Determinants of increasing serum POPs in a population at high risk for cardiovascular disease. Results from the PREDIMED-CANARIAS study

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A B S T R A C T

Persistent organic pollutants (POPs) are well-known ubiquitous environmental chemicals which have been related to adverse health outcomes, including cardiovascular disease (CVD). The purpose of this study was to evaluate POPs burden, and its determinants, in a population at high risk of suffering CVD enrolled in the PREDIMED Study (Spanish acronym for PREvention by means of MEDiterranean Diet). This cohort was formed by 343 participants (55 – 80 y.o.), which were selected for a preventive nutritional intervention for CVD based on the Mediterranean Diet. Relevant information on demographic, behavioral, dietary, and socioeconomic characteristics was obtained from each participant through a specific questionnaire, and their anthropometric and clinical measurements were recorded. In addition, the levels of 35 POPs were determined in serum samples taken before the beginning of the nutritional intervention. All the samples showed detectable levels of, at least, one POP, being DDT-derivatives and marker-PCBs the most frequently detected compounds. Our results showed that people at high risk for CVD showed a higher level of contamination by POPs as compared to other studies done in cohorts of Western people at no special risk of CVD. Although educational level seems to be a relevant determinant for POPs burden in our population, the main determining factor seems to be the diet. Thus, while the intake of food of animal origin was significantly associated with levels of PCBs, especially in men, the intake of vegetal-origin food was positively related to levels of organochlorine pesticides, indicating a different dietary source for these two groups of chemicals. Our results suggest that dietary interventions could be a useful tool for decreasing the body burden of certain POPs, but also clearly indicate that there is not a “safe” dietary pattern regarding POPs’ exposure. Our results showing that subjects at high risk for cardiovascular

disease present elevated POPs burden might have a relevant public health impact given the generalized and difficult to avoid exposure to POPs and the elevated worldwide frequency of the CVD.

Keywords: PREDIMED, Cardiovascular disease, Persistent organic pollutants, dietary habits, Canary Islands

1. Introduction

Lipophilic persistent organic pollutants (POPs) are ubiquitous and found globally due to long-range transport. These chemicals are resistant to degradation and tend to accumulate in the environment, food chains and living organisms [1]. Many studies indicate that most human beings exhibit POPs at detectable levels all over the world [1, 2]. Nowadays, there is increasing evidence of potential adverse health outcomes derived from exposure of the general population to POPs at levels traditionally considered “safe” [3]. Among POPs, organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs) may be particularly interesting because the exposure to them has been strongly linked to relatively frequent chronic diseases, including diabetes mellitus, cancer, dyslipidemia, obesity, and cardiovascular diseases [4-13]. In this regard, POPs have been proposed to play a role in the etiology of cardiovascular disease (CVD) [14]. Although atherosclerosis and adverse cardiovascular events have been observed in some studies as a result of PCB exposure, the mechanisms responsible for this relationship have not been clearly elucidated [15-17]. Furthermore, thereby favoring adverse cardiovascular events. Additionally, OCPs and PCBs have also been associated with higher risk of

cardiovascular mortality (mainly in older people with low fat mass) [18]. The possibility that the amount of fat mass can modify the associations between POPs and CVD mortality could be relevant in modern societies that suffer from an obesity epidemic [18].

In the majority of the general population (not occupationally exposed) POPs exposure occurs largely through dietary intake [19]. In fact, numerous studies have monitored the presence of residues of POPs in many types of foods, including fish, dairy products, meat, fruits and vegetables. The results of these studies indicate that meat, fish and dairy products are important contributors to total dietary intake of POPs [20-24]. However, the contribution of specific food items and lifestyle patterns to the POP burden is not completely understood [25-27].

In this context, the PREDIMED Study (a large interventional dietary study based on the Mediterranean Diet, which enrolled participants at high risk for CVD), represents an excellent opportunity to measure basal POPs levels in people at high risk to suffer CVD in order to establish the relevance of historical exposure to POPs in the development of pathological processes related to CVD, and the main determinants, of POPs burden in such a peculiar population.

2. Material and methods

2.1. Study Population

The present study was conducted within the framework of the PREDIMED Study, which aimed to assess effects of the Mediterranean diet on the primary prevention of CVDs in Spain. The PREDIMED study was a large, parallel-group,

multicenter, randomized, controlled, clinical trial designed to assess the effects of the Mediterranean diet on the primary prevention of CVD [28]. The protocol and recruitment methods have been reported in detail elsewhere [29]. Eligible participants were men aged 55–80 and women aged 60–80 years without any history of cardiovascular disease but fulfilling at least one of the following two criteria: type-2 diabetes or three or more cardiovascular risk factors (family history of early-onset CVDs, hypertension, current smoking, low HDL-cholesterol, high LDL-cholesterol, and overweight or obesity). Exclusion criteria included any severe chronic illness, previous history of CVDs, alcohol or drug abuse, body mass index (BMI) of more than 40 kg/m^2, and history of allergy or intolerance to olive oil or nuts. The trial was stopped after a median follow-up of 4.8 years due to the benefit of the Mediterranean diet with respect to major cardiovascular events: myocardial infarction, stroke, or death from cardiovascular causes compared to a control low-fat diet [30]. As previously reported [31], all participants comprised a 47-item questionnaire assessing socio-demographic characteristics, medical conditions, medication use, and lifestyle habits, a 14-item questionnaire assessing MedDiet adherence, a 137-item food frequency questionnaire, used to assess nutrient and energy intake, and the Spanish version of the Minnesota Leisure-Time Physical Activity questionnaire.

The present analysis deals with a subsample from one of the eleven recruitment centers (PREDIMED-CANARIAS). The PREDIMED-CANARIAS recruitment center included the 357 subjects participating in the trial. For this work, only the participants with available serum samples at the beginning (baseline) of the nutritional intervention were included (n = 343 subjects). Table 1 summarizes the characteristics of the study population.

2.2. Analytical chemical methods

We measured the plasma levels of 17 OCPs: the ubiquitous hexachlorobencene (HCB), hexachlorocyclohexane (isomers α-, β-, γ-, δ-HCH), *p,p'*-DDT, *o,p'*-DDT, *p,p'*-DDE, *o,p'*-DDE, *p,p'*-DDD, *o,p'*-DDD, aldrin, endrin, dieldrin, endosulfan (α-, and β-isomers), and endosulfan sulphate. We also determined 18 PCB congeners, including marker-PCBs (M-PCBs; IUPAC numbers #28, 52, 101, 138, 153, and 180) and dioxin-like PCBs (DL-PCBs; IUPAC numbers #77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169 and 189). The details of sample extraction, validated chromatographic method, and quality control have been previously reported [32, 33]. Briefly, samples were subjected to solid phase extraction using Chromabond® C18ec columns (MachereyNagel, Germany) that yielded recoveries in the range of 89-107%.

Gas chromatography separations were performed on a GC System 7890B equipped with a 7693 Autosampler (Agilent Technologies, Palo Alto, CA, USA). Two fused silica ultra-inert capillary columns Agilent J&W HP-5MS (Crosslinked 5% phenyl methylpolysiloxane, Agilent Technologies) each with a length of 15 m, 0.25mm i.d., and a film thickness of 0.25 μm, were used as the stationary phase. Helium (99.999%) at a constant flow rate of 1.0 mL/min for column 1 was used as the carrier gas. A back-flushing technique was incorporated to the GC at a constant flow rate of 1.2 mL/min for column 2. Back-flushing lasted 5 min during method post-run, at 310ªC oven temperature and 50 psi pressure at the Aux EPC (inlet pressure 2 psi). Temperatures of the oven were programmed as follows: Initial temperature of 60ªC held for 1 min, ramped at 40ªC/min to 170ªC and then at 10ªC/min to 310ªC with 3 min hold time. Total run time was 20.75 min. Injector and transfer line were set at

280ªC. Standards and samples were injected (1 µL) in the splitless mode using a 4-mm ultra-inert liner with glass wool (Agilent Technologies).

The GC was interfaced with a Triple Quad 7010 mass spectrometer (Agilent Technologies, Palo Alto, CA, USA). Retention Time Locking (RTL) of the analytes with chlorpyrifos-methyl (Rt = 9.143 min) as the time reference was used. The retention times, precursor and fragment ions, as well as the collision energies selected in this method have been previously published [33, 34]. Nitrogen (99.99% , 1.5 mL/min)) was used as the collision gas. The QqQ mass spectrometer was operated under the following conditions: ionization with electron impact at 70 eV in MRM with an emission current of 100.0 µA. The ionization source temperature was set at 230ªC. The dwell time was set at 10 for all the analytes, and the scan width was assigned to each compound using the MassHunter WorkStation software for quantitative analysis (version B.07.01/Build 7.1.524.0 for QQQ; Agilent Technology, Inc. 2008). Peak widths of m/z 0.7 Da were set in both, the first (Q1) and third quadrupole (Q3).

The quantification was based on peak area. Ten-point calibration curves were constructed using a least-squares linear regression from the injection of blank serum samples spiked with solutions to give final concentrations that ranged from 0.03 to 20 ng/mL. The limits of quantification (LOQ) ranged from 0.03 to 0.15 ng/mL [33].

The total cholesterol and triglyceride concentrations were determined enzymatically and used for the lipid adjustment of results. The results were expressed in ng/g lipid weight (lw) [35].

We expressed the total PCB body burden (∑PCBs) as the sum of the 18 PCBs measured (IUPAC congeners #28, 52, 77, 81, 101, 105, 114, 118, 123, 126, 138, 153, 156, 157, 167, 169, 180, and 189); Marker PCB body burden (∑M-PCBs) as the

sum of those congeners considered as markers of environmental contamination for PCBs (IUPAC congeners #28, 52, 101, 138, 153, and 180); and DL-PCBs body burden as the sum of the 12 DL-PCBs (IUPAC congeners #77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169 and 189) measured. Similarly, we expressed the total value of OCP residues (∑OCPs) as the sum of the 12 OCPs and metabolites measured; the total value of DDT-derivatives measured (ΣDDTs) as the sum of *p,p'*-DDT, *p,p'*-DDE, and *p,p'*-DDD; the total value of HCH residues as the sum of the 4 HCH isomers measured (α-HCH, β-HCH, γ-HCH, and δ-HCH); and the total value of cyclodienes residues (∑cyclodienes) measured as the sum of aldrin, dieldrin, and endrin,. However, due to the fact that the cyclodiene endosulfan was banned recently (Commission Decision of 2 December 2005 (2005/864/EC)), we have considered this pesticide separately, expressing the total value of endosulfan residues (∑endosulfan) as the sum of the 2 endosulfan isomers measured (α-, and β-endosulfan).

2.3. Quality of analyses and quality control (QA/QC)

The analytical methods have been previously validated in our laboratory [1, 36, 37] As reported previously in other human biomonitoring studies from our research group [38, 39], all of the measurements were performed in triplicate. In each batch of samples, three controls were included for every 18 vials (6 samples): a reagent blank consisting of a vial containing only cyclohexane; a vial containing 2 ng/mL of each of the pollutants in cyclohexane; and an internal laboratory quality control sample (QC) consisting of blank serum (Lyophilized human serum, Medidrug Basis Line, Medichem, Germany) spiked at 20 ng/mL of each of the analytes. The QC was processed using the same method as the plasma samples. The results were

considered to be acceptable when the concentration of the analytes determined in the QC sample was within 15% of the deviation of the theoretical value.

2.4. Statistical analysis

We used PASW Statistics v 19.0 (SPSS Inc., Chicago, IL, USA) to manage the database of the study and to perform statistical analyses. To ensure enough statistical power, only POPs detected in ≥ 50% of the series were included in the analyses. The POPs distributions lacked normality and homoscedasticity; therefore, we used non-parametric tests. We used the chi-square test to examine the relationships between the categorical variables. The results were reported as medians and interquartile ranges. Probability levels of less than 0.05 (two tailed) were considered statistically significant.

3. Results and discussion

Serum levels of POPs were determined in a cohort of 343 participants which were selected for a preventive nutritional intervention for CVD based on the Mediterranean Diet. As shown in Table 1, our series was very homogeneous. Only a number of significant differences in relation to gender were evident. Thus, women showed a higher BMI, serum lipids, and education level as compared to men, while among men there was a higher percentage of smokers than among women.

As expected, given the characteristics of the PREDIMED Cohort, we found a high degree of homogeneity in the concentrations and frequencies of detection of serum POPs. It is noteworthy that all analytes included in the study were detected at

least in one sample, and the following chemicals were present in more than 50% of the subjects: HCB, β-HCH, γ-HCH (lindane), aldrin, dieldrin, *p,p'*-DDT, *p,p'*-DDE, and PCB congeners, 28, 52, 101, 105, 118, 138, 153, 156, 167, 180 (Supplementary material 1). Table 2 shows the levels of contamination by POPs (grouped by chemical group) found in the serum of subjects enrolled in the PREDIMED-CANARIAS cohort.

In relation to OCPs, all the analyzed samples showed detectable levels of, at least, one organohalogenated pesticide. As shown in Table 2, the most frequently detected compounds were DDT-derivatives (99.7% of the samples), mainly due to the high frequency of detection of DDE (the main DDT metabolite) that was present in more than 99% of the samples, but also to the high frequency of detection of the parental compound (*p,p'*-DDT) which was present in 88% of the serum samples (Supplementary material 1). Similarly, cyclodiene pesticides were also found in almost all the serum samples (98.8%), mainly due to the high presence of subjects (95.3%) showing detectable levels of dieldrin (data not shown). The median concentration of the most frequently detected compounds were (in ng/g lipid): 3,945.4 for *p,p'*-DDE, 32.56 for *p,p'*-DDT, and 591.23 for HCB (Supplementary material 1). While DDT levels found in subjects included in PREDIMED Study were similar to those described in other population-based studies from Spain [27, 40] and other Western populations including USA [41, 42], *p,p'*-DDE levels found in subjects from PREDIMED-CANARIAS were around 6 fold higher in the present study in relation to levels showed by older people in other population-based studies (Table 3). Similarly, levels of HCB and β-HCH were also higher in subjects at high risk for CVD in relation to results reported in other studies in Spain or other Western countries. Specifically, it has drawn our attention the fact that β-HCH levels were 8 times higher

in subjects at high risk for CVD than in older people from other population-based studies (Table 3). Although recent works have linked OCPs to accelerated atherosclerosis [43] and hypertension [10], a potential association with CVD still needs to be proven.

Detectable levels of any PCB were found in 338 subjects (98.5%, Table 2). As expected, the PCB congeners that contributed more to the total PCB burden (ΣPCBs) were M-PCBs (98.5%), being the congeners 28 and 153 those compounds more frequently detected (97.1 and 95.3%, respectively; supplementary material 1). Most of the samples (95.9%) also showed DL-PCBs at detectable levels, especially due to the fact that PCB-118 was present in more than 95% of the serum samples (Supplementary material 1). In this case, although average levels were similar in the present study as compared to other studies, it has to be taken into account that values showed by the most contaminated subjects (those included in percentile 90) were clearly higher than those reported in other non-risky populations, reaching values as high as 408 ng/g lipid for PCB 153 (Table 3). Such result is of concern because it has been reported that PCBs can increase the expression of vasoconstriction factors such as cyclooxygenase, prostaglandins and reactive oxygen species and decrease the production of the vasodilator nitric oxide [16]. It has been postulated that such PCB-mediated dysfunction in the vascular endothelium is related to the activation of the aryl hydrocarbon (Ah) receptor by PCBs [44]. Consequently, PCB exposure may increase the risk to suffer hypertension and other adverse cardiovascular events [45-47]. In addition, some studies indicate an association between highly chlorinated PCBs and HDL protein alterations that may result in a less functional particle, thus favoring the development of atherosclerotic processes [48]. Endothelial dysfunction, hyperlipidemia and hypertension, are corner

stones in the development of atherosclerosis [17] and, therefore, CVD. In addition, recent works have associated PCB exposure with leukocyte telomere shortening, a phenomenon associated to the occurrence of age-related diseases such as CVD. As a consequence, the leucocyte telomere shortening may thus be a novel predictor of CVD through its association with POPs burden and other risk factors related with risk for development of CVD [49, 50].

Although age is known to be a relevant predictor of serum POPs [1, 51, 52], there were not differences in serum POPs in relation to age in the present study (Table 4). Age correlates in particular with levels of OCPs and those PCB congeners considered as indicators of contamination by PCBs, Marker-PCBs [52]. This positive association among some POPs and age might be explained by previous exposure, even prior to the ban of production and use of certain POPs (such as DDT and PCBs). As shown in Table 4, in our series there was not any relationship among serum POPs and age. This result could be due to the high average age showed by people enrolled in PREDIMED-CANARIAS and to the homogeneity of our series (67.6 ± 5.8 years old; range 55-80 years).

Regarding gender, it is noticeable the important influence that gender seems to exert in total OCPs body burden, with women showing higher levels of these organochlorines than men [53, 54]. On the contrary, significantly higher levels of PCBs were found in males than in females [55, 56]. There is no clear explanation for this gender-related difference. It might be speculated that the low PCB levels in women could be a result of previous lactation [57]. As shown in Table 4, we did not observed significant differences in POPs levels among men and women. Perhaps the homogeneity and increased age of our series may explain such result.

In relation to BMI, our results showing no associations between POPs serum levels and BMI (Table 4) agree with those reported previously. In fact, there are conflicting results in the literature on the association between the obesity rate and POPs burden, with researchers reporting positive, negative, or even no association [58-62].

With regard to educational levels, we found that the level of contamination by DL-PCBs was higher in subjects with lower educational levels for the whole series (Table 4). Even more so, serum levels of M-PCBs, DL-PCBs and Total PCBs among men seem to be positively associated to low educational level (data not shown). Some evidence is available worldwide on the relative influence of educational level (and social class) on body concentrations of POPs in the general population. Thus, it has been reported that educational level influenced serum POPs more than occupational social class, especially in men [63]. However, the potential role played by the educational status on POPs burden is not still resolved, showing contradictory results in epidemiological studies. Nevertheless, our results agree with studies developed on Flemish adolescents showing higher levels of PCBs, and some OCPs, among participants with a higher socioeconomic status [64]. Similarly, in pregnant women from Spain, levels of PCBs and HCB were higher in the uppermost educated groups [65]. On the contrary, education was not associated with POPs burden in Germany population [66] nor in American population [67]. Although our result is not obviously explained by specific dietary patterns in the more educated individuals [68-70], the possibility exists that socially constructed factors, as dietary and lifestyle habits, may play an important role in serum POPs [64]. Nonetheless, with few exceptions [65, 71], POPs have not been documented to contaminate more or less the types of foods preferentially consumed by certain socioeconomic/educational

groups. Even more so, little research has been conducted on the relationship between socioeconomic/educational-related dietary patterns and levels of contamination by environmental chemicals. It is a fact that people in the upper educational levels try to avoid environmental and lifestyle hazards (smoking, sedentarism), but concerns regarding exposure to environmental contaminants remains uncommon [63].

In relation to diet, the characteristics of the food consumption showed in our series were similar between men and women (Table 5). Only some differences between genders were evident: a higher intake of dairy products and bakery in women as compared to men, and a higher intake of cereals (including potatoes) in men with respect to women. As stated previously, the dietary pattern is estimated to account for the majority of human exposure to POPs [19, 72, 73]. In spite of the similarities in dietary pattern between men and women in our series, we have found a number of dietary patterns capable of affecting POPs burden differently in men and women (Table 6). Interestingly, men showing the highest intake (those included in the fourth quartile) of foods of animal origin (dairy products, meat, and fish) had higher serum PCBs (both dioxin-like and non-dioxin-like PCBs), while women showing the highest intake of foods of animal origin showed increasing serum HCB. On the contrary, men showing the highest intake of vegetable foods (cereals, fruits, legumes, and vegetables) showed higher serum OCPs. These findings have to be taken with caution due to the limited number of subjects in each quartile (Table 6), although agree with our previous reported data in the sense that meat-consumption increased the risk of exposure to DL-PCBs [25], and to those reported by others suggesting that meat, dairy products, and fish account for more than 90% of PCB intake in the general population [73-76]. In any case, the present results reinforce the

possibility of interaction between POPs and the amount of fat mass —determined by the diet— on risk of mortality from chronic diseases, an association clinically important in modern societies with an obesity epidemic [18]. However, other factors influencing serum levels of POPs (i.e., smoking) must be taken into account [77].

Despite the fact that POPs have been proposed to play a role in the etiology of CVD [17], to the best of our knowledge, this work is one of the few studies describing the basal level of contamination by POPs showed by a population at high risk to suffer CVD, evaluating, additionally, the main determining factors of serum POPs in such a specific population.

4. Conclusions

In summary, our study demonstrate that most subjects enrolled in the PREDIMED-CANARIAS cohort showed high levels of contamination by POPs, being especially remarkable the high levels of PCBs (especially dioxin-like PCBs) because of their known toxic effects on vascular system. Having into account that our series is made up of subjects at high risk for CVDs, and that POPs have been associated to the disease, our results are highly interesting because suggest a potential association among historical exposure to POPs and risk of CVD. Additionally, our results seem to indicate that modifying dietary patterns may be useful to decreasing POPs burden and, therefore, to decrease the risk to suffer CVD. Nevertheless, because foods of animal origin are linked to increasing PCBs, but vegetable foods are also related to increasing serum OCPs, it could be said that there is not a “safe” diet in relation to POPs exposure. Furthermore, our reported association between dietary pattern and contamination with these chemicals should be considered a public health concern, requiring continued monitoring of POPs levels in food.

Interestingly, our findings showing different dietary determinants for serum POPs for men and women deserve special attention because it is recognized that gender may play a relevant role as a health inequality factor [78]. In any case, further research is needed on this regards, designing case controls studies aimed to better understand complex role of diet, exposure to POPs and CVDs.

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Declaration of interest

The authors have no conflicts of interest to declare.

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Tables

Table 1
Characteristics of the participants.

	Total (n = 343)		Men (n = 117)	Women (n = 226)
Variables	Mean ± SD or proportion	Range	Mean ± SD or proportion	Mean ± SD or proportion
Age (years)[a]	67.6 ± 5.8	55.0 – 80.0	67.1 ± 6.1	67.9 ± 5.6
Total lipids (g/L)	6.2 ± 1.3	3.1 – 16.4	5.8 ± 1.2	6.4 ± 1.4***
BMI (kg/m^2)	31.0 ± 3.8	21.4 – 40.0	30.2 ± 3.5	31.5 ± 3.9**
Smoking habits (n, (%): yes)	31 (9.0)		27 (23.1)	4 (1.8)***
Married (n, (%): yes)[b]	247 (72.0)		106 (90.6)	141 (62.4)***
Level of studies (n, (%): yes)				
Primary school	295 (86.0)		87 (74.3)	208 (92.0)***
Secondary school	33 (9.6)		21 (17.9)	12 (5.3)
High school/University	15 (4.4)		9 (7.7)	6 (2.6)

Abbreviations: BMI: body mass index; SD: standard deviation.
[a] Variable normal distributed.
[b] Other civil status included: single, divorcee and widower.
**$p < 0.001$; *** $p < 0.0001$.

Table 2
Concentrations of persistent organochlorine pollutants (ng/g lipid) in the whole series (n = 343)

				Percentile			
	Detection (n, %)	Geometric mean	Minimum	**25th**	**50th**	**75th**	Maximum
PCBs							
ΣM-PCBs	338 (98.5)	627.9	2.4	353.5	527.7	760.2	3899.5
ΣDL-PCBs	329 (95.9)	96.6	3.6	50.3	77.7	126.5	662.6
ΣTot-PCBs	338 (98.5)	724.6	2.4	409.3	607.6	886.9	4183.3
OCPs							
HCB	330 (96.2)	823.3	2.6	221.8	591.2	1173.9	5120.6
ΣHCH	331 (96.5)	2282.6	3.6	803.3	1639.8	2789.6	22940.4
ΣCyclodienes	339 (98.8)	192.4	6.1	105.5	164.2	234.7	1382.2
ΣEndosulfans	2 (0.6)	0.05	6.4	0.0	0.0	0.0	10.5
ΣDDTs	342 (99.7)	6663.3	4.3	1866.3	3970.0	8278.7	52429.1
ΣOCP	343 (100.0)	9966.7	11.1	3676.5	7182.7	13315.2	61366.6

Abbreviations: PCBs: polychlorinated byphenils; OCPs: organochlorine pesticides; HCB: hexachlorobenzene; HCH: hexachlorocyclohexane; DDT: dichloro-diphenyl-trichloroethane; ΣM-PCBs: sum of marker PCBs (IUPAC congeners #28, 52, 101, 138, 153, and 180); ΣDL-PCBs: sum of dioxin-like PCBs (IUPAC congeners #77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169 and 189); ΣTot-PCBs: sum of all 18 PCBs cited above; ΣCyclodienes: sum of aldrin, endrin and dieldrin; ΣHCH: sum of α-, β-, γ-, and δ-isomers; ΣEndosulfans: sum of α- and β-endosulfan, and endosulfan-sulphate; ΣDDTs: sum of *o,p'*-DDD, *p,p'*-DDD, *o,p'*-DDE, *p,p'*-DDE, *o,p'*-DDT, and *p,p'*-DDT; ΣOCP: sum of all OCPs.

Table 3
Serum POPs in the present study (PREDIMED-Canarias) in relation with POPs levels described in other studies evaluating general population. Data express median values and percentiles in ng/g lipid. Basic characteristics of each series are described.

	PREDIMED CANARIAS (age 55-80) 2003 p75-p90	USA NHANES (age >20) 2003-04[1] p75-p90	CHS CATALONIA (age 60-74) 2002[2] p25-p75	BHS (BARCELONA) Men (age >65) 2006[3] p25-p75	BHS (BARCELONA) Women (age >65) 2006[3] p25-p75	FRANCE Women (age ≥50) 2005-07[4] p75-p90
p,p'-DDT	32.56 (65.05-144.76)	<LOD (<LOD-11.9)	45.1 (25.8-79.7)	40.6 (18.3-61.6)	33.1 (12.2–650.1)	-
p,p'-DDE	3945.4 (8236.30-15456.54)	233 (557-1270)	945.6 (540.4-1507.0)	662 (255-1859)	650 (265-989)	105.9 (196.5-345.3)
HCB	591.23 (1173.96-1800.68)	13.4 (16.7-20.7)	415.0 (214.3-777.9)	214 (122-351)	568 (438-712)	-
β-HCH	1632.07 (2774.37-4399.44)	<LOD (<LOD-<LOD)	252.8 (140.1-440.7)	193 (104-275)	289 (229-467)	-
PCB-118	45.03 (72.84-111.15)	5.19 (10.4-21.8)	41.9 (25.0-61.9)	17.6 (10.5-27.2)	31.1 (20.1-41.5)	-
PCB-138	140.01 (201.99-276.32)	15.1 (30.5-55.4)	124.3 (85.3-174.0)	107 (61.8-160)	106 (60.2-142)	<LOD (79.1-155.7)
PCB-153	194.17 (286.71-408.01)	20.8 (43.3-71.8)	173.9 (120.1-252.9)	172 (92.6-255)	167 (87.9-218)	106.3 (162.3-240.8)
PCB-180	144.74 (225.93-362.54)	18.8 (37.1-63.7)	126.0 (89.1-169.0)	129 (70.2-210)	106 (75.0-163)	<LOD (100.1-173.3)

Abbreviations: p, percentile of the distribution; LOD, limit of detection.
[1] CDC, 2015; [2] Porta et al., 2010; [3] Porta et al., 2012; [4] Bachelet et al., 2011.

Table 4
Persistent organochlorine pollutant serum levels (ng/g lipid) in relation to characteristics (n = 343).

Characteristics	N (%)	∑M-PCBs	∑DL-PCBs	∑Tot-PCBs	HCB	∑HCHs	∑Cyclodienes	∑DDTs	∑OCPs
Age (years)									
55-65	127 (37.0)	491.3	81.6	575.3	575.1	1771.3	148.9	3676.8	6918.2
66-75	185 (53.9)	559.0	76.8	630.3	546.8	1531.2	179.2	4276.7	7604.1
>75	31 (9.1)	580.7	77.5	653.7	717.0	1681.2	155.9	2959.7	6241.8
Gender									
Male	117 (34.1)	547.8	82.7	644.1	642.4	1713.7	167.7	3637.7	7100.3
Female	226 (65.9)	505.9	77.1	596.7	588.1	1605.4	158.3	4086.7	7265.6
BMI (kg m^{-2})									
18.5-24.99	22 (6.4)	693.3	83.4	799.9	727.6	1872.4	161.4	5319.6	8520.1
25-29.99	107 (31.2)	555.4	86.4	648.1	575.4	1813.2	176.6	4210.8	7270.8
>30	214 (62.4)	503.0	75.3	578.4	570.5	1518.7	158.3	3648.5	6968.8
Tobacco smoking									
Yes	102 (29.7)	544.6	85.9	652.9	601.2	1668.1	167.8	3639.1	7156.3
No	241 (70.3)	508.3	75.0	596.6	589.6	1628.1	158.7	4085.5	7224.2
Married									
Yes	247 (72.0)	525.8	77.3	611.2	574.1	1713.9	164.3	3752.2	7171.4
No	96 (28.0)	532.8	79.9	601.3	593.5	1492.4	160.5	4299.8	7583.0
Education level									
Primary School	295 (86.0)	510.6	77.1*	596.1	546.6	1592.3	160.5	3714.8	7044.3
Secundary/High School	48 (14.0)	661.3	103.6	752.4	754.4	2026.2	160.7	5016.6	8255.1

Abbreviations: BMI: body mass index.
Values shown are medians.
***** $p < 0.05$ (Kruskal-Wallis test).

Table 5
Total intake (g/day) of the main food groups.

	Total (n = 343)		Men (n = 117)	Women (n = 226)
Variables	Mean ± SD	Range	Mean ± SD	Mean ± SD
Vegetables	390.7 ± 129.5	27.3 – 914.3	380.1 ± 107.5	396.1 ± 139.4
Fruits	448.9 ± 253.1	21.7 – 1678.6	424.6 ± 258.9	461.5 ± 249.7
Legumes	38.7 ± 19.3	0.0 – 102.9	39.9 ± 17.2	38.0 ± 20.2
Cereals[a]	239.1 ± 106.2	8.6 – 1191.6	244.8 ± 84.2	236.1 ± 116.1*
Dairy products	555.4 ± 269.3	0.0 – 1389.6	516.3 ± 267.4	575.6 ± 268.6**
Meat products	84.7 ± 46.9	0.0 – 334.3	85.4 ± 48.5	84.4 ± 46.3
Fish	78.1 ± 43.2	0.0 – 245.0	79.6 ± 40.5	77.3 ± 44.6
Confectionery and biscuits	17.3 ± 26.4	0.0 – 179.3	15.5 ± 31.5	18.2 ± 23.4***
Olive oil	24.2 ± 14.7	0.0 – 75.0	25.0 ± 14.8	23.7 ± 14.7
Nuts	12.3 ± 18.6	0.0 – 105.0	11.6 ± 18.5	12.6 ± 18.7
Wine	11.1 ± 34.2	0.0 – 250.0	26.4 ± 53.9	3.2 ± 9.7***

Abbreviations: BMI: body mass index; SD: standard deviation.
[a] Including potatoes.
* $p < 0.05$; ** $p < 0.001$; *** $p < 0.0001$.

Table 6
Persitent organochlorine pollutant serum levels (ng/g lipid) in relation to food intake (g/d) among males and females

Food group		∑M-PCBs	∑DL-PCBs	∑Tot-PCBs	HCB	∑HCHs	∑Cyclodienes	∑DDTs	∑OCPs
Men									
∑ of vegetables	Quartile 1 (<907.1)	591.3	99.9*	704.2	493.6	1568.5	165.1	4785.9	7597.8*
	Quartile 2 (907.1 to <1060.1)	519.2	76.9	597.4	999.0	2323.4	202.1	3480.8	9152.1
	Quartile 3 (1060.1 to <1234.4)	580.5	97.9	663.2	829.3	2062.0	200.0	6829.8	9897.6
	Quartile 4 (≥1234.4)	458.8	67.1	533.2	221.7	727.0	150.5	2541.3	4098.1
∑ of food of animal origin	Quartile 1 (<476.8)	691.4**	111.6**	868.6**	556.8	1867.4	192.5	3478.9	7597.8
	Quartile 2 (476.8 to <707.7)	454.2	62.3	533.6	458.1	1452.8	135.9	3637.8	6379.1
	Quartile 3 (707.7 to <847.8)	587.8	88.3	659.6	697.2	1602.8	164.4	4535.5	8078.7
	Quartile 4 (≥847.8)	518.0	81.6	586.8	721.6	2302.2	192.5	3159.9	7272.7
Women									
∑ of vegetables	Quartile 1 (<889.5)	501.8	82.1	595.5	493.7	1573.8	156.1	3506.5	6025.6
	Quartile 2 (889.5 to <1112.9)	565.9	85.9	631.8	646.5	1548.3	167.1	5343.7	7741.0
	Quartile 3 (1112.9 to <1338.8)	488.5	71.4	545.1	593.3	1837.6	158.9	4271.6	8057.8
	Quartile 4 (≥1338.8)	472.8	74.6	532.7	546.6	1589.1	142.9	3402.0	6305.8
∑ of food of animal origin	Quartile 1 (<550.8)	532.6	74.3	596.4	736.7*	1625.0	168.9	5028.2	8304.3
	Quartile 2 (550.8 to <768.0)	515.9	77.3	622.9	483.0	1805.7	163.9	3970.0	6792.0
	Quartile 3 (768.0 to <903.9)	505.9	82.1	603.4	570.4	1746.7	152.8	4309.8	7583.0
	Quartile 4 (≥903.9)	477.9	76.5	549.7	412.1	1156.1	142.2	3002.2	6053.3

∑ of vegetables: sum of vegetables, fruits, legumes and cereals; ∑ of food of animal origin: sum of meat, fish and dairy products.
Values shown are medians.
***** $p < 0.05$ (Kruskal-Wallis test); ****** $p < 0.01$ (Kruskal-Wallis test).