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Systematic investigation of organochlorine pesticides and polychlorinated biphenyls blood levels in Greek children from the Rhea birth cohort suggests historical exposure to DDT and through diet to DDE

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ABSTRACT

The blood levels of organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs) have been thoroughly investigated in Greek children from the Rhea birth cohort study. This investigation aimed to assess exposure levels, explore their possible relationship with children's age and sex, and indicate potential sources of exposure. Exposure patterns and common sources of PCBs and OCPs were analyzed using bivariate and multivariate statistics.

A total of 947 blood samples from study participants were analyzed for OCP and PCB exposure, with 375 samples collected at 4 years old, 239 at 6.5 years old, and 333 at 11 years old. Elevated levels of DDE were observed in 6.5-year-old children compared to corresponding levels in other European countries. Higher levels of DDE were found in 4-year-old children, with the lowest concentrations in the 11-year-old group. The DDT/DDE ratio was consistently less than 1 among all the examined subjects. These results indicate exposure to DDT and DDE both in utero and through breastfeeding and dietary intake. For the entire cohort population, the highest concentration was determined for PCB 28, followed by PCBs 138, 153, and 180. The sum of the six indicator PCBs implied low exposure levels for the majority of the cohort population. Spearman correlations revealed strong associations between PCBs and OCPs, while principal component analysis identified two different groupings of exposure. DDE exhibited a correlation with a series of PCBs (153, 156, 163, 180), indicating a combined OCP-PCB source, and an anticorrelation with others (52, 28, 101), implying a separate and competing source.

1. Introduction

Human environmental exposure to toxic pollutants is determined through measurements in various environmental media, such as indoor and outdoor air, water, and food. Concurrently, biomonitoring serves as a means to assess both internal and external human exposure from different pathways (Steckling et al., 2018). These approaches are essential for Environment-Wide Association Studies (EWAS), which investigate the connections between exposure to multiple environmental factors and health status (Patel et al., 2010; Steckling et al., 2018). The term 'exposome' has been introduced to describe the combined effects of exposure to these factors (Vrijheid, 2014; Wild, 2005).

Halogenated persistent organic pollutants (POPs), which include organochlorine pesticides (OCPs) like 4,4′-dichlorodiphenyltrichloroethane (DDT) and hexachlorobenzene (HCB), as well as polychlorinated biphenyls (PCBs), have been recognized by UNEP as having a significant health impact on humans (UNEP, 2023). DDT, HCB, and PCBs bioaccumulate in fatty tissues, biomagnify in the food chain, exert adverse effects on humans following chronic exposure, and undergo long-range transportation (WHO, 2012). Their toxic effects, including carcinogenicity, have been observed even after exposure to low doses (Alharbi

et al., 2018; Li et al., 2006; Margetaki et al., 2022a; Mrema et al., 2013; Schug et al., 2011).

Diet is considered the primary route of human exposure to POPs (Zhou et al., 2012). Children are initially exposed in utero and, after birth, through breastfeeding and food consumption (Handakas et al., 2023; Zhou et al., 2012). The energy requirements of children (per kilogram of body weight) are much higher than those of normal adults, thus increased food intake can elevate exposure (Casas et al., 2011; Wittassek et al., 2007). In addition, for young children, hand-to-mouth transfer may also contribute to exposure through the ingestion of contaminated soil and/or traces of construction materials (Handakas et al., 2023; Sanders et al., 2018). Early-life exposures that can affect critical life stages of organ and tissue development are of particular concern (Robinson and Vrijheid, 2015; WHO, 2010), as illustrated in recent years by numerous studies focusing on the early-life exposome and related health outcomes (Maitre et al., 2018; Petrick et al., 2020; Vrijheid et al., 2020; Warembourg et al., 2019). While fetuses and neonates are usually referred to as being more vulnerable to toxic chemicals, children and adolescents can also be considered more sensitive than adults, as critical systems like the endocrine and reproductive system are still developing in them (Burns et al., 2016; Lam et al., 2015; Schug et al., 2011).

DDT and HCB, once used in agriculture for fungus and pest control, have been characterized as possible carcinogens and endocrine-disrupting chemicals (IARC 2018; Miret et al., 2019) with adverse effects, including neurological issues (Kyriklaki et al., 2016) and immunological disorders (Gascon et al., 2014), alterations in thyroid function (Llop et al., 2017), and allergies (Margetaki et al., 2022a). Although their use was banned in the 1970s (Mrema et al., 2013; WHO, 2012), DDT, along with its main metabolite 4,4′-dichlorodiphenyldichloroethylene (DDE), and HCB, are still detected in human blood (Bandow et al., 2020; Barmpas et al., 2020; Korrick et al., 2000; Koureas et al., 2019; Schoeters et al., 2017). The European Union Agency for Law Enforcement Cooperation (Europol) has identified a growth in the trade of illegal and counterfeit pesticides (Europol 2012). More than 14 percent of the pesticides in circulation in certain EU Member States are estimated to originate from the illegal pesticide market. In Europol's operation Silver Axe, conducted in 2015 and 2017, over 300 tons of counterfeit or illegal pesticides were seized, with an additional 2040 tons seized in 2023 (Europol, 2023). Such illegal pesticides threaten the health of farmers and consumers and pose a risk to the natural environment (Commission and Safety 2015; CropLifeEUROPE 2023). Food of animal origin is the major source of human exposure to DDT and related compounds. Studies conducted in several EU Member States indicate a mean dietary intake for adults and children of 5 to 30 ng/kg body weight per day, which is more than two orders of magnitude below the provisional tolerable daily intake (PTDI) of 0.01 mg/kg body weight established by the Joint FAO/WHO Meeting on Pesticide Residues (EFSA 2006a).

PCBs belong to a group of 209 synthetic chlorinated organic compounds, referred to as congeners, known for their properties such as nonflammability, chemical stability, and thermal insulation, which have made them suitable for various industrial applications (Weitekamp et al., 2021). Despite the ban on their production in the USA in the 1970s and in Europe in the 1980s, PCBs are still detected in human blood. The Stockholm Convention on POPs and the European Food Safety Authority (EFSA) have recommended six congeners, namely PCB 28, PCB 52, PCB 101, PCB 138, PCB 153, and PCB 180, as indicative of total PCB levels for monitoring studies. These are commonly referred to as indicator PCBs (ind-PCBs) (EFSA, 2018; Zhou et al., 2012).

Other congeners of toxicological concern are the non-ortho substituted (n.o.-PCBs: PCB 77, PCB 81, PCB 126, PCB 169) and the mono-ortho substituted (m.o.-PCBs: PCB 105, PCB 114, PCB 118, PCB 123, PCB 156, PCB 157, PCB 167, and PCB 189), which belong to the dioxin-like PCBs, and their concentration is expressed as World Health Organization Toxic Equivalents (WHO-TEQs). A Toxic Equivalency Factor (TEF) has been assigned to each of them, assuming 2,3,7,8-tetrachlorodibenzodioxin (TCDD) as the reference with a TEF of one (1) (Van den Berg et al., 1998). The concentration of each compound multiplied by its TEF results in the Toxic Equivalency (TEQ), and the sum of TEQs of compounds detected in a sample corresponds to its overall dioxin-like toxicity. In 2005, WHO re-evaluated the 1998 TEF values and introduced the TEFs-2005 (Van den Berg et al., 2006).

Levels of DDT-DDE, HCB, PCBs and PBDEs in blood during pregnancy and the resulting in utero exposure to them have been previously assessed in the Rhea birth cohort in Crete, Greece (Chatzi et al., 2017), and were found to be related to children's neuropsychological development (Kyriklaki et al., 2016). Furthermore, levels of specific PCBs, DDE, and HCB corresponding to these substances have been found to be negatively associated with blood pressure (Warembourg et al., 2019) and birth weight (Vafeiadi et al., 2014), while showing a positive association with body mass index (BMI) (Colicino et al., 2022; Vrijheid et al., 2016).

The Human Early-Life Exposome (HELIX) collaborative project (Vrijheid et al., 2014), which involves six established population-based birth cohort studies in Europe, assessed in-utero and childhood exposure to a wide range of environmental contaminants, including their concentrations, differences, and correlations between mothers and their children. Concurrently, clinical measurements and neurological testing were performed (Maitre et al., 2018).

Exposomic data published by HELIX revealed elevated blood levels of DDE in both mothers and children within its Rhea sub-cohort (Haug et al., 2018; Jedyna et al., 2021; Tamayo-Uria et al., 2019). Specifically, DDE concentrations in the 197 children from Rhea were significantly higher compared to corresponding sub-cohorts in the United Kingdom, France, Spain, Lithuania, and Norway (Haug et al., 2018; Tamayo-Uria et al., 2019). This suggests that in utero and/or dietary exposure to DDT/DDE are the primary reasons for the relatively high concentrations observed in children from the Rhea sub-cohort.

The aforementioned data have raised significant concerns, prompting the current study to undertake further research aimed at gaining a deeper understanding of children's exposure and the associated health risks in the area. A comprehensive literature search revealed a lack of systematic studies on the presence of Organochlorine Pesticides (OCPs) in food and maternal milk in Greece. Only a few studies have reported the presence of OCPs and PCBs in the atmospheric environment and agricultural soils of the area (Iakovides et al., 2021; Tsiantas et al., 2023). Tsiantas et al., 2023 assessed the levels of thirty-three organochlorine pesticides (OCPs) in sixty Greek agricultural soils between 2019 and 2020. Despite being discontinued from the market, DDTs, along with other OCPs, were the major compounds, reaching a maximum cumulative concentration (ΣDDTs) of 1273.4 µg kg^{-1} dry weight. Environmental exposure assessment was conducted, indicating lower concentrations for the majority of OCPs compared to the predicted values, except for DDE (DDT's metabolite), where the measured and predicted soil concentrations were nearly equal. In Crete, specifically in Tympaki, one of the most crucial agricultural areas supplying the majority of fruits and vegetables to Heraklion (Rhea study area), only DDT and DDE were detected. Based on compositional profiles and diagnostic ratios, the authors suggested that the presence of DDT residues can be attributed to historical inputs. Iakovides et al., 2021 reported levels of OCPs and PCBs in the gas and particulate phase of 34 air samples collected from 2013 to 2015 in the same study area as the Rhea cohort, within the broader region of Heraklion. The concentrations of PCBs (49 congeners, 77–93 pg/m^3) and OCPs (23 substances, 77–140 pg/m^3) were comparable to those reported for similar locations worldwide. The most abundant OCPs included p,p'-DDE, p,p'-DDD, p,p'-DDT, o,p'-DDE, o,p'-DDD, o,p'-DDT, and hexachlorobenzene (HCB). Among them, p,p'-DDE exhibited the highest concentration, reaching at least one to three orders of magnitude higher than those measured at background sites in Europe and at a remote coastal site in northern Crete. The consideration of parent-metabolite ratios for most OCPs excluded fresh inputs.

Multiple-linear regression analysis, conducted to correlate atmospheric concentrations with meteorological conditions, identified long-range transport as the primary controlling factor for both OCPs and PCBs.

The objectives of the present study are defined as follows: I) to assess the exposure levels of children in Rhea to PCBs and OCPs, II) to provide an overview of exposure levels in Greece (Rhea is located in Crete but is the only mother–child cohort in Greece) and systematically compare our results with relevant studies from other countries, III) to investigate the potential relationship between exposure levels and the age and sex of the children, and IV) to identify the possible sources and patterns of exposure.

To the best of our knowledge, the present work, along with the corresponding study by Bandow et al., 2020 conducted in Germany, represents the most systematic longitudinal study on the presence of OCPs and PCBs in the blood plasma of children in Europe.

2. Materials and methods

2.1. Study design and recruitment

The present study is part of the Rhea Study, a prospective mother–child cohort that examines a population sample of pregnant women and their children in the prefecture of Heraklion, Crete, Greece. One thousand six hundred ten (1,610) pregnant women agreed to participate, and one thousand three hundred three (1,363) singleton pregnancies were followed up until delivery. The detailed methods are described elsewhere (Chatzi et al., 2017). In summary, women of both Greek and non-Greek origins, who became pregnant during a one-year period starting in February 2007, were invited to participate in the study. The first contact occurred at the time of the initial comprehensive ultrasound examination (mean ± SD 11.96 ± 1.49 weeks), followed by several subsequent contacts. Pregnant women were additionally contacted at 6 months of pregnancy, at birth, and their children were followed up after birth (at 9 months, 1 year, 4 years, 6.5 years, and 11 years old). To be eligible for inclusion in the study, women needed to have a good understanding of the Greek language and be older than 16 years old. The study received approval from the ethics committee of the University Hospital in Heraklion, Crete, Greece, and all participants provided written informed consent after receiving a complete description of the study. A total of 947 blood samples from study participants were analyzed for POP exposure, with 375 samples collected at 4 years old, 239 at 6.5 years old, and 333 at 11 years old.

2.2. Blood collection and lipid analysis

Non-fasting < 10-mL blood samples were collected in silicone gel separator vacutainers (Becton Dickinson). They were centrifuged within 2 h at 2500 rpm for 10 min, and serum samples were then aliquoted and stored at −80 °C until assayed. Analyses of serum lipid concentrations (total cholesterol and high-density lipoprotein cholesterol) were conducted using standard enzymatic methods (Medicon Hellas S.A., Athens, Greece) on an automatic Olympus AU5400 high-volume chemistry analyzer (America, Inc., Melville, New York) (Haug et al., 2018).

2.3. Chemical analysis

2.3.1. Materials

For the analysis of PCBs, DDT, DDE, and HCB, all solvents used were of residue analysis picograde quality and were purchased from JT Baker (USA). The alumina was Basic Activity Super 1 for dioxin analysis, obtained from MP Biochemicals GmbH, and was activated overnight at 200 °C. The sulfuric acid-impregnated silica gel was prepared by mixing silica gel (100 g, 60–200 mesh, Merck) activated at 200 °C with concentrated sulfuric acid (44 g).

Individual indicator PCB congeners (PCB 28, 52, 101, 138, 153, 180), mono-ortho substituted congeners (PCB 105, 114, 118, 123, 156, 157, 167, 189), 4,4′-DDT, 4,4′-DDE, HCB, and their ^{13}C-labelled analogues for the preparation of labeled internal and calibration standard solutions, as well as ^{13}C$_{12}$ PCB-80 for injection solutions, were purchased from Cambridge Isotope Laboratories Inc. The internal quantification standards used were ^{13}C-labelled solutions of 4,4′-DDT, 4,4′-DDE, HCB, and PCBs in toluene and were added to each sample prior to the clean-up process.

2.3.2. POPs analysis and quality assurance

Levels of 14 PCB congeners (28, 52, 101, 105, 114, 118, 123, 138, 153, 156, 157, 167, 180, 189), DDT, DDE, and HCB were measured in 947 serum samples from children aged 4–11 years old. Compound analysis in serum was conducted using the method previously described for PCBs (Costopoulou et al., 2006), which was adjusted to a smaller scale. In brief, 0.5–1 mL of blood serum was spiked with ^{13}C-labelled analogues for all analytes and was subsequently extracted with equal volumes of methanol and diethyl ether/petroleum ether. The clean-up of the lipid extract from interfering substances was performed using a multi-layer column containing, from top to bottom, 1 g of acid silica, 1 g of basic alumina, and 1 g of sodium sulfate, eluted with 10 mL of a mixture of hexane:dichloromethane. The eluent was concentrated to dryness and re-dissolved in 50 μL of n-nonane containing 2 ng/mL of the injection standard ^{13}C$_{12}$ PCB-80. The quantification of compounds was carried out using High-Resolution Gas Chromatography-High-Resolution Mass Spectrometry (Electron-Impact) (HRGC-HRMS, EI) in Multiple Ion Detection (MID) mode.

A Trace 1310 gas chromatograph (ThermoScientific), equipped with an Agilent DB-5MS GC column (60 m length, 0.25 mm I.D., 0.10 μm film), and a TriPlus RSH autosampler, was coupled to a DFS mass spectrometer (ThermoScientific) operating at a 10,000 resolving power (10 % valley definition). The method detection limit (LOD) was 0.2 pg mL^{-1} for all monitored analytes. In each series of 16 samples, a method blank and a reference sample (inter-laboratory trial serum sample with a known concentration) were analyzed. The laboratory is accredited by EN/ISO 17,025 for PCBs, DDT, DDE, and HCB analysis in blood serum/plasma. The reliability of the analysis method is also confirmed by participation in three inter-laboratory trials per year, such as the AMAP Ring Test for Persistent Organic Pollutants in Human Serum, organized by the Quebec National Institute of Public Health.

2.4. Statistical analysis

Concentration levels below the detection limits were replaced by the detection limit divided by the square root of two, as is commonly performed in similar studies (Myridakis et al., 2016; Myridakis et al., 2015). Lipid adjustment was conducted by normalizing concentrations with blood total cholesterol (TC) and triglycerides (TG), using the equation for total lipids (TL, g/L) = 2.27 TC (g/L) + TG (g/L) + 0.623, as previously described (Egsmose et al., 2016). Percentiles, geometric means, and relevant confidence intervals were not calculated for features with less than a 50 % detection rate. Log10 transformation was applied before univariate and multivariate statistical analysis. The data showed skewness after transformation; therefore, non-parametric tests were employed, including Mann-Whitney U for two-group comparisons and Kruskal-Wallis for comparisons involving more than two groups. Tukey's Honestly Significant Difference (HSD) was performed post-hoc to account for multiple comparisons. Heatmaps were generated based on two-tailed Spearman correlations. P-values < 0.05 were considered significant for correlations and univariate statistics after correction for multiple comparisons. Descriptive statistics were performed in Excel (Microsoft), univariate and correlation analysis in Metaboanalyst (Pang et al., 2021), and multivariate analysis in SIMCA (Sartorius).

Toxicity Equivalents Concentration for PCBs (TEQ-PCBs), human biomonitoring values (HBM), and the sum of six indicator PCBs (ind-PCBs) were calculated as described elsewhere (Bandow et al., 2020; Kraft et al., 2017; Megson et al., 2019; Van den Berg et al., 2006). Only

one subject exceeded the HBM of 1 and was removed from further statistical analysis as an outlier.

2.5. Systematic comparison with relevant literature reports

A literature search for similar studies was conducted in the PubMed, Scopus and Web of Science databases on April 4th, 2024. The search query was "((polychlorinated) OR (pcb) OR (pcbs) OR (organochlorine*)) AND ((child*) OR (or adolesc*) OR (early-life)); with "AND" and "OR" serving as Boolean operators and "*" as truncation. The selection criteria required articles to be in English, published after 2010, and to present at least five common PCBs or one common OCP in over 40 serum or plasma samples from children and adolescents less than 18 years old, with lipid-normalized median concentrations available. Initially, 175 articles were identified, and 10 of them met the search criteria (Bach et al., 2020; Bandow et al., 2020; Caspersen et al., 2016b; Gonzalez-Alzaga et al., 2018; Guo et al., 2020; Hernandez et al., 2019; Marek et al., 2014; Morck et al., 2014; Sisto et al., 2015; Sjodin et al., 2014). The references of the selected papers were also reviewed, but no additional articles were identified.

3. Results and discussion

Serum samples were analyzed for a total of 947 children, including 556 males and 391 females, with 375 samples at 4 years old, 239 at 6.5 years old, and 333 at 11 years old, respectively. All monitored OCPs and PCBs were detected in most of the samples, with detectability ranging from 70.7 % to 100.0 %, except for PCB 189, which was found in 44.9 % of the samples (Table 1). Results are presented both in serum and normalized to total lipid levels, enabling more efficient comparisons with relevant studies (Egsmose et al., 2016). Detailed descriptive statistics for each age group are provided in the Supplementary Material (Tables S1-S3). The most abundant OCP was DDE, with median levels of 80.5 pg/mg of serum lipids in all three age groups combined. Among PCBs, PCB 28 was found at the highest median levels at 26.9 pg/mL of serum. After lipid normalization, PCB 28 and PCB 153 were the most abundant, with median levels at 5.4 pg/mg of lipid. Generally, the exposure pattern is similar before and after normalization for both OCPs and PCBs.

3.1. OCPs

Levels of HCB, DDT and DDE in the total study population are presented in Table 1 and levels per age group in Tables S1 to S3. DDT/DDE

Table 1

Descriptive statistics of OCP and PCB levels – pg/mL serum (pg/mg lipid) of Rhea study children (N = 947).

pg/mL (pg/mg)	%> LOD	Ar. Mean	Std. Dev.	Geo. Mean	Lower 95 %CI	Higher 95 %CI	Min.	Median	95th perc.	Max.
HCB	100	72.9	90.9	56.4	54.3	58.7	15.5	52.0	155.0	1007.0
		(14.7)	(19.1)	(11.2)	(10.8)	(11.7)	(2.8)	(10.4)	(31.7)	(204.8)
DDE	100	807.2	1345.8	470.4	442.8	499.8	34.0	402.0	2600.8	22603.0
		(166.0)	(285.2)	(94.4)	(85.9)	(103.8)	(8.8)	(80.5)	(544.1)	(4681.6)
DDT	100	36.1	51.5	24.3	23.0	25.6	1.0	23.2	91.3	858.0
		(7.3)	(11.4)	(4.9)	(4.4)	(5.4)	(0.2)	(4.6)	(18.3)	(210.1)
DDE + DDT	–	843.3	1367.0	506.2	477.5	536.7	70.0	432.0	2677.6	22647.0
		(173.3)	(289.9)	(101.6)	(79.4)	(129.9)	(14.0)	(86.2)	(553.3)	(4690.8)
DDT/DDE	–	0.080	0.100	0.052	0.047	0.057	0.000	0.052	0.240	1.388
PCB 28	100.0	81.6	255.9	33.1	31.3	35.1	9.2	26.9	405.2	3651.4
		(16.1)	(55.6)	(6.6)	(3.4)	(12.6)	(1.9)	(5.4)	(71.9)	(1086.6)
PCB 52	99.3	28.5	131.2	3.2	3.0	3.6	<0.2	2.3	134.5	1679.7
		(5.4)	(26.8)	(0.6)	(0.2)	(1.9)	(–)	(0.5)	(26.6)	(449.4)
PCB 101	99.9	13.7	65.5	3.9	3.6	4.2	<0.2	3.2	40.4	966.7
		(2.6)	(14.0)	(0.8)	(0.3)	(1.8)	(–)	(0.6)	(6.7)	(287.7)
PCB 105	98.4	3.2	14.8	1.4	1.3	1.4	<0.2	1.3	7.0	316.4
		(0.6)	(3.6)	(0.3)	(0.2)	(0.4)	(–)	(0.3)	(1.4)	(94.2)
PCB 114	70.7	1.2	4.6	0.5	0.4	0.5	<0.2	0.4	3.3	84.0
		(0.2)	(0.9)	(0.1)	(0.1)	(0.1)	(–)	(0.1)	(0.6)	(15.8)
PCB 118	99.9	9.6	33.8	5.1	4.8	5.4	<0.2	4.8	20.9	688.6
		(1.9)	(8.1)	(1.0)	(0.6)	(1.6)	(–)	(0.9)	(4.0)	(204.9)
PCB 123	90.3	0.9	2.3	0.6	0.5	0.6	<0.2	0.5	2.3	35.7
		(0.2)	(0.5)	(0.1)	(0.1)	(0.2)	(–)	(0.1)	(0.5)	(10.6)
PCB 138	100.0	23.6	36.7	15.4	14.6	16.2	1.8	13.7	63.2	493.0
		(4.7)	(7.8)	(3.1)	(1.5)	(6.1)	(0.3)	(2.7)	(13.0)	(119.2)
PCB 153	100.0	43.5	61.9	30.1	28.6	31.6	<0.2	26.7	121.2	1146.6
		(8.7)	(12.7)	(6.0)	(3.0)	(11.7)	(–)	(5.4)	(23.9)	(237.5)
PCB 156	99.8	2.8	3.6	1.9	1.8	2.0	<0.2	1.8	8.2	60.8
		(0.6)	(0.8)	(0.4)	(0.2)	(0.6)	(–)	(0.3)	(1.7)	(12.6)
PCB 157	89.0	1.7	2.4	0.9	0.9	1.0	<0.2	0.9	6.2	33.4
		(0.3)	(0.5)	(0.2)	(0.1)	(0.4)	(–)	(0.2)	(1.3)	(6.5)
PCB 167	84.3	0.8	1.2	0.5	0.5	0.6	<0.2	0.5	2.5	14.6
		(0.2)	(0.2)	(0.1)	(0.1)	(0.2)	(–)	(0.1)	(0.5)	(3.0)
PCB 180	100.0	26.4	33	18.4	17.5	19.4	1.2	17.2	73.0	333.6
		(5.3)	(6.5)	(3.7)	(1.8)	(7.4)	(0.2)	(3.4)	(15.2)	(69.1)
PCB 189	44.9	0.4	1.3	–	–	–	<0.2	<0.2	1.0	23.9
		(0.1)	(0.3)				(–)	(–)	(0.2)	(6.0)
Total TEQ m.o.-PCBs pg/L (pg/g lipid)	–	0.8	4.9	0.4	0.4	0.4	0.1	0.4	1.6	141.8
		(0.15)	(0.8)	(0.08)	(0.06)	(0.11)	(0.02)	(0.07)	(0.32)	(22.36)
Sum of ind-PCBs	–	218.4	506.2	120.9	114.6	127.6	6.0	100.0	782.0	6890.0
		(43.0)	(108)	(23.9)	(17.2)	(33.3)	(1.2)	(19.9)	(148.6)	(2050.4)
HBM (2x PCBs 138, 153 & 180)	–	187	246.8	131.2	125	137.6	19.6	114.9	516.7	3946.4
		(37.5)	(50.8)	(26.1)	(18.8)	(36.2)	(3.5)	(23.6)	(105.0)	(817.4)

ratio and DDT + DDE sum are also presented.

As mentioned earlier, elevated levels of DDE have been reported in 6.5-year-old children from the RHEA cohort in Crete, in comparison to the levels observed in children from other European countries. In the study conducted by Haug and colleagues (Haug et al., 2018), levels of DDT, DDE, and HCB were presented for mother–child cohorts from six European countries: the UK, France, Spain, Lithuania, Norway, and Greece, as part of the HELIX project (Maitre et al., 2018). Mothers participating in the study by Haug and colleagues (Haug et al., 2018) constitute a subset of the mothers whose children are involved in the current study. The median concentration of DDE in the RHEA cohort was 60.1 pg/mg lipid, compared to 11.1 in the BIB cohort from the UK, 12.9 in the EDEN cohort from France, 17.3 in the INMA cohort from Spain, 47.1 in the KANC cohort from Lithuania, and 17.9 in the MoBa cohort from Norway. Consequently, it was considered significant to further investigate OCP levels in children from the RHEA cohort. In the present study, the levels determined in the total study population were as follows: for HCB, they ranged from 2.8 to 204.8 pg/mg lipid (with a median of 10.4 pg/mg lipid); for DDE, the range was 8.8 to 4682 pg/mg lipid (with a median of 80.5 pg/mg lipid); and for DDT, the range was 0.2 to 210 pg/mg lipid (with a median of 4.6 pg/mg lipid), as shown in Table 1. The elevated levels previously reported by Haug and co-workers (Haug et al., 2018) in 6.5-year-old children from Crete were confirmed by the findings of the present study in this age group, with a median of 88.4 pg/mg lipid. The increased median DDE levels in the 6.5-year-old group (88.4 pg/mg lipid) compared to the study by Haug et al., 2018 (60.1 ng/g lipid) can be attributed to the different number of subjects in this group (239 vs. 199 in the previous study). Additionally, longitudinal birth cohorts, from which our study draws resources, are exposed to the risk of losing subjects to follow-up and possible selection bias (Maitre et al., 2018). The maximum concentrations of DDE for this age group were 3732 ng/g lipid in the present study and 2158 in the study by Haug et al., 2018. Furthermore, elevated levels of DDE were also found in the 4-year-old children (median 111 pg/mg lipid), while the lowest concentrations of DDE were determined in the 11-year-old group (median 54.9 pg/mg lipid).

The DDT/DDE ratio, which provides an indication of the timing of exposure, was also calculated. Ratio values > 1 indicate recent exposure to DDT (Zhang et al., 2018), while values < 1 are attributed to past exposure to DDT and suggest possible ongoing indirect exposure through food consumption (Ahlborg et al., 1995; Koepke et al., 2004). The DDT/DDE ratio does not take into consideration the contribution of dicofol, where DDD (dichlorodiphenyldichloroethane) is included in the formula. Nevertheless, it remains a useful indicator for continued DDT use. Among all the examined subjects, only two individuals showed a DDT/DDE ratio > 1, one in the 6.5-year-old group and another in the 11-year-old group (see Supplementary Material, Tables S1-S3).

In the study conducted by Haug and colleagues (Haug et al., 2018), elevated levels of DDE were also reported for mothers in the RHEA cohort in Crete, compared to mothers from six other European countries within the HELIX project. The median concentration of DDE in the RHEA cohort was 168 ng/g lipid, compared to 24.9 in the BIB cohort from the UK, 64.1 in the EDEN cohort from France, 62.8 in the INMA cohort from Spain, and 26.6 ng/g lipid in the MoBa cohort from Norway.

Given the decrease in DDE concentration from birth to 11 years of age and the estimated half-life of DDT/DDE in humans (between 3–5 years) (EFSA, 2006b), we can infer that children in Crete were exposed to DDT/DDE either in utero or through breastfeeding and food intake during their early years, when energy demands are high and food intake per kilogram of body weight is elevated. DDT and DDE were detected in breast milk of nursing mothers, with median concentrations of 2.0 ng/g fat and 68 ng/g fat respectively (Rovira et al., 2022). Additionally, breastfeeding duration was significantly associated with serum concentrations of DDE in adolescents (Zamaratskaia et al., 2022). It is noteworthy that approximately 52 % of Rhea children were breastfed during their first six months of life (Leventakou et al., 2015). Moreover,

the increase in body size with age is accompanied by an increase in blood volume, which could also partially account for the decline in DDE concentration at 11 years.

The relatively high serum levels of DDE in the present study raise concerns regarding DDT levels in food products in Crete. As mentioned in the introduction, according to Europol, illegal and counterfeit pesticides circulate in EU member states (Europol, 2012; Europol, 2023). The use of these pesticides in agriculture may result in elevated levels in food, representing a significant route of exposure for humans. Further investigation into DDT levels in food appears necessary to safeguard public health. Additionally, it is important to note there is a significant lack of data of DDT and DDE levels in food in Greece. Therefore, further investigation, encompassing both human exposure and food contamination, is essential to protect public health.

3.2. PCBs

Levels of PCBs in the total study population are presented in Table 1, and the corresponding levels per age group can be found in Tables S1 to S3. In addition to the congener-specific concentrations, the sum of ind-PCBs, and the total TEQ of m.o.-PCBs and human biomonitoring (HBM) values are also reported. The non-ortho PCB congeners, which are also dioxin-like and contribute to the total PCB TEQ, were not included in the study due to their very low levels in the blood and determining them in the available sample amount was not possible. Consequently, the calculation of the total PCB TEQ was not feasible. Data for m.o.-PCBs are considered significant due to their toxicity (Bora Plaku et al., 2023; Korrick et al., 2000); therefore, the total TEQ of m.o.-PCBs is reported in the present study. For the total study population, the maximum median concentration of 26.9 pg/mL (5.4 pg/mg lipid) was determined for PCB 28, followed by PCB 153 at 26.7 pg/mL (5.4 pg/mg lipid) and PCB 180 at 17.2 pg/mL (3.4 pg/mg lipid), respectively. In all age groups, the most abundant compounds, in addition to PCB 28, were the non-dioxin-like congeners 138, 153, and 180, which belong to the ind-PCBs group.

The median concentrations of dioxin-like m.o.-PCBs for the entire cohort population ranged from below the limit of detection (LOD) for PCB 189 up to 4.8 pg/mL (0.9 pg/mg lipid) for PCB 118, which was the most abundant congener in this category across all age groups. A similar observation was reported in a study conducted in Norway (Caspersen et al., 2016a). The TEQ concentrations of m.o.-PCBs in the total population of the present study ranged from 0.02 to 22.36 pg/g lipid.

Concentration thresholds in human plasma have also been proposed by the French Food Safety Agency (AFSSA) as follows: 700 pg of total PCBs/mg plasma lipids for pregnant women, women of childbearing age, lactating women, and children under three years old. Due to the bioaccumulative potential of PCBs in the body and the resulting increase in concentration levels with age, the AFSSA also proposes this threshold for young and adolescent girls (AFSSA, 2010). The same agency also suggests the value of 1800 pg of total PCBs/mg of plasma lipids as the critical concentration level for the rest of the population, including boys over three years old, adult men, and women over 45 years old. Based on the AFSSA's opinion, previous studies have considered that for the sum of six indicator PCBs, representing 50 % of all PCBs, the critical concentration threshold (EFSA 2006b; 2018; Jansen et al., 2018) should be respectively 350 pg/mg and 900 pg/mg of plasma lipids (Jansen et al., 2018).

The sum of ind-PCBs levels determined for the total population ranged from 1.2 to 2050 pg/mg lipids, with median values of 25.3, 24.1, and 14.4 pg/mg lipids for the 4-, 6-, and 11-year-old participants, respectively. Among the female children, 0.8 % (N = 3) exceeded the 350 pg/mg lipids threshold, and among the entire cohort, 0.03 % (N = 3) exceeded the 900 pg/mg lipids threshold for the sum of six indicator PCBs, indicating generally safe exposure levels for the majority of the Rhea cohort's population, but with some concerning exceptions. The Human Biomonitoring (HBM) value for PCBs, derived by the German Human Biomonitoring Commission for infants, toddlers, and women of

childbearing age, is based on the finding that the sum of three PCB congeners, 138, 153, and 180, represents about 50 % of the total PCBs in human serum (Grandjean et al., 2001; Morck et al., 2014). It is calculated by adding the concentrations of PCB 138, 153, and 180 and multiplying the sum by 2. There are two proposed limits set at 3500 pg/mL in serum (HBM-I), where no adverse health effects are expected, and at 7000 pg/mL in serum (HBM-II), where no increased risk is expected, and there is no urgent need for exposure reduction (Bandow et al., 2020). Only one participant in the 4-year age group was found to have an elevated HBM value of 3946 pg/mL (Supplementary Material; Table S1), but it still remained below the HBM-II threshold. HBMs for all subjects (N = 946) were found below HBM-I, ranging from 19.6 to 2298 pg/mL, with median values of 144.3 pg/mL for the 4-year-old group, 148.4 pg/mL for the 6.5-year-old group, and 85.62 pg/mL for the 11-year-old group (Supplementary Material; Tables S1 – S3).

3.3. Exposure patterns

Exposure patterns and common sources of OCPs and PCBs were investigated using bivariate and multivariate statistics. Bivariate analysis (Spearman correlations) revealed numerous strong correlations between OCPs and PCBs, which are presented in heatmap form in Fig. 1 (corresponding p-values are shown in the Supplementary Material; Table S4). The analysis was performed on the entire population (all three age groups combined) and on data unadjusted for lipids since it yielded similar results when performed separately for each age group and for lipid-adjusted data (Supplementary Material; Figures S1-S4). The heatmap illustrates a positive correlation between HCB and DDE

(DDT probably isn't correlating due to much lower levels and being closer to the limit of detection). This correlation might be attributed to contaminated food resulting from illegal pesticide use. However, DDE and HCB also positively correlate with PCBs 138, 153, and 180, implying combined dietary exposure since these congeners have been found to accumulate in food of animal origin (EFSA 2010; Montano et al., 2022). Moreover, PCBs 138, 153, and 180 have been found to correlate well in breast milk, which is a significant exposure source for young children (Skrbic et al., 2010). They are highly chlorinated homologues (hexa- and hepta-chlorinated biphenyls) containing a phenyl group with 2,4,5-substitution, which seems to render them resistant to degradation with high bioaccumulation potential (Megson et al., 2015). This could also explain their strong correlation with PCB 118, 156, and 167, while they exhibit an inverse correlation with the lower-chlorinated PCB 28, 52, and 101, indicating two distinct competing exposure sources. PCBs 28 and 52 are also considered to have lower bioaccumulation potential (Bjermo et al., 2013; Megson et al., 2015). For PCB 28, which showed the maximum median concentration in the study population, previous studies have suggested that this might be attributed to additional exposure through inhalation. Although dietary exposure is considered the primary human exposure route for PCBs, airborne exposure and its correlation with body burden are also under investigation for the lower-chlorinated PCB 28 (Harrad et al., 2009; Meyer et al., 2013; Morck et al., 2014).

We concurrently performed principal component analysis (PCA, Fig. 2) to simplify data interpretation and more effectively investigate the sources of OCP-PCB exposure. Similar results were obtained for unadjusted OCP-PCB levels in the entire population, as well as when analyzed by age and lipid normalization (Supplementary Material;
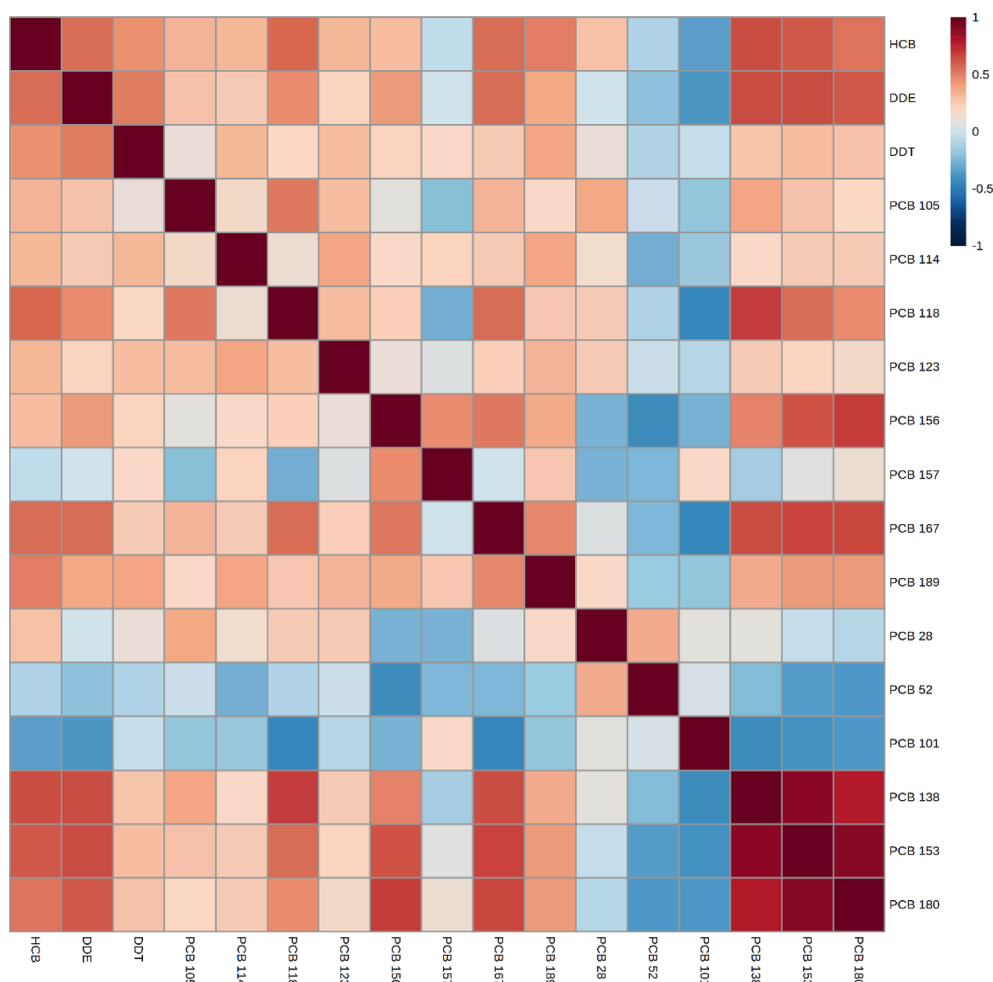

Fig. 1. Heatmap based on two-tailed Spearman correlations between unadjusted levels of OCPs and PCBs in Rhea children.
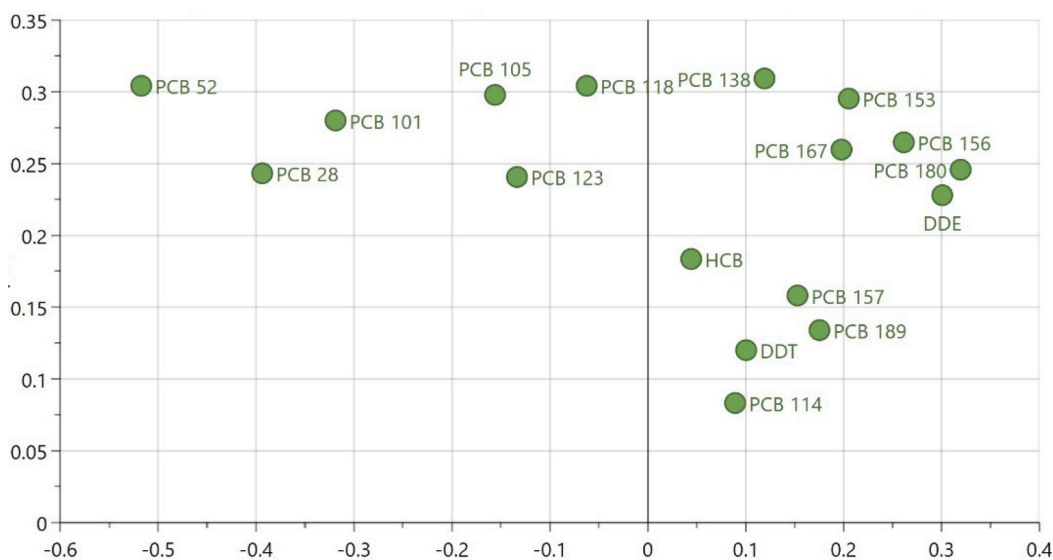
Fig. 2. Principal component analysis – Loading plot: Two distinct groups of OCP and PCB exposure .
Sources were identified

Figures S5-S8). PCA revealed two distinct groupings of exposure, as shown in the loading plot (Fig. 2): I) DDE with a series of PCBs (153, 156, 163, 180), indicating a combined OCP-PCB source, and II) an anti-correlation of PCBs 52, 28, and 101, indicating a separate and competing source. These findings confirm and enhance the results of the bivariate analysis.

3.4. Correlation with child sex and age

There is no significant difference in PCB or OCP levels based on child sex when tested with the Mann-Whitney U test and multiple comparison correction.

A clear negative correlation between child age and the concentration levels of all measured compounds (OCPs and PCBs) and calculated parameters (DDT/DDE ratio and sum, HBM, and TEQ-PCBs) was observed.
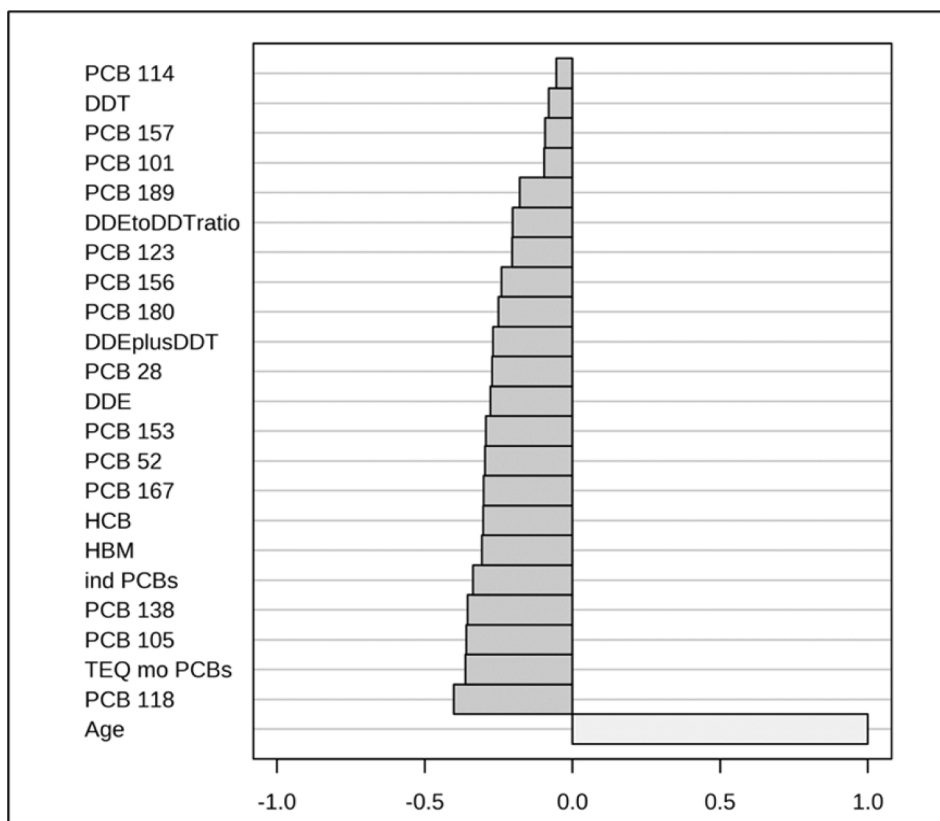

Fig. 3. OCP-PCB levels and age: A two-tailed Spearman correlation analysis was performed to examine the relationship between OCP-PCB levels and age across all groups, revealing a negative correlation for all examined PCBs, OCPs, and calculated parameters.

This negative correlation is evident in the Spearman correlations (Fig. 3) when the entire population was analyzed. Additionally, significant differences were observed when comparing the three age groups using univariate statistics (Kruskal-Wallis test followed by Tukey HSD correction, see Supplementary Material; Table S5).

A subset of N = 34 subjects provided samples at ages 4, 6.5, and 11 years old, and a similar declining concentration trend was observed, as presented for selected parameters in the Supplementary Material (Figure S9). The matched samples have substantially lower numbers, primarily due to operational reasons such as loss of follow-up, a typical issue in such studies (Maitre et al., 2018). However, the fact that the observed trends align fully with the unmatched samples from the full cohort reinforces the validity of the presented findings.

Blood levels of HCB, DDE, and PCB were observed to decrease with age. This can be partially attributed to the decline in food intake per kilogram of body weight with increasing age, while blood volume increases (refer to Fig. 3). Notably, there is a more significant decline in the case of PCBs compared to that of DDE and HCB, as depicted in the corresponding figure. One possible explanation for this difference is that at earlier ages, the influence of breastfeeding has a stronger effect on PCB levels.

3.5. Comparison with other studies – Meta-analysis table

In all the considered studies (Tables 2 and 3), there is a general declining trend in the absolute levels of OCPs and PCBs, although substantial levels of all the examined chemicals are still observed.

The OCP exposure assessed in our study generally differs from the corresponding reports in other countries (Table 2). Exposure to DDE was found to be higher for children in Greece compared to all the mentioned studies, except for one report from the USA (Hernandez et al., 2019) and another from Slovakia (Sisto et al., 2015). DDT values determined in the present investigation were also the highest, following those reported in Slovakia (Sisto et al., 2015). The highest ratios were observed in Denmark (8 %), Slovakia (7 %), and Greece (6 %). Children's HCB concentration levels in Greece were generally lower than in the other countries (Table 2), except for one report from the USA (Hernandez et al., 2019).

The exposure to PCB congeners measured in the present study differs from that reported in other countries (Table 3). The exposure to m.o.-

PCB congeners 105, 114, 118, 123, 156, 157, 167, and 189 is difficult to compare, as there are few reports in the scientific literature. However, the levels in Greece are generally lower than those reported for Norway (Caspersen et al., 2016b). For the indicator PCBs (28, 52, 101, 138, 153, and 180), the levels in Greece are lower than in China (Guo et al., 2020), Germany (Bandow et al., 2020), Norway (Caspersen et al., 2016b), and Spain (Gonzalez-Alzaga et al., 2018). The congeners belonging to the HBM group were measured in lower concentrations than the corresponding ones in Norway (Caspersen et al., 2016b) and Spain (Gonzalez-Alzaga et al., 2018). Despite the influence of nutritional variations between the examined countries and the inevitable differences in exposure levels, the comparisons above suggest a clear need for harmonization in both the acquisition and reporting of such results. This includes detailed reporting of analytical methodologies, results from intercalibration studies or ring-trials, common storage and sample handling conditions, and the incorporation of a specific set of descriptive statistics along with both raw and lipid-normalized results.

Furthermore, a repository for exposomics studies, such as MetaboLights (Haug et al., 2020) or GNPS (Wang et al., 2016) for metabolomics, will enable the effective co-analysis of multiple studies from various cohorts and different contaminants. This will facilitate the drawing of general conclusions about a broader geographical impact of environmental pollution and a more effective investigation of the possible cumulative exposure effects that can ultimately influence policymakers.

4. Conclusions

The systematic investigation of blood levels of OCPs and PCBs in Greek children from the Rhea study birth cohort revealed that DDE and PCB 28 were the most abundant compounds in their respective categories.

Elevated levels of DDE were reported for 6.5-year-old children in the Rhea cohort compared to levels in other European countries. Furthermore, higher levels of DDE were found in the 4-year-old children, with the lowest concentrations observed in the 11-year-old group. The DDT/DDE ratio, among all the examined subjects, showed values less than 1, with only two individuals exceeding it. A decline in DDE concentration from birth to 11 years of age was observed, suggesting that Rhea children in Crete were exposed in utero to DDT/DDE and possibly through breastfeeding and food intake during the first years of their lives.

For the total study population, the highest concentration was determined for PCB 28, followed by the non-dioxin-like congeners 138, 153, and 180. The sum of the 6 indicator PCBs indicated generally safe exposure levels, with some concerning exceptions, for the majority of the Rhea cohort's population. The HBM value for PCBs across all age groups was found to be below 3500 ng/L, a value where no adverse health effects are expected.

Exposure patterns, investigated using bivariate and multivariate statistics, showed a positive correlation between HCB and DDE, attributed to contaminated food from pesticide use. PCA confirmed combined OCP-PCB sources.

The comparison of our results with those of other countries highlights the clear need for harmonization in the reporting of results.

The relatively high serum levels of DDE in the present study raise concerns about the levels of DDT in food products in Crete, for which further investigation appears necessary to protect public health.

CRediT authorship contribution statement

Danae Costopoulou: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation. **Kleopatra Kedikoglou:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Marina Vafeiadi:** Resources, Formal analysis. **Theano Roumeliotaki:** Resources. **Katerina Margetaki:** Resources, Formal analysis. **Euripides G. Stephanou:** Writing – review & editing, Writing – original draft, Supervision,

Table 2

Comparison of OCP levels with similar studies, lipid adjusted, median levels, pg/mg lipid.

Country	Age (y)	N	HCB	DDE	DDT
Greece-present study	4–11	947	10.4	80.5	4.6
Greece- (Haug et al., 2018)	6.5	197	7.5	60.1	1.7
Denmark (Morck et al., 2014)	9	116	14.0	38.0	3.0
Germany (Bandow et al., 2020)	3–17	1135	<LOD	26.7	<LOD
Jamaica (Bach et al., 2020)	2–8	169	<LOD	71.1	<LOD
Norway (Caspersen et al., 2016b)	3	99	26.0	57.0	1.7
Slovakia (Sisto et al., 2015)	0.5	351	72.1	451.4	30.5
Slovakia (Sisto et al., 2015)	1	351	66.5	542.6	19.2
Slovakia (Sisto et al., 2015)	4	351	51.7	462.1	16.2
Spain (Gonzalez-Alzaga et al., 2018)	9	133	90.0	62.0	–
USA-urban (Marek et al., 2014)	12–15	50	–	–	–
USA-rural (Marek et al., 2014)	12–15	49	–	–	–
USA-Texas_A (Hernandez et al., 2019)	5–18	57	6.2	91.4	2.8
USA-Texas_B (Sjodin et al., 2014)	0–2	50	–	36.3	–
USA-Texas_A (Hernandez et al., 2019)	2–4	50	–	63.1	–
USA-Texas_B (Sjodin et al., 2014)	4–6	50	–	50.2	–
	6–8	50	–	57.7	–
	8–10	50	–	55.6	–
	10–13	50	–	73.0	–

Table 3

Comparison of PCB levels with similar studies, lipid adjusted, median levels, pg/mg lipid.

Country	Age (y)	N	PCB 28	PCB 52	PCB 101	PCB 105	PCB 114	PCB 118	PCB 123	PCB 138	PCB 153	PCB 156	PCB 157	PCB 167	PCB 153	PCB 180
Greece-present study	4–11	947	5.4	0.5	0.6	0.3	0.1	0.9	0.1	2.7	5.4	0.3	0.2	0.1	5.4	3.4
Greece- (Hauget al., 2018)	6.5	197	–	–	–	–	–	1.6	–	3.7	7.8	–	–	–	–	1.8
China-exposed (Guoet al.,2020)	12	57	30	71	28	–	–	–	–	9.1	5.9	–	–	–	5.9	110
China-control (Guoet al., 2020)	12	57	0.1	41	10	–	–	–	–	0.04	0.04	–	–	–	0.04	87
Denmark (Morcket al., 2014)	9	116	3	<LOD	<LOD	<LOD	–	<LOD	–	16	23	<LOD	–	–	23	14
Germany (Bandowet al., 2020)	3–17	1135	<LOD	<LOD	2.86	–	–	1.99	–	9.41	13.1	–	–	–	13.1	6.44
Jamaica (Bachet al., 2020)	2–8	169	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	13.7	<LOD	<LOD	<LOD	13.7	5.8
Norway (Caspersen et al., 2016b)	3	99	–	–	–	2.1	0.5	14.0	–	29.0	57.0	3.8	0.8	1.3	57.0	26.0
Slovakia (Sisto et al., 2015)	0.5	351	–	–	–	–	–	–	–	–	129.7	–	–	–	129.7	–
	1	351	–	–	–	–	–	–	–	–	141.5	–	–	–	141.5	–
	4	351	–	–	–	–	–	–	–	–	121.3	–	–	–	121.3	–
Spain (Gonzalez-Alzagaet al., 2018)	9	133	–	–	–	–	–	–	–	35.0	65.0	–	–	–	65.0	82.0
USA-urban (Marek et al., 2014)	12–15	50	–	<LOD	–	<LOD	<LOD	<LOD	–	–	–	–	–	<LOD	–	–
USA-rural (Marek et al., 2014)	12–15	49	–	<LOD	–	<LOD	<LOD	<LOD	–	–	–	–	–	<LOD	–	–
USA Texas A (Hernandez et al., 2019)	5–18	57	–	–	–	–	–	–	–	–	–	–	–	–	–	–
USA Texas B (Sjodin et al., 2014)	0–2	50	–	–	–	–	–	–	–	–	2.1	–	–	–	2.1	–
	2–4	50	–	–	–	–	–	–	–	–	1.2	–	–	–	1.2	–
	4–6	50	–	–	–	–	–	–	–	–	1.5	–	–	–	1.5	–
	6–8	50	–	–	–	–	–	–	–	–	2.1	–	–	–	2.1	–
	8–10	50	–	–	–	–	–	–	–	–	2.2	–	–	–	2.2	–
	10–13	50	–	–	–	–	–	–	–	–	1.9	–	–	–	1.9	–

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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.

Acknowledgments

Author statement

The revised manuscript, ENVINT D-23-04882, incorporates feedback from the reviewers and follows the suggestions provided by the handling Editor. We are submitting our revised manuscript in two versions: I) a version with tracked changes, and II) a 'clean' manuscript. We also submit the revised Supporting Information file and a document with the replies to reviewer comments and suggestions.

As such, we anticipate that our results will be of interest to the broader scientific community in the field of Environment International.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.108686.

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