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Review

Persistent organic pollutants in Croatian breast milk: An overview of pollutant levels and infant health risk assessment from 1976 to the present

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ABSTRACT

This review article summarizes our research of persistent organic pollutants (POPs) in human milk from Croatian mothers over the last few decades. Our studies make up the bulk of all POPs research in human milk in Croatia and show a state-of-the art in the research area. The first investigations were made in 1970's. Aim of our review article is to document the comprehensive results over several decades as the best tool to: 1.) contribute to understanding of POPs and their potential health risks, 2.) evaluate effectiveness of legislative bans and restrictions on human exposure to POPs in Croatia, and 3.) to suggest further actions. In our review we discuss: 1.) Human milk between 2011 and 2014 - evaluation of interrelations of organochlorine pesticides (OCP) and polychlorinated biphenyls (PCB) in human milk and their association with the mother's age and parity using artificial intelligence methods; and our yet unpublished research data on health risks for infants assessed through daily PCB and OCP intake. 2.) Time trends of PCB and OCP in human milk between 1976 and 2014. 3.) polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofuran (PCDD/F) in human milk in 2000., and yet unpublished data on PCDD/F and polybrominated diphenyl ethers (PBDE) in 2014.

1. Introduction

Polychlorinated biphenyls (PCB), organochlorine pesticides (OCP), polychlorinated dibenzo-p-dioxins (PCDD) and polychlorinated dibenzofurans (PCDF) are well-known organochlorine compounds and the most persistent and widespread environmental contaminants of the 20th and 21st century (Jones, 2021; van den Berg et al., 2017). PCB and OCP have had intensive and wide commercial applications, while PCDD and PCDF have never been used, being unwanted by-products (Lerche et al., 2002). For more than 50 years, their toxic effects have been evidenced in the top predator species (Jensen, 1972) and other animals and humans, which they owe to their persistence, lipophilicity and related bioaccumulation, toxicity, and long-distance air transport. This is why in 2001, representatives of 92 countries signed the Stockholm Convention on POPs and committed themselves to controlling the release of POPs into the environment. The Convention entered into force in 2004, and today, it is endorsed by 185 countries including Croatia, whose parliament approved it in 2006 (OG-11/2006). Usage of „legacy POPs" (PCB, OCP) was banned or restricted during the 1970s and 1980s in many industrial countries, and levels have declined in primary sources. However, one OCP, which is among the initial POPs listed under the Stockholm Convention, dichlorodiphenyltrichloroethane (DDT), is continuously used for control of malaria and leishmaniosis (Van den Berg et al., 2017). PCB, OCP, and PCDD/PCDF are inherently persistent, their loss in the environment is not complete and they are removed from surface compartments to deeper horizons of soils, water bodies and sediment. At a global level, the oceans are their final sink due to the absence or slow degradation mechanisms through which pollutants enter the food chain through marine organisms living at the bottom. They are transferred from one part of the environment to the other (air -

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surface of water, air - soil, plants; gaseous phase in air - particles in air; water - soil, sediment) and subjected to long-range transport via air masses. In short, PCB, OCP, and PCDD/PCDF are everywhere (even the Arctic and Antarctic), in all parts of abiotic and biotic parts of environment, and such diffuse sources are difficult to control.

PCB, OCP, and PCDD/PCDF accumulate in human tissues which contain fat, and their elimination from the human body is very slow. Relevant matrices for assessing human exposure are adipose tissue, blood, and human milk, but the first two require invasive techniques for biomonitoring, which is why human milk is an ideal matrix to measure POP content in the adipose tissue of lactating mothers (Global Environment Monitoring System (GEMS), UNEP & WHO, 1983; Aerts et al., 2019 and references herein), as it corresponds to that in the plasma, serum lipids, and adipose tissue and can be used as an indicator of overall exposure to POPs in women and breastfeeding children (Van den Berg et al., 2016). Since 1950, numerous studies on the levels in human milk in the world have been published (Global Environment Monitoring System GEMS, UNEP & WHO, Uppsala, 1983; Fång et al., 2015 and references herein). Studies show that maternal pregnancy overweightness and obesity (BMI $\geq$25.0 kg/m^2) are associated with higher PCB levels in human milk (Ellsworth et al., 2020; Tang-Peronard et al., 2014) while milk fat content does not change as a consequence of maternal weight status. In addition, there are increased levels of placental PCB in women with obesity (Jeong et al., 2018). The elevated PCB in milk during a transition period of colostrum to mature milk may reflect increased adipose stores of PCB (Jeong et al., 2018).

Levels of organic pollutants in milk may depend on several factors, e. g. parity and duration of lactation (during lactation pollutants secretes from the mother's body); maternal age (as it is assumed that amount of pollutants in the body increase with age) (Polder et al., 2009; Hassine et al., 2012), and diet (food of animal origin) (Engeset et al., 2015 and references therein), but this dependence has not been observed in all studies (Ingelido et al., 2007), and the subject is still somewhat controversial. Thus, Ingelido et al. (2007) found no correlation between levels of organochlorine compounds in milk and maternal fish consumption. Nevertheless, some studies have proven the opposite, Aerts et al. (2019) published results from the 6th World Health Organization (WHO) Coordinated Survey on POPs in human milk in Belgium and found that inclusion of fatty fish into the diet, particularly predatory fish, was associated with higher levels. They recommended that diet and exposure routes other than diet deserve more attention in future research. Komprda et al. (2019) reported the importance of detailed food questionnaires in biomonitoring studies considering specific food commodities due to the impact of food contamination, while factors such as body weight or age at delivery had no significant impact on concentrations of PCB in breast milk. For example, Hassine et al. (2012) reported an increase of POPs with the age, while Vigh et al. (2013) found the opposite.

Most countries show a temporal downward trend of POPs in human milk (Van den Berg et al., 2016; Gyllenhammar et al., 2021; Mikeš et al., 2012). According to a comprehensive global review on POPs in human milk summarized by Fång et al. (2015), longer time series (through three or four decades) are scarce in research temporal trend studies, and the only two countries with long temporal trend studies are Japan and Sweden. At the same time, some new studies in Asia show high levels POPs in human milk, as found in Pakistan (Naqvi et al., 2019) and in China (Mianyang) (Guo et al., 2021). The human milk samples collected from Taizhou and Lin'a in China (known as a largescale e-waste recycling site in China, and for recycling transformers and capacitors since the late 1980s/early 1990s) showed extraordinarily high PCB levels (363 and 116 ng g^{-1} lipid, respectively (Man et al., 2017).

As a consequence of ban/control of PCB and OCP primary sources, their levels have declined in most countries, however, scientific research does not abate because baseline of POP residues are still in human and animal tissues, including unborn fetuses via placental transfer, newborns via mother's milk, and in all parts of the abiotic environment, as well (Suzuki et al., 2005; Naqvi et al., 2018; Vijaya Bhaskar Reddy et al., 2019).

One of the "new POPs" with similar properties to original "legacy POPs" under Stockholm Convention are polybrominated diphenyl ethers (PBDE) (UNEP/Stockholm Convention). Since the 1970s, PBDEs have widely been used as flame retardants in a variety of textile materials, furniture fillers, and electronic equipment. In comparison with "legacy POPs", the input/decline trend of PBDE is delayed by 20–30 years, because PBDE was manufactured and restricted more recently (Jones, 2021). PBDE concentrations in human milk reached the peak during the period of late 1990s – early 2000s, followed by downward trend in some countries as consequence of Stockholm Convention implementation (Fängström et al., 2008; Ryan and Rawn, 2014). Important exposure source is contact with electronic and other products containing PBDE (Frederiksen et al., 2009), while primary route of human exposure is inhalation/ingestion of contaminated airborne particles and indoor dust (Jin et al., 2019).

This review article summarizes our research of POPs in human milk from Croatian mothers over the last few decade, that has been underway at the Institute for Medical Research and Occupational Health in Zagreb, Croatia (Herceg Romanić and Krauthacker, 2006; Krauthacker et al., 2009; Klinčić et al., 2014, 2016; Šimić et al., 2020; Jovanović et al., 2019, 2021). Our studies make up the bulk of all POP research in human milk in Croatia, and the first investigations about OCP in human milk in Croatia were made around 1970 (Krauthacker et al., 1978; Krauthacker et al., 1980; PhD Thesis of Krauthacker, 1984; Bažulić et al., 1978). The aim of our review article is to document our comprehensive results over several decades as the best tool to evaluate effectiveness of legislative bans and restrictions on human exposure to POPs in Croatia. Our summarized results is a contribution to understanding of POPs and their potential health risks, and show a state-of-the art of POPs monitoring in Croatia. Review could be valuable for policy decision making to protect public health and to suggest further actions. Insight into time trends is important to observe if levels are stabilizing or decreasing, giving base for data in the next decade for estimation of future breast milk levels.

The review includes: 1.) Human milk between 2011 and 2014 - evaluation of interrelations OCP and PCB in human milk and their association with the mother's age and parity using artificial intelligence methods; and our yet unpublished research data on health risks for infants assessed through daily PCB and OCP intake. 2.) Time trends of PCB and OCP in human milk between 1976 and 2014. 3.) PCDD/F in human milk in 2000, and yet unpublished data on PCDD/F and PBDE in 2014.

2. Human milk samples, analyzed compounds, methods, and health risk

2.1. Sampling sites

Sampling sites (Fig. 1.) and number of samples were chosen according to geographical features and small population (amounts to approx. 3.8 million in 2022). Croatia is country located in the southern part of Central Europe and in the northern part of the Mediterranean at Eastern Adriatic coast. The land area is 56,594 km^2, and the coastal sea area is 31,067 km^2. The territory of Croatia extends from the Pannonian Plain through the narrow area of the Dinaric Mountains to the coast of the Adriatic Sea (5835 km long and consists of 1246 islands). Representative sampling sites were chosen in the continental part and at the Adriatic coast. In the continental part, Zagreb was selected, and at the Adriatic coast, Zadar and the island of Krk. Zagreb is the Croatian capital, whose metropolitan area has about one million residents, while Zadar is a central Adriatic seaside town with about 70,000 inhabitants, and island of Krk is the largest and the northernmost island in the Adriatic Sea.

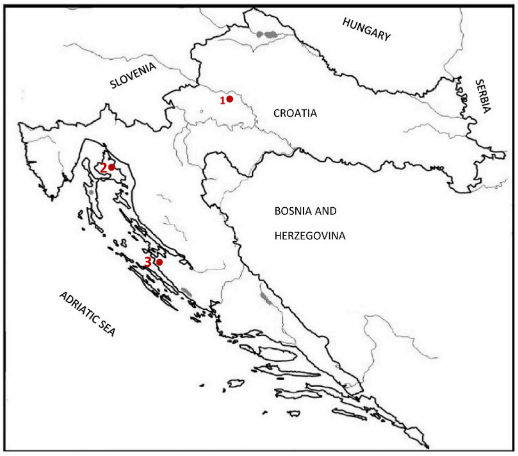

Fig. 1. Sampling locations: 1. Zagreb; 2. Krk; 3. Zadar.

2.2. Analyzed compounds, samples and methods

2.2.1. Analyzed compounds

PCB are synthetic, aromatic, and organic compounds encompassing 209 isomers and homologues (differing in the number and position of chlorine atoms) called congeners. Our research has been focused on: six indicator PCB congeners (IUPAC number: 28, 52, 101, 138, 153, 180), summarily presented as ΣIndPCB, whose selection was based on their dominant presence in technical mixtures, environment, and animal and human tissues; four dioxin-like congeners (IUPAC number: 77, 81, 126, 169) having two pairs and at least two meta chlorine atoms can easily achieve a co-planar configuration similar to dioxins; and other 11 toxicologically relevant congeners to determine them (IUPAC number: 60, 74, 105, 114, 118, 123, 156, 157, 167, 189, 170), summarily presented as ΣToxRelPCB.

The most widely used OCP are 1,1,1-trichloro-2,2-di(4-chlorophenyl)ethane (*p,p'*-DDT), α-, β- and ɣ-hexachlorocyclohexane (α-, β - and ɣ-HCH; the ɣ-isomer is known as lindane), and hexachlorobenzene (HCB). Biotransformation further degrades (*p,p'*-DDT) in its very persistent metabolite 1,1-dichloro-2,2-di(4-chlorophenyl)ethylene (*p,p'*-DDE). Our primary concern have been HCB, α-, β-, and ɣ-HCH (summarily presented as ΣHCHs) and *p,p*-DDT, 1,1-dichloro-2,2-di(4-chlorophenyl)ethane (*p,p*-DDD), and *p,p*-DDE (summarily presented as ΣDDT).

PCDD and PCDF have 210 congeners in total. 17 toxicologically important (2,3,7,8-chlorinated PCDD and PCDF) are analyzed. PBDE encompass 209 congeners divided into 10 congener groups depending on the number of bromine atoms. Tri - to hepta-brominated PBDE congeners (BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, BDE-154, BDE-183) and deca-brominated BDE-209 are analyzed.

2.2.2. Samples and methods

2.2.2.1. Samples. Human milk samples were collected from healthy volunteer mothers from the general population living in Zagreb, Zadar and Krk in Croatia between 1976 and 2014 Croatia (Krauthacker et al., 1978; Krauthacker et al., 1980; PhD Thesis of Krauthacker, 1984; Herceg Romanić and Krauthacker, 2006; Krauthacker et al., 2009; Klinčić et al., 2014; Klinčić et al., 2016; Šimić et al., 2020; Jovanović et al., 2019, 2021). Before providing milk samples, each participant gave their informed consent. All of the studies were approved by the ethics committees before the start of data collection, and all took place in accordance with the ethical standards of the Declaration of Helsinki. Before providing milk samples, the purpose of sampling was explained to each participant and each participant gave their informed consent and filled out a paper-and-pencil questionnaire prepared for sampling needs. The subjects were allowed to withdraw from the studies at any time.

2.2.2.2. Methods. PCB and OCP were analyzed in the Biochemistry and Organic Analytical Chemistry Unit of Institute for Medical Research and Occupational Health, Zagreb, Croatia. The analytical procedure was described in detail in by PhD Thesis of Krauthacker (1984), Herceg Romanić and Krauthacker (2006); Krauthacker et al. (2009), Klinčić et al. (2014), Klinčić et al. (2016) and Šimić et al. (2020).

Interpretation of PCB and OCP results using the artificial intelligence (AI) algorithms implemented via machine learning (ML), were made in collaboration with the Institute of Physics Belgrade, University of Belgrade, Serbia (Jovanović et al., 2019, 2021). Following advanced ML methods were applied: eXtreme Gradient Boosting (XGBoost), SHapley Additive exPlanations (SHAP) attribution method, and SHAP value fuzzy clustering (Jovanović et al., 2021), Guided regularized random forest (GRRF) (Jovanović et al., 2019). For pollutant source apportionment Unmix were applied (Jovanović et al., 2019). Time trends of PCB and OCP in human milk between 1976 and 2014 were done based on data for 10 points: 1976 (27 samples), 1981/82 (50 samples), 1985 (18 samples), 1986/87 (41 samples), 1987/89 (22 samples), 1990/91 (30 samples), 1991/93 (54 samples), 1994/95 (45 samples), 2000 (29 samples), 2014 (150 samples) (Bažulić et al., 1978; Krauthacker et al., 2009; Jovanović et al., 2021).

PCDD/F analyses in human milk were part of 1st (Environmental Health Series No 34, 1989), 2nd (Environmental Health in Europe No. 3, 1996), 3rd (Malisch and van Leeuwen, 2003) and 6th WHO POP surveys (unpublished results). PBDEs were analyzed in the framework of 6th WHO POP survey (unpublished results). 1st, 2nd, 3rd 6th WHO POP survey was carried out in collaboration with Institute for Medical Research and Occupational Health, Zagreb (Biochemistry and Organic Analytical Chemistry Unit).

2.3. Health risk assessment for breastfed infants

In this review, PCB and OCP concentrations used for health risk assessment were the topics of our research of Jovanović et al. (2021) while results on health risks were not published before. PCB and OCP results are disscussed in detail in the next section *3.1.1. PCB and OCP levels*. Details about the sampling were in study of Jovanović et al. (2021), and details about analytical procedure in study of Klinčić et al. (2014).

Estimated daily intake (EDI) of POPs by infant consumption of human milk was assessed based on an average one-year (≈12 months) breastfeeding period. The formula for risk assessment has been adopted from the Risk Assessment Information System (RAIS, 2014), Meconen et al. (2021), and Milićević et al. (2018) and adapted to infant milk consumption, as follows:

$$EDI_{POPs} = \frac{Cmilk \times Cfat \times Ir \times \rho}{Bw}$$

$$\Sigma EDI = \Sigma EDI_{HCH} + \Sigma EDI_{DDT} + \Sigma EDI_{dioxin\ like} + \Sigma EDI_{non-dioxin\ like}$$

where C_{milk} is the concentration of POPs in human milk (ng/g); C_{fat} is the average milk fat content (4.4%); ρ is milk density (1.03 gmL^{-1}); Ir is average milk consumption by infants (660 mL day^{-1}), and Bw is average infant body weight at the age of 1 year (7.43 kg). The sums of each group of POPs (EDIs for HCH, DDT, dioxin-like and non-dioxin-like groups) were calculated separately, as well as the sum of all EDIs.

3. Results and discussion

3.1. PCB and OCP levels and risk assessment between 2011 and 2014

3.1.1. PCB and OCP levels

Human milk samples were collected between 2011 and 2014 from 150 healthy primiparae, secundiparae, and multiparae (having given birth in three separate pregnancies) from Zadar aged between 19 and 45 years (Jovanović et al., 2021; Master thesis of Samardžić, 2021). Descriptive statistics are presented in Table 1. PCB and OCP levels are divided in four groups by mothers' age: 19–24 years (group 1), 25–30 years (group 2), 31–36 years (group 3), and 37 and older (group 4). Beside age groups, PCB and OCP levels are divided into three groups by the number of births (Fig. 2.; Fig. 3.; Fig. 4.).

3.1.1.1. OCP levels. *p,p'*-DDE, *p,p'*-DDT, showed the highest levels and we saw a rise in *p,p'*-DDE, *p,p'*-DDT, HCB, β-HCH, and γ-HCH with the number of births and mother's age, while α-HCH, *p,p'*-DDD showed an opposite trend (Fig. 2.). The *p,p'*-DDT to *p,p'*-DDE ratio has for long been used to identify recent DDT pollution, as ratios higher than 1 indicate recent input (Ballschmiter and Wittlinger, 1991). Yet, even though DDT has not been used in Croatia for about fifty years, this ratio is higher than 1 in 30% of milk samples, which indicates recent exposure to *p,p'*-DDT. The oldest age group shows the lowest difference between the 25th and 75th percentile (both percentiles with ratios below 1) and median *p,p'*-DDT/*p,p'*-DDE ratios are also lower than 1 in all age groups. The most extreme *p,p'*-DDT levels occur in milk samples of the oldest mothers who had two or three childbirths (peaking at 92.6 ng g^{-1} milk fat, Table 1.). The highest *p,p'*-DDT level of 46.7 ng g^{-1} milk fat in age group 1 was recorded in one primipara and is similar to 48.8 ng g^{-1} milk fat found in the sample of another primipara from age group 2, whose *p,p'*-DDE concentration was 9.8 times lower. Other outliers concern samples with lower DDT levels yet also with significantly lower *p,p'*-DDE concentrations, which results in a high *p,p'*-DDT to *p,p'*-DDE ratio reflecting recent exposure to *p,p'*-DDT. The highest p,p'-DDE levels were measured in the milk of mothers in the oldest age group 4 (Fig. 2.), which resulted in a low p,p'-DDT to *p,p'*-DDE ratio (Fig. 3.).

β-HCH is a very persistent isomer and was almost consistently higher than other HCH isomers. HCB is usually an indicator of industrial activity because it occurs as a by-product in the chemical and metallurgical industries described by Mamontova et al. (2017) and Runkel et al. (2021). High levels of some OCP are present in samples of breast milk in areas where there is input into the environment as in Tsygankov et al. (2020).

3.1.1.2. PCB levels. Indicator PCB PCB-138, PCB-153, and PCB-180 levels showed an increase with maternal age, as does PCB-170. The highest PCB-118, PCB-156, and PCB-74 levels were found in age group 4 (Fig. 4.). Judging by median concentrations, the number of births was associated with higher PCB-74, PCB-118, and PCB-170 levels. PCB-74 and PCB-118 levels were higher only in the multiparae, while PCB-170 increased in both secundiparae and multiparae. It is interesting to note the presence of PCB-170, which is an infrequently analyzed di-ortho heptachlorobiphenyl, and in our study levels were comparable to group of indicator PCB. The literature reports little about PCB-170, save for Goa et al. (2021), who reported two times lower PCB-170 than PCB-153 and -138 levels in the colostrum, but twice as high as those of PCB-180. According to one report from Spain (Gómara et al., 2011), the PCB profile in human milk samples was as follows (from highest to lowest): PCB138, PCB-153, PCB-180, and PCB-170.

3.1.1.3. Research of causative occurrence of PCB and OCP in human milk using machine learning. To obtain a more precise insight into the influence on PCB and OCP levels in human milk and their mutual interrelations and associations with mother's age and parity we used machine learning models (Jovanović et al., 2019, 2021). In previous years, the application of artificial intelligence implemented in machine learning (ML), supported by the large availability of high-dimensional data, has had a strong presence in environmental science (Stojić et al., 2019). In a paper by Jovanović et al. (2021), we chose PCB-138 as one of the most prominent indicator PCB for investigating relationships between PCB-138 and other non-dioxin congeners, mother's age, and the number of births, using the advanced machine learning methods eXtreme Gradient Boosting (XGBoost) and SHapley Additive exPlanations (SHAP) attribution method to examine these key parameters. These methods provide insight into pollutant behavior by attributing environmental factor importance, impacts, mutual relations, and interactions. The eXtreme Gradient Boosting regression was employed successfully, with a predicted/observed relative error below 20% and a high correlation coefficient ($r = 0.97$). Our results show significant linear correlation coefficients ($r \geq 0.90$) found between the following pairs of investigated variables: PCB-170-PCB-138; PCB-170-PCB-153; PCB-170-PCB-180; PCB-153-PCB-180 and PCB-153-PCB-138 indicating similar molecular structures and metabolic pathways. The SHAP analyses revealed that PCB-170 and PCB-153 were the most important variables that shaped the PCB-138 behavior patterns in milk samples, suggesting that congeners substituted with chlorine atoms at ortho positions are more prone to bioaccumulation in human milk compared to other PCB. These results explain the presence of PCB-170 in human milk, supporting the importance of PCB-170 in future measurements. Furthermore, PCB-28, PCB-52, PCB-180, PCB-118, PCB-189, PCB-156, as well as *p,p'*-DDE had minor impact on PCB-138 distribution. A fuzzy clustering of the SHAP values gave ten clusters, representing groups of variable interrelations associated with PCB-138. Results imply a similar origin/input of OCP and PCB in the maternal body suggesting that future investigations should be performed on dietary habits and the health burden of POPs in residential and working environments. Indicated by low SHAP values, no significant functional dependencies between PCB-138 patterns and maternal age or parity (Jovanović et al., 2021) were determined. In our earlier study (Jovanović et al., 2019), an ML method Guided regularized random forest (GRRF) was applied for the selection of features (pollutants and mother's age/parity) that are most relevant to one another. ML methods provided prediction relative errors lower than 30% and correlation coefficients higher than 0.90, suggesting a possible strong non-linear relationship among the pollutants and consequently, the complexity of their pathways in breast milk. GRRF

Table 1
Descriptive statistics for OCP and PCB concentrations [ng g^{-1} milk fat] in the breast milk collected between 2011 and 2014 from 150 healthy mothers (Jovanović et al., 2021; Master thesis of Samardžić, 2021).

	α-HCH	β-HCH	γ-HCH	HCB	*p,p'*-DDE	*p,p'*-DDD	*p,p'*-DDT	PCB-28	PCB-52	PCB-101	PCB-138	PCB-153
Min	0.10	0.15	0.15	0.10	0.15	0.10	0.30	0.52	0.51	0.54	0.51	0.60
Max	29.13	14.05	30.85	19.31	77.75	49.48	92.65	10.80	9.60	18.57	23.69	43.61
Median	0.52	0.60	0.94	2.07	4.98	0.30	2.95	1.15	1.60	2.13	3.04	4.73
Mean	1.54	1.88	2.03	2.88	8.43	2.66	5.56	1.75	2.33	3.65	4.03	7.42

	PCB-180	PCB-105	PCB-114	PCB-118	PCB-123	PCB-156	PCB-157	PCB-167	PCB-189	PCB-60	PCB-74	PCB-170
Min	0.53	0.52	0.57	0.51	0.54	0.50	0.50	0.54	0.52	0.52	0.51	0.53
Max	36.33	5.69	8.35	2.71	2.65	4.21	6.53	8.66	2.16	2.63	5.98	25.62
Median	2.35	0.93	1.89	0.82	0.72	0.85	0.87	0.79	0.63	0.92	1.20	1.99
Mean	3.99	1.16	2.17	1.07	1.11	1.13	1.27	1.24	0.84	1.11	1.59	2.96

The limit of detection for the analyzed compounds were 0.5 ng g^{-1} milk fat for PCB congeners, 0.1 ng g^{-1} milk fat for *α*-HCH and HCB, 0.2 ng g^{-1} milk fat for *p,p'*-DDE, 0.3 ng g^{-1} milk fat for *β*-HCH, *γ* –HCH and *p,p'*-DDD, and 0.6 ng g^{-1} milk fat for *p,p'*-DDT.

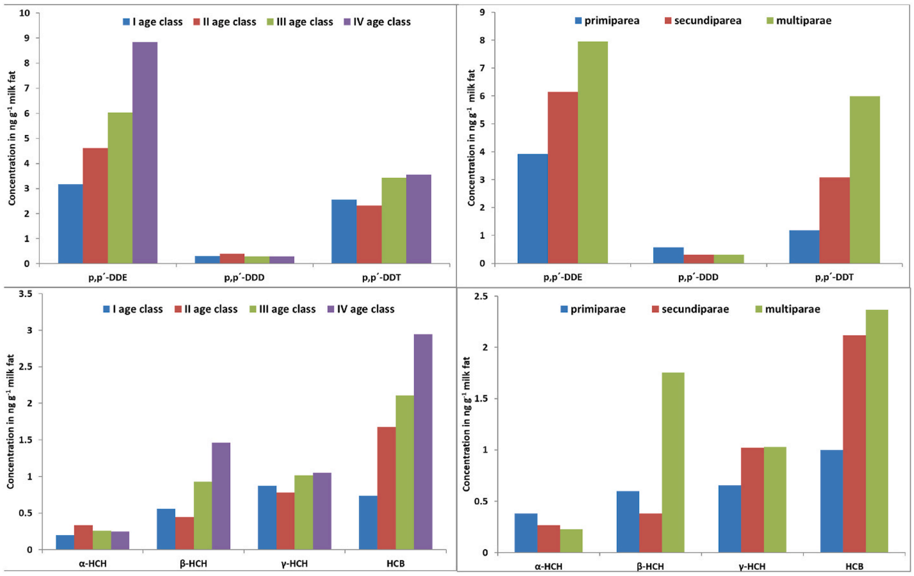

Fig. 2. Median OCP levels in human milk by mothers' age and number of childbirths (N = 150) (Jovanović et al., 2021; Master thesis of Samardžić, 2021).

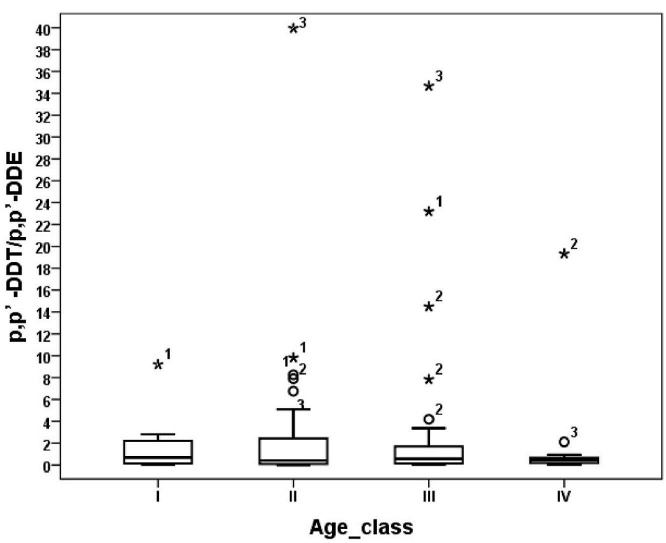

Fig. 3. *p,p'*-DDT to *p,p'*-DDE ratios in milk samples by age groups and number of childbirths (1 - primiparae, 2 - secundiparae, and 3 - multiparae) (N = 150) (Jovanović et al., 2021; Master thesis of Samardžić, 2021).

recognized PCB-153, PCB-180, PCB−170, PCB−118, PCB−156, PCB−105, and PCB−138 as the most important for the mutual prediction, and some importance of p,p'-DDE and β-HCH. Both studies (Jovanović et al., 2019, 2021) suggested the ortho position in the biphenyl ring is essential for PCB profiles in breast milk regardless of the ring coplanar structure. GRRF proposed a slight influence of the mother's age on the PCB and OCP composition of milk regardless of the first, second or third child delivery. For the pollutant source apportionment, Unmix (Jovanović et al., 2019) was performed, and GRRF to analyze the importance of Unmix-derived sources. Unmix characterized four individual source groups. The highest attributions of β-HCH, HCB, and γ-HCH characterized the first and the second group. The "heavy" hexa-to hepta-chloro occupational congeners: PCB-180, PCB-170, PCB-156, PCB-153, and PCB-138 moderately contributed to the third group. The fourth group was recognized as a metabolic pathway of p, p'-DDT, and partially belongs to the „light" tetra-to penta-chloro congeners PCB. These results are in accordance with the mutual associations of pollutants selected by GRRF because each source represents a specific mixture of the pollutants grouped according to similar chemical structure or behavior. Results implied they were mostly not related to child delivery.

Our results suggest that reduction via parity is related to mother's age, as older mothers tend to have higher cumulative exposure to PCB and OCP. Although our results, presented as comparison of medians (Figs. 2 and 4.), indicate that there is a trend of increasing levels with age, ML models indicate that this trend is not significant. PCB and OCP are inherently present and persistent, and in future measurements attention should be paid to PCB-170. PCB congeners substituted with chlorine atoms at ortho positions appeared to be compounds of the outmost importance for mutual prediction with reference to their interrelations regarding chemical structure and metabolic processes in the mother's body.

3.1.1.4. Comparison with literature. In the literature older mothers tend to have higher cumulative exposure to POPs, and parity is usually associated with decreasing levels of POPs in multiparae, because breastfeeding is one of the most important factors in the reduction of body burdens (Polder et al., 2009). In Polder's study (2009) during 2002–2006 across Norway, 423 breast milk samples were collected and analyzed to determine influence of age, parity. Age was associated with increased POP levels, and parity with decreasing levels. Newer comprehensive studies of Aerts et al. and Komprda et al. (2019) highlighted the importance of diet on POP levels in human milk. Aerts et al. (2019), in a survey of POPs in human breast milk, in a cross-sectional sample of 206 primiparous mothers in Belgium found that fatty fish, fish oil supplements and home-produced eggs influenced DDT/DDE concentrations, while fatty fish and reception of breastfeeding impacted HCH/HCB concentrations. They concluded that, although in most cases, the associations of POPs and age are statistically significant, the age range (19–30) is too small for establishing POP effects. They indicate that it is important to consider the influence of diet and childhood nursing history for prediction of individual POPs in human milk. The same observation was found in Komprda et al. (2019) for seven indicator PCB in human milk measured between 1996 and 2011. The data set contained information from more than 1000 primiparous women from the Czech Republic and PCB concentrations in breastmilk, individual physiology and living characteristics. They found that exposure of children via breast feeding to PCB with a half-life of less than three years can be influenced by the food composition of mothers' diets a few years before and during pregnancy. Body weight and age at delivery did not

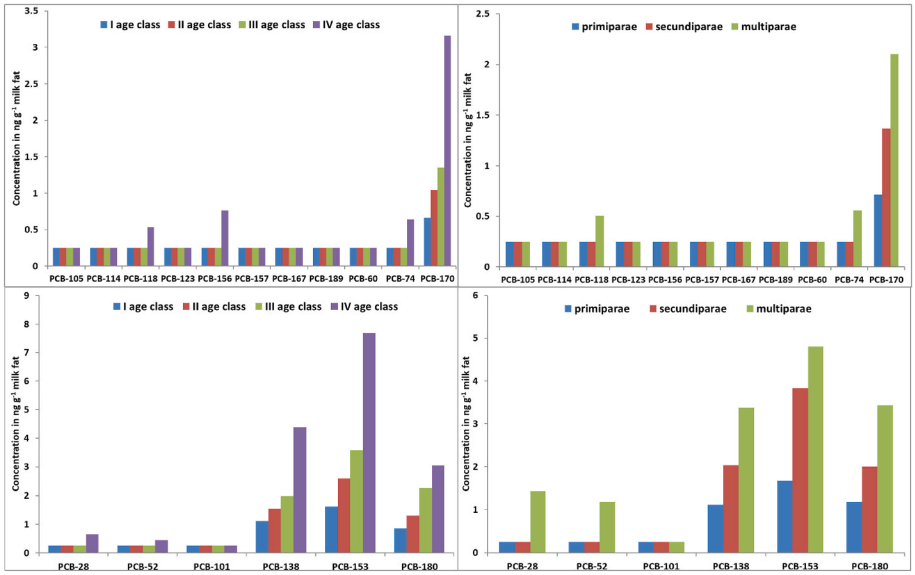

Fig. 4. Median PCB congener levels in milk of mothers by age groups and number of childbirths (N = 150) (Jovanović et al., 2021; Master thesis of Samardžić, 2021).

have any significant impact on PCB levels in human milk. In their conclusion, food contamination and biomonitoring studies with detailed food questionnaires were singled out as important. For understanding PCB with longer half-lives, data about history of usage of products containing these compounds is important.

3.1.2. *Health risk assessment for breastfed infants*

We assessed health risks for breastfed infants based on PCB and OCP analysis in 150 samples described in previous section 3.1.1 *PCB and OCP levels*. To the best of our knowledge, this is the first risk assessment of its kind based on such a large number of samples in Croatia, and this is the first time we publish it. Our estimated daily intake (EDI) for POPs points to no or negligible risk for newborns. All of the compounds in all of the

Table 2
Estimated daily intake of POPs in infants from mothers in our sample and comparison with TDI/ADI, MRL, RfD, and reference values recommended by the FAO/WHO (unpublished results).

	Estimated daily intake (EDI) - our study				Minimum risk levels (MRL)	Reference dose	FAO/WHO (van Leeuwen et al., 2000)
EDI (ng/kg day)	Median	Max	Min	Tolerable/Acceptable daily intake (TDI/ADI) (Wilhelm et al., 2002)	ATSDR (2001)	US U.S. EPA, 2001 (RfD)	
ΣEDI_HCH group	19.48	230.8	2.25	300			5000[a]
ΣEDI_DDT gropu	40.59	519.3	2.21	500			10,000
ΣEDI_dioxin like group	20.79	166.9	11.07				
ΣEDI_non-dioxin like group	35.50	427.4	6.04				
ΣEDI_POPs	131.79	944.2	27.92				
α-HCH	1.06	117.2	0.20	1000	8000		
β-HCH	2.43	56.5	0.60		600		
γ-HCH	3.80	124.1	0.60	5000	10	300	
HCB	8.11	77.7	0.20	800/500	20	800	600
p,p'-DDE	20.05	312.9	0.60				
p,p'-DDD	1.21	199.1	0.40				
p,p'-DDT	11.86	372.8	1.21		500	500	
PCB-28	1.01	43.4	1.01		30	20	
PCB-52	1.01	38.6	1.01		30	20	
PCB-101	1.01	74.7	1.01		30	20	
PCB-138	7.28	95.3	1.01		30	20	
PCB-153	12.66	175.5	1.01		30	20	
PCB-180	7.02	146.2	1.01		30	20	
PCB-105	1.01	22.9	1.01		30	20	
PCB-114	1.01	33.6	1.01		30	20	
PCB-118	1.01	10.9	1.01		30	20	
PCB-123	1.01	10.7	1.01		30	20	
PCB-156	1.01	17.0	1.01		30	20	
PCB-157	1.01	26.3	1.01		30	20	
PCB-167	1.01	34.9	1.01		30	20	
PCB-189	1.01	8.7	1.01		30	20	
PCB-60	1.01	10.6	1.01		30	20	
PCB-74	1.01	24.1	1.01		30	20	
PCB-170	4.86	103.1	1.01		30	20	

[a] For Lindane

150 samples were lower than the tolerable/acceptable daily intake (TDI/ADI) values (Table 2.). Only the ΣDDT group had one outlier sample (Fig. 5.) close to TDI. This is an interesting finding, as a notable number of Croatian mothers showed recent exposure to DDTs according to a *p,p'*-DDT/*p,p'*-DDE ratio higher than 1 in 30% of milk samples (Fig. 5.).

Median and even maximum EDI for the HCH group and *p,p'*-DDT are significantly lower than the minimum risk level (MRL) and reference dose (RfD) (Table 2.). Risk levels for PCB are not defined in detail, but some recommendations 30 ng/kg day for MRL (ATSDR, 2001) and 20 ng kg^{-1} day for RfD (US U.S. EPA, 2001). In that respect, most of our samples are safe for consumption (Table 2.) with a few outliers where the EDI of PCB slightly exceeds 30 ng kg^{-1} day (Fig. 6.). These outliers mostly concern milk samples of women predominantly from age group 3 (Fig. 5.). The ΣEDI of HCH group I, DDT group I, and HCB were also significantly lower than FAO/WHO recommendations (Table 2.), which confirms that the investigated milk samples were safe for infants. We therefore shifted our focus on identifying groups of compounds that had the highest contribution to EDI and singled out ΣEDI of DDT and non-dioxin-like groups as slightly higher contributors. Median and maximum EDI values were slightly higher in multiparae than primiparae, and most outliers concern EDI for women in age groups 3 and 4.

3.2. Dioxin-like PCB: PCB-77, PCB-81, PCB-126, and PCB-169

Due to the development a rapid and sensitive gas chromatographic method with electron ionization tandem mass spectrometry (GC-EI-MS-MS), we were able to determine the levels of PCB-77, PCB-81, PCB-126, and PCB-169 in 46 samples from primiparae and secundiparae from the Zadar area collected in 2014 (Table 3.) (Šimić et al., 2020). The overall prevalence of individual PCB had the following pattern: PCB-126>PCB-77>PCB-169≫PCB-81, but the highest levels were measured for PCB-169.

The PCB levels measured in the Zadar region were significantly lower than those reported in lactating women from the Taizhou region in China, which topped the list of 32 countries/regions in the third WHO round (Man et al., 2017). However, our PCB-126 levels exceeded those reported for breast milk in Slovakia (Chovancova et al., 2011), Turkey (Çok et al., 2012), New Zealand (Mannetje et al., 2013), Sweden (Fång et al., 2013), some regions in France (Focant et al., 2013), and the rest of China (Sun et al., 2011), and were lower than those reported for

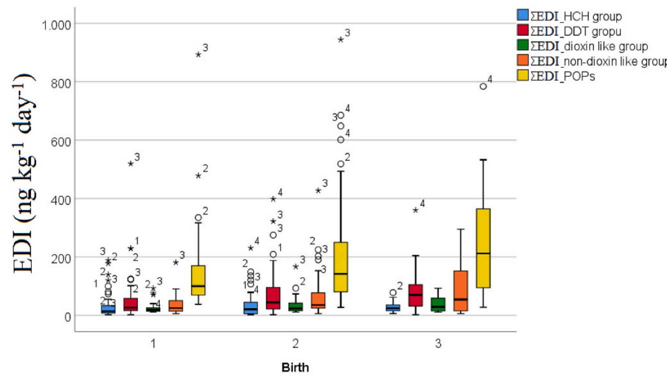

Fig. 6. Sum of EDI for all investigated POPs and by POP groups (N = 150) (unpublished results).

In order to illustrate time trend, PCB are determined as total PCB with respect to the standard Aroclor 1260 mixture, since commercial PCB mixture served for comparison in the first PCB analyses.

Table 3
Dioxin-like PCB concentrations in human milk of primiparae and secundiparae collected from the Zadar area in 2014 (N = 46) and corresponding toxic equivalents (Šimić et al., 2020).

Concentration [pg g^{-1} milk fat]	Min	Max	Mean	Median
PCB-77	5.44	288.80	29.10	18.59
PCB-81	1.00	10.42	3.49	3.08
PCB-126	2.54	705.99	45.53	25.41
PCB-169	0.0014	1643.65	91.83	15.16
Toxic equivalents (pg WHO-TEQ g^{-1} milk fat)				
$WHO_{2005}TEQ$[a]	0.38	116.26	7.25	3.17
$WHO_{1998}TEQ$[a]	0.30	85.84	5.45	2.72

Limit of detection [pg g^{-1} milk fat]: PCB-77 0.3, PCB-81 0.4, PCB-126 1, PCB-169 0.3.

[a] Calculated on the basis of WHO_{1998} and WHO_{2005}TEF (Van den Berg et al., 2006).

Japanese (Todaka et al., 2008; Suzuki et al., 2005), Hungarian (Vigh et al., 2013), Danish, Finish, and French mothers (Antignac et al., 2016). Monitoring PCB-126 in human milk is of high interest, as it can increase the risk of type 2 diabetes (Zong et al., 2018). Similar findings were

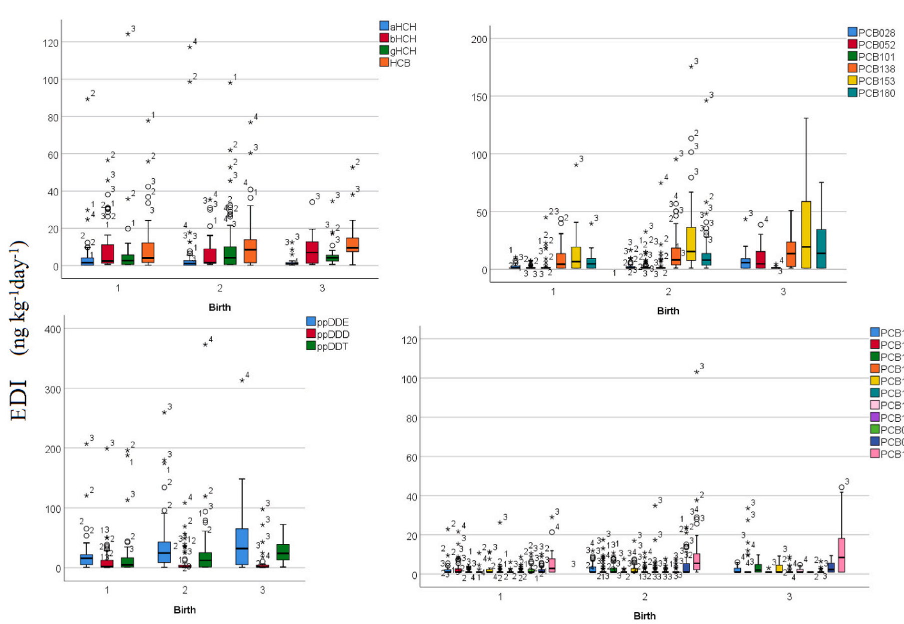

Fig. 5. EDIs of POPs by parity (primiparae, secundiparae and multiparae) (N = 150) (unpublished results).

observed for the levels of PCB-169. PCB-77 levels are lower than in the milk samples collected worldwide, except for Denmark, Finland, and France (Antignac et al., 2016). As noted in numerous studies before, this variability is owed to combined effects of mother's age and parity, lifestyle, and living and occupational environment rather than food consumption (fish and seafood in particular) alone (Engeset et al., 2015; Xing et al., 2010).

Judging by the calculated toxic equivalents (TEQ), which represent an estimate of total 2,3,7,8-TCDD-like activity of a mixture, PCB-126 and PCB-169 individually contributed the most to mixture toxicity (Table 3.). Our TEQ results were in the range or even lower than those reported for Turkey, Hungary, Asia, Africa, America, and Europe (Fång et al., 2015; Ulaszewska et al., 2011).

4. PCB and OCP time trend

The first data on the level of DDE (1537 ng g^{-1} milk fat), DDD (60 ng g^{-1} milk fat), D DT (256 ng g^{-1} milk fat), α-HCH (78 ng g^{-1} milk fat), and β-HCH (150 ng g^{-1} milk fat), in mother's milk in Croatia

refer to samples collected in 1976 (two smaller cities in continental Croatia, Bjelovar and Zabok) (Bažulić et al., 1978). In 1977, the first samples were collected in Zagreb (the capital city), and the results of DDE (31 ng g^{-1} milk), DDD (10 ng g^{-1} milk), DDT (11 ng g^{-1} milk) were expressed per mass of milk (Krauthacker et al., 1978, Krauthacker et al., 1980) making difficult comparison by newer data for Zagreb. Fig. 7 shows the levels of OCP and PCB in human milk from 1976 to 2014 (Bažulić et al., 1978; Krauthacker et al., 2009; Jovanović et al., 2021). Since commercial PCB mixture served for comparison in the first PCB analyses, PCB are determined as total PCB with respect to the standard Aroclor 1260 mixture, in order to illustrate time trend.

Regression analysis and log normal transformation of the data showed a significant decreasing trend of total PCB ($p < 0.02$), β-HCH ($p < 0.02$) and p,p'-DDE ($p < 0.01$) while the trend observed for the levels of HCB appeared to be non-significant ($p < 0.09$). Fång et al. (2015) discussed temporal trends in Sweden and Japan, starting from the 1970s to 2010. They covered a period that was the same as ours. Our first measured value for DDE in 1976 was similar to that in Sweden, but in Japan DDE are higher (above 2000 ng g^{-1} milk fat). Between 1980 and 1990, DDE levels in Japan were characterized by fluctuations, as in Croatia, while in Sweden the downward trend was more pronounced, i.e. without fluctuations. Common for all three countries was a drop in levels in 1990 compared to 1980. Since 1990, all three countries were characterized by a slower decline in DDE levels. As for PCB, the situation was similar as with DDEs. The levels in Croatia measured in the 1980s were similar to those in Sweden and higher in Japan (above 1000 ng g^{-1} milk fat). All three countries had a drop in levels up to the 1990s. A comparison of the trend for β-HCH was possible for Japan and Croatia. In Japan, the levels were significantly higher for any given year (until 1990, β-HCH was higher than 1000 ng g^{-1} milk fat) than in Croatia. In both countries, levels are falling over five decades. All three countries had a pronounced drop for PCB, DDE (and β-HCH in Croatia and Sweden) until the 1990s, probably as a consequence of the first actions against primary sources of pollution. However, today there are many diffuse sources, such as atmospheric deposition, or sea food (fatty fish) which is difficult to control.

5. PCDD/F and PBDE

5.1. PCDD/F

PCDD/F investigation were done in collaboration with WHO studies 1st round (1987–1988) (Environmental Health Series No 34, 1989), 2nd round (1992–1993) (Environmental Health in Europe No. 3, 1996), 3rd round (2000–2003) (Malisch and van Leeuwen, 2003) and 6th round (2012–2015), and data obtained in the WHO 6th round have not been published before. Table 4 shows their concentrations in three groups of milk samples collected from primiparae in Zagreb, the island of Krk (in 2000) (Malisch and van Leeuwen, 2003) and in Zadar (in 2014) (unpublished results). All three groups of milk samples contained all of the analyzed congeners in the range from <0.029 pg g^{-1} for 2,3,4,6,7,8-HxCDF to 42 pg g^{-1} for OCDD. Levels of PCDD and PCDF from the island of Krk and Zagreb collected in the same year did not differ significantly, and the congener profiles were similar to those in most human milk from Europe sampled around the same time (Polder et al., 1998; Focant et al., 2002; Vartiainen et al., 1997), which suggests that women in European countries are exposed to these compounds similarly. PCDD/F levels from 2014 are comparable to levels reported in the Spanish BETTERMILK study (Hernández et al., 2020) for samples collected in 2015. In this study, levels internationally reported over the period from 2012 to 2020 are discussed (see Table 4 and references

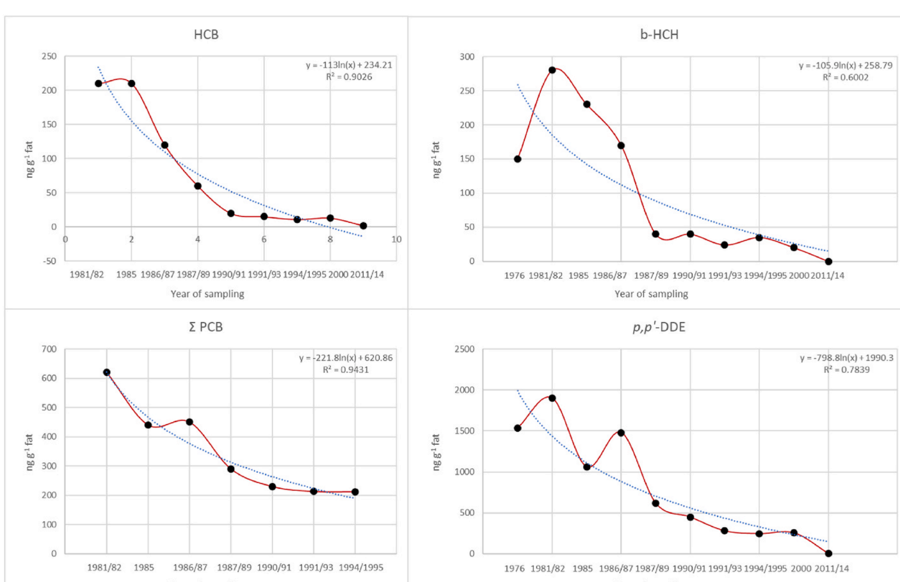

Fig. 7. Temporal trends (red line) of the concentrations of organochlorine compounds (ng g^{-1} fat) sampled in Croatia from 1976 (Bažulić et al., 1978; Krauthacker et al., 2009) to 2014 (Jovanović et al., 2021), and the results of log-linear regression (blue dotted line and the corresponding equation).). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 4
Levels and toxic equivalents of PCDDs and PCDFs in human milk collected in Zagreb, the island of Krk and in Zadar.

PCDD/F (w/pg g^{-1} milk fat)	Krk, 2000; 10 pooled samples; 3rd WHO study (Malisch and van Leeuwen, 2003)	Zagreb, 2000; 12 pooled samples; 3rd WHO study (Malisch and van Leeuwen, 2003)	Zadar, 2014; 50 pooled samples; 6th WHO study (unpublished results)
2,3,7,8-TCDD	0.85	0.89	0.34
1,2,3,7,8-PeCDD	1.67	1.90	0.72
1,2,3,4,7,8-HxCDD	0.93	1.07	0.36
1,2,3,6,7,8-HxCDD	3.61	4.06	1.72
1,2,3,7,8,9-HxCDD	1.38	1.41	0.47
1,2,3,4,6,7,8-HpCDD	8.79	9.73	2.4
OCDD	41.87	41.62	17.9
2,3,7,8-TCDF	1.39	1.49	0.3
1,2,3,7,8-PeCDF	0.37	0.49	0.13
2,3,4,7,8-PeCDF	4.47	2.01	2.68
1,2,3,4,7,8-HxCDF	1.62	2.01	0.84
1,2,3,6,7,8-HxCDF	1.40	1.71	0.84
1,2,3,7,8,9-HxCDF	0.68	0.80	0.45
2,3,4,6,7,8-HxCDF	0.10	0.25	<0.029
1,2,3,4,6,7,8-HpCDF	1.59	1.81	0.73
1,2,3,4,7,8,9-HpCDF	0.07	0.42	0.043
OCDF	0.33	0.42	0.097
PCDD/F toxic equivalents (pg WHO-TEQ g^{-1} milk fat) from 1988, 1993, 2000 and 2014			
1988; 1st WHO study; (Environmental Health Series No 34, 1989)	12 (14 pooled samples)	11.8 (42 pooled samples)	–
1993; 2nd WHO study; (Environmental Health in Europe No. 3, 1996)	8.4 (10 pooled samples)	13.5 (12 pooled samples)	–
2000; 3rd WHO study; (Malisch and van Leeuwen, 2003)	6 (12 pooled samples)	6.8 (12 pooled samples)	–
2014; 6th WHO study; (unpublished results)	–	–	2.4 (50 pooled samples)

therein), and Croatian levels are comparable to studies reporting lower concentrations. In our samples, 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD, and OCDD are the most abundant in all three groups, OCDD in particular. OCDD, 1,2,3,4,6,7,8-HpCDD and 1,2,3,6,7,8-HxCDD are among the dominant congeners reported by other researchers (Focant et al., 2013; Hernández et al., 2020) including in areas contaminated by dioxins as in Vietnam. In Vietnam, for PCDD, the most abundant congeners were 1,2,3,6,7,8-HxCDD, 1,2,3,4,6,7,8-HpCDD and OCDD; OCDDs in particular contributed over 40–50% to the total PCDD/F mass concentration. The pattern of PCDF indicates 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, 1,2,3,6,7,8-HxCDF and 1,2,3,4,6,7,8-HpCDF as highly abundant congeners (Hue et al., 2014).

Given the difference of 14 years in sampling in our study, a decreasing trend in the concentrations of each congener was observed, except for 2,3,4,7,8-PeCDF. Also, 2,3,4,7,8-PeCDF was slightly higher in 2014 (Zadar) than in 2000 (Zagreb), and was more toxic than other CDF congeners (Knutsen et al., 2018). PCDD/F and dioxin-like compounds had half-lives typically between 7.2 years and 15 years, but Matsumoto et al. (2015) found that half-life of blood 2,3,4,7,8-PeCDF tended towards infinity.

Considering the temporal trend expressed by toxic equivalents, when results were compared over a ten (and more) year period, a decreasing trend was observed (Table 4.). Gyllenhammar et al. (2021) researched the temporal trend from 1996 to 2017 in human milk from Swedish mothers, and they found out that PCDD have declined faster than PCDF, resulting in an increased proportion of PCDF compared to PCDD towards the end of the study. Among the PCDD/F, 1,2,3,6,7,8-HxCDD (5.7 pg g^{-1} lipid) and 2,3,4,7,8-PeCDF (4.9 pg g^{-1} lipid) showed the highest mean concentrations. The results of PCDD/F measurements in Croatia were insufficient to show a time trend because a time series requires a minimum of five reported data points, but the Croatian levels were in the range of measurements in Sweden. Gyllenhammar et al. (2021) concluded that the slower decline of PCDD/F (including CB-169, CB-180 and HCB) during the last decade is worrying, and that it is important to continue monitoring in breast milk from Swedish mothers in order to further observe if the concentrations of POPs are stabilizing at their current levels or would continue decrease. This is in agreement with findings of WHO surveys which indicated that PCDD, PCDF, and PCB levels in human milk are still significantly above those considered toxicologically safe (Van den Berg et al., 2016).

5.2. PBDE

Table 5 shows PBDE levels (ng g^{-1} milk fat) measured in a number of countries as part of the 6th WHO/UNEP round, whereas the rest have been taken from Zhang et al. (2017) covering the period from 2000 to 2015. Croatian data from 2014 as part of the 6th WHO/UNEP round have not been published before. North America stands out with the highest levels, probably owing to their more intense use of PBDEs. Croatian levels are comparable to the European ones and belong to the lower tier. BDE 153 and BDE 47 are dominant, which is in accordance with Zhang et al. (2017).

PBDE occurrence in the environment, accumulation in tissue, and related health risks have been studied from the outset (Wu et al., 2020), and the number of studies on BDE-209 in human samples has increased considerably in recent years thanks to more sensitive analytical techniques. Darnerud et al. (2015) reported that the ratio of low- and medium-brominated BDE congener levels in serum and milk is around 1 but that it increases with six bromines and upwards. They found decreasing levels of some bromine flame retardants in serum and breast milk over time and concluded that risk management fairly rapidly resulted in reduced human exposure.

6. WHO studies, benefits of breastfeeding, and the role of health centers in Croatia

Since 1987, WHO has coordinated six international studies of POP levels and trends in human milk in collaboration with other international organizations and national institutions on possible health risks, emphasizing health risk of infants. Croatia (carried out by Institute for Medical Research and Occupational Health, Zagreb) participated in four of these rounds: 1st, 2nd, 3rd, and 6th. In the 6th round, an important role was given to the University of Zadar, Department of Health Studies and its cooperative institution Zadar County Health Center, Community and Primary Health Care Division (visiting nurses) who collected the milk and promoted breastfeeding among mothers. Visiting nurses are in a unique position to inform mothers about environmental pollution and related health risks.

WHO recommends exclusive breastfeeding for the first 6 months of life to be continued in combination with appropriate complementary foods for up to 2 years or beyond because a risk-benefit analysis pointed to many benefits of breastfeeding for the infant and mother (Global strategy for infant and young child feeding Geneva: WHO, 2022; van den Berg et al., 2016). Exclusive breastfeeding is considered an effective way to provide balanced nutrition with all of the necessary nutrients which allow better growth and development of the infant and protection against chronic and infectious diseases (Global strategy for infant and young child feeding Geneva: WHO, 2022; WHO, 2001).

Table 5
PBDE levels (ng g^{-1} milk fat) in human milk samples worldwide.

	Belgium (Aerts et al., 2019)	China (Zhang et al., 2017)	The Netherlands (Zeilmaker et al)	Croatia (unpublished results)	Sweden (Darnerud et al., 2015)	Europe (Zhang et al., 2017)	North America (Zhang et al., 2017)
BDE28	NI	0.118	NI	0.016	0.01–0.47	0.08	2.1
BDE47	0.24	0.137	0.492	0.218	0.10–2.1	1.04	30.8
BDE99	0.1	0.0468	0.132	0.0685	0–0.48	0.34	6.5
BDE100	NI	0.0513	NI	0.0756	0.03–1.4	0.25	6.3
BDE153	0.46	0.527	0.741	0.242	0.21–3.4	0.66	6.2
BDE154	0.13	0.0139	NI	0.0125	0.01–0.11	0.07	0.57
BDE183	NI	0.0929	NI	0.0268	0–0.04	0.13	0.18

Data of 6th WHO/UNEP round for Croatia (unpublished results), Belgium (Aerts et al., 2019), The Netherlands (Zeilmaker et al).
Netherlands: ∑BDEs −17, −28, −66, −100, −154: 0.227 ng g^{-1} milk fat (Zeilmaker et al).
Croatia: BDE17: 0.0022; BDE66: 0.0063; BDE138:<6 (unpublished results).
Sweden: BDE66: 0–0.05; BDE138:0 0.01 (Darnerud et al., 2015).
NI-no information.

7. Conclusion and suggestion for further actions

Although nearly 40 years has passed since the ban of OCB and OCP usage, and 20 years after the Stockholm convention that listed 12 substances (PCB, OCP and PCDD/F-“12 dirty dozen”) for international control, legacy PCB, OCP and PCDD/F are still present in human milk. The time trend between 1976 and 2014 for DDE, HCB, β-HCH and PCB in Croatian human milk has a decreasing trend, always reported in lower concentrations, but despite this, they are still present in breast milk.

Review of data about PCB, OCP and PCDD/F in human milk pointed to a few interesting facts for future research: the first of them is DDT, median values of *p,p'*-DDT/*p,p'*-DDE ratio for all age classes are lower than 1 and in approximately 30% of the samples this ratio is higher than 1 indicating more recent *p,p'*-DDT pollution of these mothers; the second is the importance of PCB-170 in future measurements including congeners substituted with chlorine atoms at ortho positions; whereas the third is that 2,3,4,7,8-PeCDF was more toxic than other CDF congeners, stressed as persistent over decades and therefore deserving more attention. PCB, OCP and PCDD/F provide an example of multi-decade environmental pollution and threat to human health, and for this reason they will be monitored and researched in all parts of the environment for many years to come.

Based on our comprehensive report, our suggestion is further monitoring of POPs in Croatian breast milk with emphasis on importance of diet on POP levels. Detailed food questionnaires is recommended.

Funding

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Ethics approval

The study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by Ethics Committee of the Institute for Medical Research and Occupational Health, Zagreb, Croatia.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Before providing milk samples, the purpose of sampling was explained to each participant and each participant gave their informed consent for publishing and filled out a paper-and-pencil questionnaire prepared for sampling needs. The subjects were allowed to withdraw from the studies at any time.

CRediT authorship contribution statement

Snježana Herceg Romanić: All authors contributed to the study, Conceptualization, and design, Material preparation, data collection and, Formal analysis, were performed by all authors, The draft of, the manuscript, was written, all authors commented on previous versions of, the manuscript, All authors read and approved the final manuscript. **Tijana Milićević:** All authors contributed to the study, Conceptualization, and design. Material preparation, data collection and, Formal analysis, were performed by all authors, all authors commented on previous versions of, the manuscript, All authors read and approved the final manuscript. **Gordana Jovanović:** All authors contributed to the study, Conceptualization, and design. Material preparation, data collection and, Formal analysis, were performed by all authors, all authors commented on previous versions of, the manuscript, All authors read and approved the final manuscript. **Marijana Matek Sarić:** All authors contributed to the study, Conceptualization, and design. Material preparation, data collection and, Formal analysis, were performed by all authors, all authors commented on previous versions of, the manuscript, All authors read and approved the final manuscript. **Gordana Mendaš:** All authors contributed to the study, Conceptualization, and design. Material preparation, data collection and, Formal analysis, were performed by all authors, all authors commented on previous versions of, the manuscript, All authors read and approved the final manuscript. **Sanja Fingler:** All authors contributed to the study, Conceptualization, and design. Material preparation, data collection and, Formal analysis, were performed by all authors, all authors commented on previous versions of, the manuscript, All authors read and approved the final manuscript. **Goran Jakšić:** All authors contributed to the study, Conceptualization, and design. Material preparation, data collection and, Formal analysis, were performed by all authors, all authors commented on previous versions of, the manuscript, All authors read and approved the final manuscript. **Aleksandar Popović:** All authors contributed to the study, Conceptualization, and design. Material preparation, data collection and, Formal analysis, were performed by all authors, all authors commented on previous versions of, the manuscript, All authors read and approved the final manuscript. **Dubravka Relić:** All authors contributed to the study, Conceptualization, and design. Material preparation, data collection and, Formal analysis, were performed by all authors, all authors commented on previous versions of, the manuscript, All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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