springer.

# FOOD SAFETY AND QUALITY SERIES

30. FAO. 2024. *Exposure to endocrine disrupting chemicals – Changes from 2002 to 2024*.
29. FAO. 2024. *Food Safety in a Circular Economy*.
28. FAO & WHO. 2024. *Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption: Meeting report, Rome, 9–13 October 2023*.
27. FAO & WHO. 2024. *FAO/WHO background document on the risk and benefits of fish consumption.*
26. FAO. 2024. *Report of the FAO Technical Meeting on the gut microbiome in food safety chemical risk assessment*. In progress.
25. FAO. 2024. *Risk assessment of 3-monochloropropane-1,2-diol, glycidol, and their fatty acid esters in lipid-based nutrient supplements and ready-to-use therapeutic food*.
24. FAO. 2023. Food safety implications from the use of environmental inhibitors in agrifood systems.
23. FAO and WHO. 2023. *Risk assessment of food allergens. Part 5: Review and establish threshold levels for specific tree nuts (Brazil nut, macadamia nut or Queensland nut, pine nut), soy, celery, lupin, mustard, buckwheat and oats*.
22. FAO and WHO. *The impact of food additives on the gut microbiome and health - A food safety perspective*. In progress.
21. FAO. 2023. *The impact of microplastics on the gut microbiome and health – A food safety perspective*.
20. FAO. 2023. *The impact of veterinary drug residues on the gut microbiome and human health – A food safety perspective*.
19. FAO. 2023. *The impact of pesticide residues on the gut microbiome and human health – A food safety perspective*.
18. FAO. 2022. *Microplastics in food commodities – A food safety review on human exposure through dietary sources*.
17. FAO and WHO. 2024. *Risk assessment of food allergens – Part 4: Establishing exemptions from mandatory declaration for priority food allergens*.
16. FAO and WHO. 2023. *Risk assessment of food allergens – Part 3: Review and establish precautionary labelling in foods of the priority allergens*.
15. FAO and WHO. 2022. *Risk assessment of food allergens. Part 2: Review and*

*establish threshold levels in foods for the priority allergens*.

14. FAO and WHO. 2022. *Risk assessment of food allergens. Part 1: Review and validation of Codex Alimentarius priority allergen list through risk assessment*.
13. FAO and WHO. 2022. *Report of the expert meeting on food safety for seaweed - Current status and future perspectives*.
12. FAO. 2022. *Technical guidance for the implementation of e-notification systems for food control*.
11. FAO and WHO. 2020. *Joint FAO/WHO expert meeting on tropane alkaloids*.
10. FAO. 2020. *FAO guide to ranking food safety risks at the national level*.
9. FAO and WHO. 2020. *Report of the expert meeting on ciguatera poisoning*.
8. FAO. 2020. *Climate change: unpacking the burden on food safety*.
7. FAO and WHO. 2019. *Food control system assessment tool*.
   - > *Introduction and glossary*
   - > *Dimension A – inputs and resources*
   - > *Dimension B - control functions*
   - > *Dimension C - interaction with stakeholders*
   - > *Dimension D - science/knowledge base and continuous improvement*
6. FAO. 2019. *Technical guidance principles of risk-based meat inspection and their application*.

5a. FAO and WHO. 2021. *Technical guidance for the development of the growing area aspects of bivalve mollusc sanitation programmes, second edition*.

5. FAO and WHO. 2018. *Technical guidance for the development of the growing area aspects of bivalve mollusc sanitation programmes*.
4. FAO. 2017. *Food safety risk management: evidence-informed policies and decisions, considering multiple factors*.
3. FAO. 2016. *Enhancing early warning capabilities and capacities for food safety*.
2. FAO and WHO. 2016. *Risk communication applied to food safety, handbook*.
1. FAO. 2016. *Risk based imported food control, manual*.


©FAO/Giulio Napolitano


©FAO/Patrick Morin


©FAO/Kai Wiedenhoefer

# EXPOSURE TO ENDOCRINE DISRUPTING CHEMICALS
## CHANGES FROM 2002 TO 2024

This report, commissioned by the Food and Agriculture Organization of the United Nations (FAO), provides a comprehensive analysis of the evolving landscape of human and food-producing animal exposure to endocrine disrupting chemicals (EDCs) over the past two decades. Focusing on a range of chemicals consistently identified as EDCs, the report examines temporal trends in exposure and links these changes to factors such as regulatory actions, voluntary industry measures, and heightened consumer awareness. Drawing on biomonitoring data, the report offers critical insights into both progress and remaining challenges in reducing EDC exposure globally. This resource offers valuable insights for researchers, policymakers, and stakeholders into the effectiveness of risk management strategies and ongoing challenges posed by EDCs.

AGRIFOOD SYSTEMS AND FOOD SAFETY - ECONOMIC AND SOCIAL DEVELOPMENT
WEBSITE: WWW.FAO.ORG/FOOD-SAFETY
**FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS**
ROME, ITALY

ISBN 978-92-5-139296-6 ISSN 2415-1173
9 789251 392966
CD3005EN/1/11.24