ANÀLISI DE LA CONTAMINACIÓ DE LA POBLACIÓ GENERAL PER COMPOSTOS TÒXICS PERSISTENTS I D'ALGUNS DELS SEUS EFECTES ADVERSOS PER A LA SALUT

TESI DOCTORAL / 2019

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Disseny de la coberta: Sergio Escalona

A la memòria del meu pare

PRESENTACIÓ

La present tesi doctoral ha estat realitzada en el *Grup de Recerca en Epidemiologia Clínica & Molecular del Càncer* (GRECMC) de l'Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), part del Parc de Salut Mar (PSMar) i del Parc de Recerca Biomèdica de Barcelona (PRBB), sota la direcció del Dr. Miquel Porta Serra i amb la col·laboració de tots els membres del GRECMC. La tesi es basa en una de les principals línies de recerca del grup, la que analitza la contaminació de la població general per Compostos Tòxics Persistents (CTPs) i altres agents químics ambientals. Aquesta línia es vertebra principalment en els següents dos projectes:

- *Determinació sanguínia de Compostos Tòxics Persistents en la població de Catalunya*, projecte en col·laboració amb el Departament de Salut de la Generalitat de Catalunya.

- *Determinació sanguínia de Compostos Tòxics Persistents en la població de la ciutat de Barcelona*, projecte conjunt amb l'Agència de Salut Pública de Barcelona.

Els resultats obtinguts dins el marc d'aquesta línia de recerca han donat lloc a nombroses publicacions, tant en format d'articles originals en revistes científiques com d'informes científics publicats per l'administració pública. Tenint en compte la meva participació activa en totes les publicacions i especialment el paper com a primera autora en moltes d'elles, la present tesi és una bona manera de recopilar, plasmar i avaluar de forma conjunta tot el treball dut a terme fins al moment.

La tesi es presenta com a compendi de publicacions dins del *Programa de Doctorat en Metodologia de la Recerca Biomèdica i Salut Pública* de la Universitat Autònoma de Barcelona. Complint amb la normativa del Programa, el cos central de la tesi (capítol de *Resultats*) està format per tres articles concrets; no obstant, la tesi inclou sis articles més en l'*Annex A*; aquests articles també són part principal de la recerca inclosa en la tesi. Així doncs, podem dir que la tesi està formada en efecte per la suma dels nou articles. La tesi consta, a més, d'un resum, un capítol d'introducció, seguit pels objectius i hipòtesis, un capítol de metodologia, un capítol de discussió general i conclusions, i finalment un apartat de bibliografia, també complementària a la dels propis articles. Com és habitual en una tesi com a compendi de publicacions, el contingut d'aquestes –totes les seccions dels articles– en són el nucli: són la part fonamental de la tesi; mentre que els apartats escrits *de novo* per la tesi tenen el paper d'interrelacionar i complementar els articles, evitant sempre que sigui convenient repetir els continguts dels articles ja publicats en la literatura científica internacional.

Els tres articles inclosos en el capítol de *Resultats* són aquells que compleixen pròpiament els requisits estipulats per a poder presentar la tesi en format de compendi de publicacions (requisits com data de

publicació, filiacions, etc.). Amb tot, sí que representen una bona aproximació als diferents objectius de la línia d'estudi duta a terme. Breument, l'objectiu principal de la recerca realitzada és analitzar la contaminació de la població general per compostos tòxics persistents, i fer-ho aplicant noves o diferents formes d'avaluar aquesta contaminació, com ara mitjançant corbes de distribució poblacional i indicadors com el 'nombre de compostos detectats a altes concentracions'. La tesi també té per objectiu estudiar la relació entre les concentracions corporals d'aquests contaminants i diversos efectes adversos en la salut; en alguns aspectes ho fa de forma exploratòria, però també de forma novedosa en aquest àmbit, centrant-se en un indicador de salut general com és la salut autopercebuda, i estudiant a més de la diabetis i la prediabetis, fenotips metabòlics alterats en persones amb sobrepès i obesitat i, per primer cop en la literatura internacional, en persones amb pes normal.

ÍNDEX GENERAL

RESUM

Introducció: Pel que es coneix, la majoria de les poblacions del planeta –o potser pràcticament totes– es troben exposades a nombrosos compostos tòxics persistents (CTPs). Tanmateix, són encara relativament pocs els països i ciutats que duen a terme estudis de biomonitorització per tal de caracteritzar la contaminació per CTPs en mostres representatives de la població general. L'exposició a aquests contaminants s'ha relacionat causalment amb alguns efectes adversos per a la salut importants, com per exemple la diabetis tipus 2.

Objectius: Els objectius principals de la tesi són analitzar la contaminació de la població general per CTPs, així com estudiar la relació entre les concentracions corporals d'aquests compostos i alguns efectes adversos en la salut. Els objectius específics són: *a)* analitzar la distribució de les concentracions sèriques de CTPs i factors sociodemogràfics que s'hi relacionen, en mostres representatives de la població general de Catalunya i de la ciutat de Barcelona; *b)* analitzar la contaminació de la població general per CTPs a través d'un nou indicador, el 'nombre de compostos detectats a altes concentracions', en la població de Catalunya i en la dels Estats Units; i *c)* analitzar les relacions entre les concentracions sèriques de CTPs i la salut autopercebuda, la prevalença de diabetis, prediabetis i de fenotips metabòlics alterats, en persones amb sobrepès i obesitat i en persones amb normopès.

Metodologia: Es van analitzar les concentracions sèriques de CTPs en una submostra de participants de l'Enquesta de Salut de Barcelona de l'any 2006 i de l'Enquesta de Salut de Catalunya (ESCA) de l'any 2002. El 'nombre de compostos detectats a altes concentracions' es va calcular pels participants de l'ESCA i pels participants del període 2003-2004 de l'enquesta de salut dels Estats Units (*National Health and Nutrition Examination Survey*, NHANES). Les relacions entre les concentracions de CTPs i efectes adversos per la salut es van estudiar en la mostra de participants de l'ESCA, a través de les dades obtingudes tant en el qüestionari de l'enquesta com en l'examen de salut.

Resultats: Més del 80% de la població general de Catalunya i de la ciutat de Barcelona presentava concentracions detectables en sèrum de policlorobifenils (congèneres PCB 118, 138, 153 i 180) i dels següents plaguicides organoclorats o els seus metabòlits: diclorodifeniltricloroetà (DDT), diclorodifenildicloroetilè (DDE), hexaclorobenzè (HCB) i β-hexaclorociclohexà (β-HCH). En la població de Barcelona, les concentracions detectades l'any 2006 van ser més baixes que les detectades l'any 2002. Es van observar diferències en les concentracions sèriques d'aquests CTPs en funció de diversos factors sociodemogràfics com el sexe, l'edat, l'índex de massa corporal (IMC) o, en homes, el nivell educatiu. Una part significativa de la població general de Catalunya i dels Estats Units presentava un cert nombre de compostos detectats a altes concentracions: un 20% dels participants en

l'estudi de Catalunya tenia concentracions en el decil superior de 2 o més compostos dels 8 més detectats en aquesta població, mentre que a l'estudi dels Estats Units, un 13% dels participants tenia concentracions en el decil superior de 10 o més compostos dels 37 més detectats.

En l'estudi de Catalunya, les persones amb majors concentracions sèriques de CTPs presentaven pitjor salut autopercebuda que les persones amb menors concentracions; aquesta relació, però, s'explicava bàsicament per l'efecte de l'edat i la prevalença de trastorns crònics. En la mateixa població, les persones amb majors concentracions sèriques de PCBs i d'HCB presentaven una major prevalença de diabetis i prediabetis, fins i tot un cop es tenia en compte l'efecte de l'edat, el sexe i l'IMC. Tant en persones amb sobrepès/obesitat com en persones amb normopès, una concentració més elevada de PCBs, HCB i β-HCH en sèrum es va relacionar amb un fenotip metabòlic alterat; les relacions observades van ser de major magnitud en els individus amb normopès.

Conclusions: Existeix una contaminació freqüent de la població general de Catalunya i de la ciutat de Barcelona per CTPs, tot i que –pels compostos estudiats– és probable que les concentracions dels contaminants hagin disminuït considerablement amb el temps. Els resultats mostren diferències en les concentracions corporals en funció de diversos factors sociodemogràfics, així com que una part de la població de Catalunya i dels Estats Units presenta un cert nombre de compostos a altes concentracions. En la població de Catalunya s'observa una relació entre l'exposició a certs CTPs, la diabetis tipus 2 i altres alteracions del fenotip metabòlic, i no només en persones amb sobrepès i obesitat sinó també, i probablement de forma més accentuada, en persones amb pes normal.

RESUMEN

Introducción: Por lo que se sabe, la mayoría de las poblaciones del planeta –o quizá prácticamente todas– están expuestas a numerosos compuestos tóxicos persistentes (CTPs). Sin embargo, son todavía relativamente pocos los países y ciudades que llevan a cabo estudios de biomonitorització para caracterizar la contaminación por CTPs en muestras representativas de la población general. La exposición a estos contaminantes se ha relacionado causalmente con algunos efectos adversos para la salud importantes, como, por ejemplo, la diabetes tipo 2.

Objetivos: Los objetivos principales de la tesis son analizar la contaminación de la población general por CTPs, así como estudiar la relación entre las concentraciones corporales de estos compuestos y algunos efectos adversos en la salud. Los objetivos específicos son: *a)* analizar la distribución de las concentraciones séricas de CTPs y factores sociodemográficos con los que están relacionadas, en muestras representativas de la población general de Cataluña y de la ciudad de Barcelona; *b)* analizar la contaminación de la población general por CTPs a través de un nuevo indicador, el 'número de compuestos detectados a altas concentraciones', en la población de Cataluña y en la de los Estados Unido; y *c)* analizar las relaciones entre las concentraciones séricas de CTPs y la salud autopercibida, la prevalencia de diabetes, prediabetes y de fenotipos metabólicos alterados, en personas con sobrepeso y obesidad y en personas con normopeso.

Metodología: Se analizaron las concentraciones séricas de CTPs en una submuestra de participantes de la Encuesta de Salud de Barcelona del año 2006 y de la Encuesta de Salud de Cataluña (ESCA) del año 2002. El 'número de compuestos detectados a altas concentraciones' se calculó para los participantes de la ESCA y para los participantes del período 2003-2004 de la encuesta de salud de los Estados Unidos (*National Health and Nutrition Examination Survey*, NHANES). Las relaciones entre las concentraciones de CTPs y efectos adversos para la salud se estudiaron en la muestra de participantes de la ESCA, a través de los datos obtenidos tanto en el cuestionario de la encuesta como en el examen de salud.

Resultados: Más del 80% de la población general de Cataluña y de la ciudad de Barcelona presentaba concentraciones detectables en suero de policlorobifenilos (congéneres PCB 118, 138, 153 i 180) y de los siguientes plaguicidas organoclorados o sus metabolitos: diclorodifeniltricloroetano (DDT), diclorodifenildicloroetileno (DDE), hexaclorobenzeno (HCB) y β-hexaclorociclohexano (β-HCH). En la población de Barcelona, las concentraciones detectadas el año 2006 fueron más bajas que las detectadas el año 2002. Se observaron diferencias en las concentraciones séricas de estos CTPs en función de distintos factores sociodemográficos como el sexo, la edad, el índice de masa corporal (IMC) o, en hombres, el nivel educativo. Una parte significativa de la población general de Cataluña y

de los Estados Unidos presentaba un cierto número de compuestos detectados a altas concentraciones: un 20% de los participantes en el estudio de Cataluña tenía concentraciones en el decil superior de 2 o más compuestos de los 8 más detectados en esta población, mientras que en el estudio de los Estados Unidos, un 13% de los participantes tenía concentraciones en el decil superior de 10 o más compuestos de los 37 más detectados.

En el estudio de Cataluña, las personas con mayores concentraciones séricas de CTPs presentaban peor salud autopercibida que las personas con menores concentraciones; esta relación, sin embargo, se explicaba básicamente por el efecto de la edad y la prevalencia de trastornos crónicos. En la misma población, las personas con mayores concentraciones séricas de PCBs y de HCB presentaban una mayor prevalencia de diabetes y prediabetes, incluso una vez se tenía en cuenta el efecto de la edad, el sexo y el IMC. Tanto en personas con sobrepeso/obesidad como en persones con normopeso, una concentración más elevada de PCBs, HCB y β-HCH en suero se relacionó con un fenotipo metabólico alterado; las relaciones observadas fueron de mayor magnitud en los individuos con normopeso.

Conclusiones: Existe una contaminación frecuente de la población general de Cataluña y de la ciudad de Barcelona por CTPs, aunque –para los compuestos estudiados– es probable que las concentraciones de los contaminantes hayan disminuido considerablemente con el tiempo. Los resultados muestran diferencias en las concentraciones corporales en función de distintos factores sociodemográficos, así como que una parte de la población de Cataluña y de los Estados Unidos presenta un cierto número de compuestos a altas concentraciones. En la población de Cataluña se observa una relación entre la exposición a ciertos CTPs, la diabetes tipo 2 y otras alteraciones del fenotipo metabólico, y no únicamente en personas con sobrepeso y obesidad sino también, y probablemente de forma más acentuada, en personas con peso normal.

ABSTRACT

Introduction: As far as is known, most populations worldwide –or perhaps virtually all– are exposed to a variety of persistent toxic substances (PTS). However, relatively few countries and cities are performing biomonitoring studies in order to characterize PTS contamination in representative samples of the general population. Exposure to such pollutants has been causally related to some important adverse health effects as, for instance, type 2 diabetes.

Objectives: The main aims of the thesis are to analyse the contamination of the general population by PTS, as well as to study the relation between body concentrations of such compounds and some adverse health effects. The specific objectives are: *a)* to analyse the distribution of serum PTS concentrations and related sociodemographic factors, in representative samples of the general population of Catalonia and of the city of Barcelona; *b)* to analyse contamination of the general population by PTS using a new indicator, the 'number of compounds detected at high concentrations', in the population of Catalonia and in the population of the United States; and *c)* to analyse the relations between PTS serum concentrations and self-rated health, the prevalence of diabetes, prediabetes, and of unhealthy metabolic phenotypes, in overweight and obese individuals and in normal-weight individuals.

Methodology: Serum concentrations of PTS were analysed in a subsample of participants of the 2006 Barcelona Health Survey and of the 2002 Catalan Health Interview Survey (CHIS). The 'number of compounds detected at high concentrations' was computed for CHIS participants and for participants of the 2003-2004 cycle of the United States health survey (*National Health and Nutrition Examination Survey*, NHANES). The relationships between POP concentrations and adverse health effects were studied in the sample of CHIS participants, using data obtained from the survey questionnaire as well as from the health examination.

Results: More than 80% of the general population of Catalonia and of the city of Barcelona had detectable serum concentrations of polychlorinated biphenyls (PCB congeners 118, 138, 153, and 180) and of the following organochlorine pesticides or their metabolites: dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE), hexachlorobenzene (HCB), and β-hexachlorocyclohexane (β-HCH). In the population of Barcelona, concentrations detected in 2006 were lower than concentrations detected in 2002. Differences in serum concentrations of the mentioned PTS were observed according to different sociodemographic factors such as sex, age, body mass index (BMI) or, in men, educational level. A significant part of the general population of Catalonia and of the United States has a certain number of compounds detected at high concentrations: 20% of participants in the Catalan study had concentrations in the top decile of 2 or more compounds

of the 8 most prevalent PTS in this population, while in the United States study, 13% of participants had concentrations in the top decile of 10 or more compounds of the 37 most prevalent PTS.

In the Catalan study, individuals with higher serum concentrations of PTS had poorer self-rated health than individuals with lower concentrations; however, this relationship was mainly due to the effect of age and the prevalence of chronic conditions. In the same population, individuals with higher serum concentrations of PCBs and HCB had a higher prevalence of diabetes and prediabetes, even when age, sex and BMI were considered. Among overweight/obese individuals and also among normal-weight individuals, a higher serum concentration of PCBs, HCB and β-HCH was related to an unhealthy metabolic phenotype; the observed relations were of higher magnitude among normal-weight individuals.

Conclusions: The contamination of the general population of Catalonia and of the city of Barcelona by PTS is frequent, although it is probable that –for the studied compounds– their concentrations may have decreased considerably over time. Results show differences in body concentrations according to sociodemographic factors, and also show that part of the population of Catalonia and of the United States has a certain number of compounds at high concentrations. A relation between exposure to certain PTS, type 2 diabetes and other disorders of the metabolic phenotype is observed in the population of Catalonia, and not only in overweight and obese individuals but also, and probably more strongly, in normal-weight individuals.

ÍNDEX DETALLAT

LLISTA D'ABREVIACIONS

Compostos

COPs [1]	Compostos Orgànics Persistents
CTPs	Compostos Tòxics Persistents
HCB	Hexaclorobenzè
HCH	Hexaclorociclohexà
α-HCH	Alfa Hexaclorociclohexà
β-HCH	Beta Hexaclorociclohexà
γ-HCH	Gamma Hexaclorociclohexà (o lindà)
δ-HCH	Delta Hexaclorociclohexà
PCBs	Policlorobifenils (o bifenils policlorats)
o,p'-DDD	Diclorodifenildicloroetà (o,p' isòmer)
o,p'-DDE	Diclorodifenildicloroetilè (o,p' isòmer)
o,p'-DDT	Diclorodifeniltricloroetà (o,p' isòmer)
p,p'-DDD	Diclorodifenildicloroetà (p,p' isòmer)
p,p'-DDE	Diclorodifenildicloroetilè (p,p' isòmer)
p,p'-DDT	Diclorodifeniltricloroetà (p,p' isòmer)
PBDEs	Polibromodifenil èters (o èters difenílics polibromats)
PCDDs	Policlorodibenzo-p-dioxines (o dibenzodioxines policlorades)
PCDFs	Policlorodibenzofurans (o dibenzofurans policlorats)

Altres

CDC	*Centers for Disease Control and Prevention*, Estats Units
ESB	Enquesta de Salut de Barcelona
ESCA	Enquesta de Salut de Catalunya
GRECMC	Grup de Recerca en Epidemiologia Clínica i Molecular del Càncer
HBM	Biomonitorització en humans (*Human Biomonitoring*)
HBM4EU	*European Human Biomonitoring Initiative*
HOMA-IR	*Homeostatic model assessment-insulin resistance*
IMC	Índex de massa corporal
IMIM	Institut Hospital del Mar d'Investigacions Mèdiques
NCHS	*National Center for Health Statistics*, Estats Units
NHANES	*National Health and Nutrition Examination Survey*, Estats Units

[1] Tot i que en català els acrònims no acostumen a portar una 's' al final, aquesta és també acceptable i creiem que, en aquest context, transmet millor el sentit plural.

1. INTRODUCCIÓ

En aquest capítol es presenten el context i els antecedents en els que es situa la recerca duta a terme en la present tesi. Així mateix, aquesta introducció permet presentar les publicacions de la tesi, tant les incloses en el capítol de *Resultats* com les incloses en l'*Annex A*, ja que totes formen un conjunt relacionat.

1.1. Biomonitorització de les concentracions de Compostos Tòxics Persistents (CTPs) en humans

Creats inicialment com a productes o subproductes de la indústria química amb finalitats concretes, tot i que molts d'ells actualment prohibits, els Compostos Tòxics Persistents (CTPs) es caracteritzen: *a)* per la seva resistència a la degradació –ja sigui física, química o biològica–, motiu pel que romanen pràcticament intactes en el medi durant llargs períodes de temps; *b)* per la seva lipofilicitat, que els dota d'una elevada capacitat de bioacumulació en els organismes vius, especialment en els teixits grassos; i *c)* per una elevada capacitat de transport a llargues distàncies, pel que la seva presència és global [1,2].

Entre els diferents tipus de substàncies químiques que engloben els CTPs, la recerca de la present tesi es centra especialment en: *a)* productes industrials com els policlorobifenils (PCBs) i *b)* en plaguicides organoclorats –com per exemple el conegut DDT (diclorodifeniltricloroetà)– i en els seus anàlegs i metabòlits; tots ells Compostos Orgànics Persistents (COPs). En determinades anàlisis de la tesi també es consideren altres COPs com les dioxines i furans (PCDDs/Fs) i retardants de la flama com els polibromodifenil èters (PBDEs).

Els CTPs suposen una complexa i preocupant problemàtica ambiental i de salut pública. Gràcies a acurades tècniques i equips de laboratori és possible mesurar i monitoritzar en quines concentracions es troben aquests compostos tòxics en el nostre entorn, en els aliments, i en els organismes vius, inclosos nosaltres mateixos, els humans. La mesura de les concentracions de substàncies tòxiques i els seus metabòlits en mostres biològiques de persones és el que es coneix com a 'Biomonitorització en humans' o en anglès, com a '*human biomonitoring*' (HBM) [3-6]. Per a les anàlisis normalment s'utilitzen mostres de sang (sèrum o plasma), però també altres matrius com orina, cabells, ungles o llet materna. La biomonitorització en humans permet, doncs, conèixer la càrrega corporal de CTPs –la qual integra les diferents fonts i rutes d'exposició– en els individus d'una determinada població. Tot i les seves limitacions, els nombrosos estudis disponibles indiquen amb claredat que pràcticament totes les poblacions del planeta es troben exposades a (i contaminades per) nombroses mescles de CTPs i altres contaminants ambientals [7-10].

Per tal de controlar i arribar a eliminar la contaminació global per CTPs, l'any 2001 es va adoptar el Conveni d'Estocolm, el qual compta amb 152 països signataris [1,11]. Es tracta d'un instrument legislatiu que té per objecte protegir la salut humana i el medi ambient davant els efectes dels Compostos Orgànics Persistents (COPs). Els COPs són un grup de CTPs que es caracteritzen per tenir en la seva estructura química àtoms de carboni i hidrogen, i generalment un halogen com el clor o el brom.

El Conveni d'Estocolm va entrar en vigor fa ja 15 anys, el 2004. Dels 12 compostos inicialment inclosos en el tractat, coneguts com '*the dirty dozen*', se n'ha anat ampliant el número i actualment inclou 16 tipus de contaminants més a eliminar o, quan això no és possible, restringir-ne la seva producció i ús. Entre altres mesures, el conveni indica que "les Parts encoratjaran i/o efectuaran les activitats de recerca, desenvolupament, vigilància i cooperació adequades respecte els Compostos Orgànics Persistents i la seva presència, nivells i tendències en les persones i en el medi ambient" (article 11.1.b) [1]. Per tant, el conveni considera necessari un seguiment de la presència, les concentracions i l'evolució d'aquests contaminants tant en el medi com en les persones.

Cada cop són més els països i regions, com la Unió Europea, que duen a terme algun programa o estudi de biomonitorització de CTPs; són majoritàriament països desenvolupats. Destaquen les iniciatives dels Estats Units i d'Alemanya, tant pels anys que fa que van començar a recopilar dades com per la seva continuïtat i pel considerable nombre de compostos analitzats [12,13]. Altres països i regions que duen a terme iniciatives de biomonitorització de CTPs i altres agents químics ambientals són: Flandes (Bèlgica), França, la República Txeca, Israel, Canadà, Corea del Sud i Nova Zelanda [14-29]. Molts d'aquests programes i estudis, excepte aquells més recents, es troben descrits en detall en un dels articles del nostre *Grup de Recerca en Epidemiologia Clínica & Molecular del Càncer* (GRECMC) de l'IMIM [9]; l'article actualment compta amb més de cent cites.

A nivell d'Europa, a part dels països anteriorment mencionats, cal destacar la iniciativa COPHES (*Consortium to Perform Human Biomonitoring on a European Scale)*, finançada per la Unió Europea amb la missió de dissenyar procediments harmonitzats per tal que els diferents estudis de biomonitorització humana que es desenvolupin a Europa obtinguin resultats que siguin comparables entre els països [30-32]. De moment el projecte DEMOCOPHES (*DEMOnstration of a study to COordinate and Perform Human biomonitoring on a European Scale*) ha permès posar a prova els protocols dissenyats i ha proporcionat dades per algunes substàncies com mercuri, cadmi o ftalats, mesurats en cabell i orina [33-36]. Espanya ha contribuït al projecte mitjançant el reclutament i la recollida de mostres de més de cent parelles mare-fill/a en escoles de zones rurals (Añover de Tajo, Toledo) i urbanes (Madrid capital) [37,38]. Una xifra massa modesta, al nostre entendre, i sense representativitat; però esperem que aquests aspectes millorin en un futur proper.

A nivell d'Europa també cal mencionar el projecte *European Human Biomonitoring Initiative* (HBM4EU) que s'està duent a terme actualment i que suposa la col·laboració entre científics i diversos serveis de la Comissió Europea, agències de la Unió Europea i representats nacionals, amb l'objectiu de construir ponts entre la recerca i la política i aconseguir que les polítiques de la Unió serveixin per minimitzar els efectes adversos per a la salut deguts a l'exposició de la població a compostos tòxics [39].

Totes aquestes iniciatives són especialment útils perquè permeten conèixer quina és la contaminació per CTPs de la població general dels diferents territoris en que es duen a terme. Més concretament, la realització de programes i estudis de vigilància o monitorització de CTPs en humans permet:
a) conèixer la distribució de les concentracions de cada compost en la població estudiada,
b) comparar les concentracions amb les d'altres poblacions,
c) plantejar possibles nivells de referència,
d) identificar subgrups de la població altament exposats,
e) conèixer l'evolució de les concentracions en el temps,
f) avaluar l'efectivitat de polítiques i mesures per la reducció de la contaminació per CTPs, i
g) contribuir a identificar possibles efectes adversos per a la salut i problemes de salut pública [7,8].

Tenint en compte tots aquests punts es fa evident l'especial rellevància de dur a terme estudis de biomonitorització en mostres que siguin representatives de la *població general*.

En aquest cas, el concepte de '*població general'* es defineix com el conjunt d'habitants d'un territori o regió geogràfica definida (país, comunitat autònoma, municipi, etc.), independentment de factors com el gènere, la ètnia, la situació professional, etc.; per tant, només en quedarien excloses aquelles persones ingressades en institucions sanitàries, penitenciàries, residències, etc., és a dir, població institucionalitzada [40].

A nivell espanyol existeixen diversos estudis que analitzen les concentracions de CTPs en subgrups rellevants de la població com les dones embarassades o la població activa [7,37,38,41-45]. Destaquen el projecte INMA (Infància i Medi Ambient) –que a través de mostres de parelles mare-fill reclutades durant l'embaràs estudia l'efecte en la salut infantil d'aquests i altres contaminants ambientals [46-49]– i el projecte Bioambient.es [50-53]. Aquest últim posat en marxa pel *Centro Nacional de Sanidad Ambiental* i realitzat en una mostra representativa de la població treballadora. Els aproximadament 1.900 participants en l'estudi es van reclutar durant els reconeixements anuals de salut laboral duts a terme en centres de prevenció de determinades mútues del treball, tenint en compte sexe, edat, àrea geogràfica i sector d'ocupació segons l'Enquesta de Població Activa de l'any 2007 [54,55].

Són també especialment rellevants diversos estudis realitzats al País Basc i a la província de Tarragona. En un d'aquests estudis, es van analitzar les concentracions d'alguns CTPs en persones voluntàries residents en zones pròximes a la fàbrica de producció i emmagatzematge massiu d'hexaclorociclohexà (HCH) de Barakaldo [56]. Altres estudis en el País Basc han analitzat en tres períodes diferents (anys 2006, 2008 i 2013) les concentracions de CTPs en habitants de quatre regions concretes, dues d'elles escollides per la seva proximitat a una planta incineradora; tot i que una part dels participants es va reclutar a través del cens, la majoria van ser voluntaris [57-60]. Així mateix, les concentracions de dioxines i altres CTPs també s'han analitzat periòdicament en diferents tipus de mostres d'habitants de zones properes a una planta incineradora construïda entre els anys 1996-1998 a Constantí (Tarragona) [61-64].

Ara bé, tot i la indubtable rellevància i valor dels estudis mencionats, cal assenyalar que a nivell espanyol l'únic estudi de biomonitorització de CTPs que s'havia dut a terme fins al moment en una mostra representativa de la població general era el que es va realitzar a les Illes Canàries l'any 1998. En aquest estudi es van analitzar les concentracions sèriques de plaguicides organoclorats com el DDT i els seus anàlegs, el lindà (γ-HCH) i els ciclodiens aldrín, dieldrín i endrín, en una mostra representativa de la població general canària formada per prop de 700 persones d'entre 6 i 75 anys, participants de la *Encuesta Nutricional de Canarias* [65,66].

Com veurem, la recerca duta a terme en la present tesi es basa, principalment, en els estudis de determinació de les concentracions de CTPs en mostres representatives de la població general de Catalunya i de la ciutat de Barcelona. Concretament es basa, per una banda, en l'estudi dut a terme en una mostra de participants de l'Enquesta de Salut de Catalunya de l'any 2002, i per l'altra, en l'estudi realitzat en una mostra de participants de l'Enquesta de Salut de Barcelona de l'any 2006 [67-74]. Aquests dos estudis –el de Catalunya i el de la ciutat de Barcelona–, juntament amb el de Canàries, són doncs els únics a nivell espanyol duts a terme fins al moment en una mostra representativa de la població general. Els tres estudis es van desenvolupar lligats a enquestes de salut o nutricionals, amb els avantatges (i també limitacions, es clar) que aquest fet suposa [7,8,41-43] (vegeu el capítol de *Discussió*).

1.2. Estudis de biomonitorització de CTPs en la població general de Catalunya i de la ciutat de Barcelona

En la present tesi es presenten els resultats més rellevants dels estudis que analitzen les concentracions sanguínies de CTPs en mostres representatives de la població general de Catalunya i de la ciutat de

Barcelona. Com s'ha comentat, són els únics estudis, junt amb el de les Illes Canàries, realitzats a Espanya en mostres d'habitants representatives de la població general d'un territori [8].

Concretament, la recerca duta terme –i que, com hem dit, aquesta tesi permet recopilar i presentar de forma conjunta– es basa, per una banda, en una mostra de més de 200 participants de l'Enquesta de Salut de Barcelona (ESB) de l'any 2006, i en una mostra de més de 900 participants de l'Enquesta de Salut de Catalunya (ESCA) de l'any 2002. L'ESCA del 2002 és la única de les enquestes a nivell de tot Catalunya que fins al moment ha inclòs un Examen de Salut amb extracció sanguínia (vegeu el capítol de *Metodologia*). Els resultats referents a la distribució de les concentracions de CTPs a la població de Catalunya i de Barcelona, i a l'anàlisi dels principals factors sociodemogràfics associats a les concentracions trobades –com per exemple l'edat, el sexe o l'índex de massa corporal (IMC)–, són els que es van publicar en els següents articles inclosos en l'*Annex A* [67,68]:

Article A1:
Porta M, **Gasull M**, Puigdomènech E, Garí M, Bosch de Basea M, Guillén M, López T, Bigas E, Pumarega J, Llebaria X, Grimalt JO, Tresserras R. *Distribution of blood concentrations of persistent organic pollutants in a representative sample of the population of Catalonia.* Environment International 2010; 36: 655-664.

Article A2:
Porta M, López T, **Gasull M**, Rodríguez-Sanz M, Garí M, Pumarega J, Borrell C, Grimalt JO. *Distribution of blood concentrations of persistent organic pollutants in a representative sample of the population of Barcelona in 2006, and comparison with levels in 2002.* Science of the Total Environment 2012; 423: 151-161.

Els resultats i altres aspectes més detallats de l'estudi sobre la determinació de CTPs en la població catalana es van recollir també en un informe publicat pel nostre Grup i el Departament de Salut de la Generalitat de Catalunya [75], i en el capítol 11 del llibre "Nuestra contaminación interna" [41].

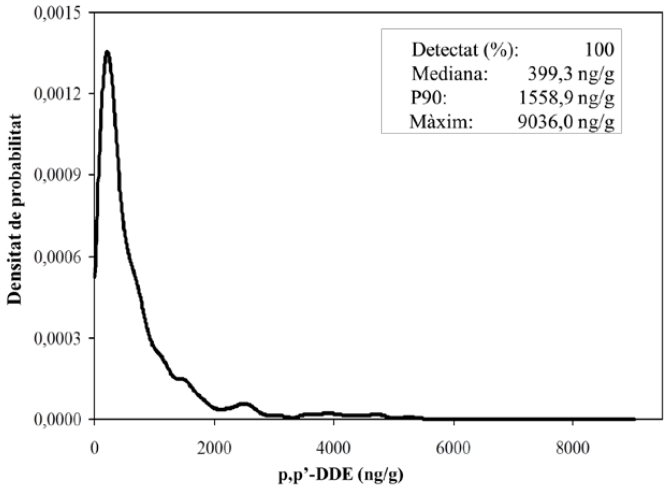
A diferència de l'estudi a nivell català, l'enquesta de salut que realitza periòdicament l'Agència de Salut Pública de Barcelona no ha inclòs mai la realització d'un examen de salut. Així doncs, per obtenir la mostra de sang i altres mesures (pes, alçada, etc.) per l'estudi de CTPs, es va convidar als participants de l'ESB de l'any 2006 a formar part d'aquest estudi; a més d'obtenir una mostra de sang, se'ls realitzava una petita exploració física i un qüestionari complementari (vegeu el capítol de *Metodologia*). Aprofitant aquest fet vam analitzar quins eren els factors sociodemogràfics que influïen en la participació en un estudi d'aquest tipus. Vam observar una major predisposició en les dones i en

les persones amb més nivell educatiu. Els resultats es van publicar en el següent article, inclòs també en l'*Annex A* [69]:

> *Article A3:*
> Porta M, **Gasull M**, Puigdomènech E, Rodríguez-Sanz M, Pumarega J, Rebato C, Borrell C. *Sociodemographic factors influencing participation in the Barcelona Health Survey study on serum concentrations of persistent organic pollutants.* Chemosphere 2009; 76: 216-225.

Per altra banda, i breument, cal destacar també el nostre interès en trobar diferents formes de descriure i analitzar de forma conceptualment innovadora –i des d'un punt de vista poblacional i de salut pública– la contaminació per CTPs. Així, a l'hora de presentar els resultats dels estudis de biomonitorització en la població de Catalunya i de Barcelona, hem utilitzat corbes de distribució de les concentracions de cada compost (vegeu com a exemple la Figura 1); aquestes corbes s'inspiren en el paradigma preventiu proposat per Geoffrey Rose a nivell de poblacions [9,76-78].

Figura 1. Corba de distribució poblacional de les concentracions de p,p'-diclorodifenildicloroetilè (p,p'-DDE) en l'estudi en la població general de Catalunya [67,75].



La corba mostra que la major part de la població té concentracions baixes, i una minoria, altes o molt més altes; també permet visualitzar la variació de concentracions que hi ha en la mateixa població, és a dir, la variabilitat entre individus (una minoria significativa[2] té concentracions molt més elevades que la resta). Aquesta mena de corbes es poden presentar tant pel total de la població com en funció de variables com l'edat o el sexe.

També és important comentar que dins la mostra de participants de l'ESCA de l'any 2002 hi havia prop de 150 participants de la ciutat de Barcelona. Aquest fet ens va permetre comparar les

[2] Al llarg de tota la tesi, paraules com aquesta ("significativa", "significatiu") s'empren d'acord amb les normes i usos establerts per la comunitat científica [40].

concentracions trobades en aquests participants amb les obtingudes posteriorment en la mostra de participants de l'ESB del 2006, avaluant així l'evolució temporal de les concentracions de CTPs en la població de Barcelona en els quatre anys transcorreguts entre l'obtenció de mostres d'ambdós estudis [68].

En el context de l'estudi de biomonitorització de CTPs en la població general de Catalunya, també vam estudiar en profunditat com es relacionaven les concentracions de CTPs observades amb el nivell educatiu i la classe social. Els resultats van ser publicats en aquest article [70]:

Article A4:
Gasull M, Pumarega JA, Rovira G, López T, Alguacil J, Porta M. *Relative effects of educational level and occupational social class on body concentrations of persistent organic pollutants in a representative sample of the general population of Catalonia, Spain.* Environment International 2013; 60: 190-201.

1.3. Exposició a múltiples compostos

A l'hora de descriure i estudiar la contaminació de la població per CTPs cal tenir en compte un factor especialment rellevant, l'exposició a múltiples compostos [3,79,80]. En efecte, la població general està exposada simultàniament a un gran ventall de compostos de diversos tipus, de tal manera que en una mostra de sang (o d'un altre teixit) d'una mateixa persona s'hi troben concentracions detectables de molts contaminants. És il·lustratiu en aquest sentit l'estudi que va realitzar a principis dels anys 2000 la Facultat de Medicina de la Universitat Mount Sinai de Nova York: en ell, els investigadors van detectar en nou voluntaris entre 77 i 106 compostos (en una mateixa persona), de les 210 substàncies que van analitzar [81-83].

La forma en que es té en compte la multiexposició poblacional no és obvia i suposa un repte a l'hora de caracteritzar-la, ja que l'anàlisi més tradicional en que cada compost s'estudia per separat no resulta prou adequada per tal d'abordar l'acumulació de barreges de compostos i els seus efectes en la salut. Més enllà de l'efecte que pugui tenir cada substància de forma aïllada, cal tenir en compte que la barreja o combinació de substàncies pot produir efectes diferents [79,84-86]. Actualment existeixen diverses iniciatives centrades en l'estudi de l'exposició a múltiples compostos, així com en l'estudi dels efectes en la salut d'aquesta exposició combinada. A nivell europeu destaquen projectes com l'EDC-MixRisk, l'EuroMix, l'EUToxRisk, o també el mencionat HBM4EU, els quals adopten diferents perspectives, ja sigui des d'una visió més toxicològica o epidemiològica [87].

Molts cops, les concentracions de determinats compostos es troben força correlacionades; per exemple, persones amb concentracions elevades de certs compostos també presenten concentracions elevades d'altres. Malgrat aquest fet, cal tenir en compte que això no succeeix per tota l'àmplia gamma de CTPs a la que es troba exposada la població, de manera que aquelles persones que presentin concentracions altes per un grup de compostos no significa necessàriament que també presentin concentracions altes per a tots els CTPs; i viceversa, presentar concentracions baixes per un grup de compostos no implica tenir concentracions baixes de tots els CTPs que s'analitzin.

Dins el nostre interès en trobar diferents formes de descriure des d'un punt de vista poblacional la contaminació per CTPs (com per exemple a través de les mencionades corbes de distribució), ja fa uns anys des del GRECMC vam idear un indicador senzill que permetés descriure l'exposició a múltiples compostos. Aquest indicador té en compte a la vegada tant *a)* el nombre de compostos detectats en una mateixa persona, com *b)* les concentracions a les que es troben aquests compostos. Consisteix en calcular el nombre de compostos que presenta una persona per sobre d'una determinada concentració, com per exemple el quartil o el decil superior de la distribució poblacional. L'anomenem '*nombre de compostos detectats a altes concentracions*'. L'indicador el vam presentar i utilitzar per primer cop en l'estudi de determinació de les concentracions de CTPs en la població general de Catalunya, i va donar lloc al següent article inclòs en l'*Annex A* [71]:

> *Article A5:*
> Porta M, Pumarega J, **Gasull M**. *Number of persistent organic pollutants detected at high concentrations in a general population.* Environment International 2012; 44: 106-111.

L'indicador i els resultats de la seva aplicació en la població general de Catalunya també estan analitzats de forma detallada en el capítol 6 del volum "Endocrine Disrupters" de *Vitamins & Hormones* [88].

Més endavant hem aplicat la mateixa metodologia en les dades disponibles de prop de 5.000 participants del període 2003-2004 de l'enquesta de salut dels Estats Units (*National Health and Nutrition Examination Survey*, NHANES) [12,89,90], descrivint així el 'nombre de compostos detectats a altes concentracions' en la població general dels Estats Units. Els resultats han donat lloc al següent article de la present tesi [91]:

Article 3 (capítol de *Resultats*):
Pumarega J, **Gasull M**, Lee DH, López T, Porta M. *Number of Persistent Organic Pollutants Detected at High Concentrations in Blood Samples of the United States Population.* PLoS One 2016; 11: e0160432.

1.4. Efectes adversos dels CTPs per a la salut

Nombrosos estudis científics mostren com l'exposició continuada i l'acumulació de CTPs en l'organisme humà poden estar o estan lligades a un ampli ventall d'importants efectes adversos per a la salut. Naturalment, no deixa d'haver-hi incerteses. Tanmateix, el fet que la contaminació es produeixi de forma continua al llarg de la vida –sovint, a dosis baixes– explica moltes de les malalties i altres efectes clínics que els CTPs contribueixen a causar. Tractem doncs de malalties d'etiologia complexa i amb llargs períodes d'inducció i de latència [40]. Alguns tipus de càncers en són exemple [3,92-96 i altres referències al llarg de la tesi].

Les concentracions de CTPs que poden acumular-se a l'organisme poden ser prou elevades com per produir efectes adversos per la salut, però a més, també cal tenir en compte els efectes a dosis baixes. En molts estudis, tant en animals com humans, s'ha observat com per molts disruptors endocrins –entre ells molts CTPs– els efectes no segueixen una dosi-resposta monotònica, sinó que s'observen efectes clínicament rellevants a dosis baixes [97-99].

Entre altres, s'ha vist que els CTPs poden provocar efectes proinflamatoris, oxidatius, metabòlics, inmunosupressius, neuroendocrins i epigenètics [92,93,100-108], i que poden contribuir a causar infertilitat, diabetis, alteracions tiroidees, diferents tipus de càncer, Alzheimer, Parkinson, malformacions congènites, alteracions en l'aprenentatge i altres trastorns neurològics, ginecològics i immunològics [92-98,109-118].

1.4.1. Trastorns crònics i salut autopercebuda

Fa temps que suggerim que, donada la varietat d'efectes adversos per a la salut dels CTPs, és probable que la distribució poblacional d'aquests compostos pugui explicar una part de la càrrega de malalties present en la població [80,97,112,119,120]. Tenint en compte aquesta hipòtesi, vam considerar d'interès analitzar la possible relació entre els CTPs i una mesura a nivell global de l'estat de salut com és la salut autopercebuda. Fins aleshores, només un estudi havia analitzat en persones d'entre 50 i

65 anys el possible efecte de les concentracions corporals de CTPs en la salut autopercebuda [121]. Tot i que en aquest estudi no es va observar relació amb les concentracions de PCBs i altres compostos, sí que es va observar una relació entre les concentracions de cadmi i una pitjor salut autopercebuda.

La salut autopercebuda és una valoració subjectiva del propi estat de salut, i normalment es mesura o classifica en cinc categories –excel·lent, molt bona, bona, regular, i dolenta. Nombrosos estudis han demostrat que és un molt bon predictor de la mortalitat, de la morbiditat i de la necessitat de serveis sanitaris, i que està vinculada a l'impacte en la salut de diferents trastorns crònics [122,123].

Així doncs, en el context de l'estudi de determinació de CTPs en la població general catalana, vam analitzar la possible influència de les concentracions de CTPs en la salut autopercebuda i també en la prevalença de trastorns crònics. Els resultats obtinguts són els que es van publicar en aquest article de la tesi [72]:

> *Article 1* (capítol de *Resultats*):
> **Gasull M,** Pallarès N, Salcedo N, Pumarega J, Alonso J, Porta M. *Self-rated health and chronic conditions are associated with blood concentrations of persistent organic pollutants in the general population of Catalonia, Spain.* Environmental Research 2015; 143: 211-220.

1.4.2. Diabetis i altres alteracions metabòliques

Un dels efectes adversos que més clarament s'ha vinculat a l'exposició a CTPs és la diabetis tipus 2 [124]. En el *workshop "Role of Environmental Chemicals in the Development of Diabetes and Obesity"* dut a terme l'any 2011, en el que es van reunir nombrosos científics de diferents àmbits i on es van avaluar més de 200 estudis, es va arribar a la conclusió que existeix una associació causal entre l'exposició a diversos agents químics ambientals –entre ells diversos CTPs– i el risc de patir diabetis; també es va concloure que la literatura existent dona plausibilitat a la contribució d'aquests contaminants a l'epidèmia de diabetis i, amb menys certesa, a la d'obesitat [109,125]. Entre els CTPs, compostos organoclorats com el DDE, els PCBs o l'hexaclorobenzè (HCB) comporten un major risc de patir diabetis tipus 2. Aquestes relacions s'observen en estudis transversals com el propi NHANES, en estudis prospectius com el *Nurses' Health Study* i en metaanàlisis amb dades de diversos estudis [98,126- 131]. Hi ha doncs diversos estudis prospectius que permeten descartar l'existència de causalitat inversa.

La relació positiva entre les concentracions sanguínies de CTPs i la prevalença de diabetis també la vam observar en el context de l'estudi de les concentracions de CTPs en la població de Catalunya. A més, vam estudiar i trobar que la relació també s'observava en estadis de prediabetis, definida aquesta com la presència de nivells de glucosa en dejú entre 110 i 125 mg/dL. Els resultats de l'estudi van ser publicats en aquest article inclòs en l'*Annex A* [73]:

> *Article A6:*
> **Gasull M**, Pumarega J, Téllez-Plaza M, Castell C, Tresserras R, Lee DH, Porta M. *Blood Concentrations of Persistent Organic Pollutants and Prediabetes and Diabetes in the General Population of Catalonia.* Environmental Science & Technology 2012; 46: 7799-7810.

Un cop vista la relació de les concentracions de CTPs amb diabetis i prediabetis en les dades de Catalunya, vam voler anar un pas més enllà i estudiar la seva relació amb la síndrome metabòlica i els fenotips metabòlics, els quals inclouen (a més de factors utilitzats per definir la síndrome metabòlica, com la glucèmia, la pressió arterial, les concentracions de colesterol i triglicèrids), mesures de resistència a la insulina i d'inflamació sistèmica (proteïna C-reactiva). Ens interessava especialment el fet que, malgrat el sobrepès i l'obesitat són factors de risc molt importants per patir trastorns metabòlics, hi ha certes persones que són obeses però metabòlicament sanes (de vegades anomenades *metabolically healthy obese*); també certes persones amb normopès poden ser considerades metabòlicament obeses (*metabolically obese non-obese*). Les característiques que diferencien aquests perfils metabòlics dels més prevalents podrien incloure diferències en les concentracions corporals de CTPs. Només dos estudis previs havien analitzat en persones amb sobrepès i obesitat la relació entre el tipus de fenotip metabòlic i les concentracions de CTPs [132,133]. En l'estudi amb dades de les concentracions de CTPs de la població de Catalunya, vam analitzar la relació entre aquestes concentracions, la síndrome metabòlica i els fenotips metabòlics, incloent –a diferència dels estudis anteriors– persones amb normopès.

L'estudi va donar lloc al següent article publicat a la revista *American Journal of Epidemology* i que forma part de la present tesi [74]:

> *Article 2* (capítol de *Resultats*):
> **Gasull M,** Castell C, Pallarès N, Miret C, Pumarega J, Téllez-Plaza M, López T, Salas-Salvadó J, Lee DH, Goday A, Porta M. *Blood concentrations of persistent organic pollutants and unhealthy metabolic phenotypes in normal-weight, overweight and obese individuals.* American Journal of Epidemiology 2018; 187: 494-506.

1.5. Justificació

La present tesi integra la recerca duta a terme per la candidata entorn als estudis de determinació de les concentracions de CTPs en mostres representatives de població general. Degut a les variacions entre poblacions i en el temps, és important que aquest tipus d'estudi es realitzi en diferents regions, ciutats o països i que, a més, es faci de forma periòdica. A nivell d'Espanya només es disposava d'un estudi sobre les concentracions d'alguns compostos en la població general de Canàries. La recerca de la present tesi aporta dades i coneixement sobre la contaminació de la població general a Catalunya i a la ciutat de Barcelona. També aporta informació i coneixement sobre com aquesta contaminació es relaciona amb factors sociodemogràfics com la classe social o l'educació.

A més, en la tesi s'apliquen noves formes de presentar i analitzar els resultats d'aquest tipus d'estudis a través de corbes de distribució poblacional i d'indicadors com el 'nombre de compostos detectats a altes concentracions', el qual també s'aplica a les dades disponibles d'un dels estudis més rellevants en aquest camp, com és l'estudi de les concentracions de contaminants ambientals en l'enquesta nacional de salut dels Estats Units (NHANES).

Finalment, la tesi també analitza la relació de la presència d'aquests contaminats en el nostre organisme i alguns efectes en la salut. Ho fa de forma exploratòria en tractar-se d'estudis transversals, però també de forma novedosa en aquest àmbit en centrar-se, per una banda, en un indicador de salut general com és la salut autopercebuda i, per l'altra, estudiant no només diabetis i prediabetis sinó també els fenotips metabòlics en persones amb sobrepès i obesitat, així com, per primer cop, en persones amb pes normal. A més, té en compte marcadors poc utilitzats en aquest context com és la proteïna C-reactiva.

2. HIPÒTESIS I OBJECTIUS

2.1. Hipòtesis

Les **hipòtesis principals** de la recerca duta a terme són que la contaminació de la població general per compostos tòxics persistents (CTPs) és freqüent i generalitzada, a concentracions baixes i altes, i que l'esmentada contaminació es relaciona amb diversos efectes adversos en la salut.

Les **hipòtesis específiques** són les següents:

1.- En mostres de sèrum de la població general de Catalunya i de la ciutat de Barcelona és freqüent detectar diversos CTPs, alguns dels quals es detecten en més del 80% de la població o inclús en la seva totalitat.
2.- Les concentracions sèriques de CTPs estan influenciades per factors sociodemogràfics com el sexe, l'edat o la cohort de naixement, l'índex de massa corporal, el nivell educatiu i la classe social.
3.- Les concentracions de cada CTP individualment considerat són baixes en una gran majoria de la població i altes en una minoria, és freqüent que els individus tinguin concentracions baixes de la majoria de CTPs i concentracions altes d'una minoria, i subgrups rellevants de la població presenten concentracions altes de diversos CTPs a la vegada.
4.- Unes majors concentracions sèriques de CTPs es relacionen amb una pitjor salut autopercebuda i amb una major prevalença de trastorns crònics.
5.- Unes majors concentracions sèriques de CTPs es relacionen amb una major prevalença de diabetis tipus 2, prediabetis i altres alteracions del perfil metabòlic.

2.2. Objectius

L'objectiu del conjunt de la recerca sintetitzada en aquesta tesi és posar a prova les hipòtesis específiques que acabem d'esmentar. Els **objectius principals** són analitzar la contaminació de la població general per compostos tòxics persistents així com estudiar la relació entre les concentracions corporals d'aquests compostos i alguns dels seus possibles efectes adversos en la salut.

Per assolir els objectius principals s'han desenvolupat els següents **objectius específics**:

1.- Analitzar la distribució de les concentracions sèriques de diversos CTPs en la població general de Catalunya (*Article A1*) [67] i en la població general de la ciutat de Barcelona (*Article A2*) [68].
2.- Analitzar factors sociodemogràfics que influencien les concentracions sèriques de CTPs en la població general de Catalunya i de la ciutat de Barcelona (*Articles A1 i A2*) [67,68], i en especial el paper del nivell educatiu i de la classe social (*Article A4*) [70].
3.- Analitzar la contaminació de la població general per CTPs a través d'un nou indicador, el 'nombre de compostos detectats a altes concentracions', en la població general de Catalunya (*Article A5*) [71] i en la població general dels Estats Units (*Article 3* capítol de *Resultats*) [91].
4.- Analitzar les relacions entre les concentracions sèriques de CTPs, la salut autopercebuda i la prevalença de trastorns crònics en la població general de Catalunya (*Article 1* capítol de *Resultats*) [72].
5.- Analitzar les relacions entre les concentracions sèriques de CTPs i la prevalença de diabetis i prediabetis (*Article A6*) [73] i altres alteracions del perfil metabòlic (*Article 2* capítol de *Resultats*) [74] en la població general de Catalunya.

Addicionalment també s'ha analitzat si alguns factors sociodemogràfics influeixen en la participació de les persones en els estudis poblacionals –com el dut a terme en la població de la ciutat de Barcelona– de determinació de substàncies contaminants (*Article A3*) [69].

El procés de realització de la tesi també ha inclòs entre els seus objectius dur a terme altres *activitats científiques addicionals* com: assistència a seminaris i congressos, impartició de seminaris, participació en seminaris del GRECMC, participació en l'elaboració de projectes de recerca i sol·licituds d'ajuts, participació en cursos d'especialització metodològica, presentacions de comunicacions en congressos i realització de tasques docents a la Unitat Docent del Parc Salut Mar (UD PSMar) de la Universitat Autònoma de Barcelona (vegeu l'*Annex C*).

3. METODOLOGIA

En aquest capítol es presenten a grans trets els tres estudis en els quals es basa la tesi. S'hi presenta el disseny de l'estudi, la població d'estudi, els compostos analitzats i altres dades d'interès de cada un d'ells. Aquella informació més específica i detallada es pot trobar en els propis articles inclosos en el capítol de *Resultats* i en el d'*Annexos* [67-74,91], així com en altres materials degudament referenciats. Al final del capítol s'inclou una taula comparativa dels tres estudis.

3.1. Estudi 'Determinació de Compostos Tòxics Persistents en l'Enquesta de Salut de Catalunya (ESCA)'

Es tracta d'un estudi transversal, emmarcat en l'Enquesta de Salut de Catalunya (ESCA), que va néixer amb l'objectiu d'avaluar i quantificar les concentracions en sang de compostos tòxics persistents en una mostra representativa de la població general de Catalunya.

La població d'estudi inclou més de 900 persones d'entre 18 i 74 anys que van participar en l'Enquesta de Salut de Catalunya i en l'Examen de Salut que es van dur a terme l'any 2002. Concretament, el Departament de Salut de la Generalitat de Catalunya (llavors Departament de Sanitat i Seguretat Social) va realitzar aquell any la que seria la segona Enquesta de Salut [134]. Hi van participar 8.400 persones no institucionalitzades; 1.374 d'aquestes persones també van participar en un Examen de Salut dut a terme pel mateix Departament [135]. En l'examen es realitzava –prèvia signatura del corresponent consentiment informat– una entrevista complementaria, un reconeixement físic (mesura de la pressió arterial, freqüència cardíaca, pes, talla, circumferència de la cintura i dels malucs) i una extracció de mostra de sang i orina. Un cop analitzats en el laboratori els nivells de diferents paràmetres immunològics i bioquímics (glucèmia, colesterol total, HDL i LDL, triglicèrids, àcid úric, GOT, GPT, GGT, insulina, entre d'altres), el sèrum restant es va emmagatzemar congelat a –80 ºC.

Uns anys després d'haver-se realitzat l'Examen, les mostres de sang obtingudes durant el mateix i guardades en previsió d'ulteriors anàlisis van permetre fer les determinacions químiques necessàries per estudiar la distribució de CTPs en la població catalana. Concretament, es van seleccionar aquells participants en els que el volum de sèrum restant era suficient per a la determinació dels CTPs (almenys 1 mL) i dels quals es disposava d'informació de les seves concentracions de colesterol total i triglicèrids –informació necessària per al càlcul de les concentracions de CTPs corregides en funció dels lípids totals. Van complir aquests requisits 919 participants, en les mostres dels quals es va analitzar les concentracions sèriques de 19 CTPs. Les anàlisis de laboratori es van dur a terme, durant els anys 2006-2008, al Departament de Química Ambiental de l'Institut de Diagnòstic Ambiental i

Estudis de l'Aigua – Consell Superior d'Investigacions Científiques (IDÆA-CSIC). Els compostos analitzats van ser concretament: cinc policlorobifenils *non-dioxin like* (PCB congèneres 52, 101, 138, 153 i 180), dos PCBs *dioxin like* (congèneres 28 i 118), i 12 plaguicides organoclorats i els seus metabòlits: diclorodifeniltricloroetà (DDT, isòmers p,p' i o,p'), diclorodifenildicloroetilè (DDE, isòmers p,p' i o,p'), diclorodifenildicloroetà (DDD, isòmers p,p' i o,p'), α-hexaclorociclohexà (α-HCH), β-HCH, γ-HCH, δ-HCH, pentaclorobenzè (PeCB) i hexaclorobenzè (HCB).

Per tal de mantenir la representativitat de la submostra de 919 participants pel que fa al sexe, l'edat i el lloc de residència (regió sanitària) de la població general de Catalunya a data 1 de gener de 2001, es van utilitzar ponderacions en les anàlisis estadístiques; és a dir, es van calcular i assignar diferents pesos mostrals a cada persona per tal de tenir en compte el complex disseny mostral aplicat tant en l'ESCA com en l'Examen de salut [75, 134-136].

En l'informe que es va publicar l'any 2009 [75], així com en el capítol 11 del llibre "Nuestra contaminación interna" [41], es descriu de forma detalla i específica tota la informació referent a l'estudi. Vegeu també l'apartat de metodologia de l'*Article A1* de l'*Annex A* de la present tesi [67].

3.2. Estudi 'Determinació de Compostos Tòxics Persistents en l'Enquesta de Salut de Barcelona (ESB)'

Es tracta d'un estudi transversal, en aquest cas emmarcat en l'Enquesta de Salut de Barcelona (ESB), que té per objectiu avaluar i quantificar les concentracions en sang de compostos tòxics persistents en una mostra representativa de la població general de la ciutat de Barcelona.

La població d'estudi està formada per una submostra de 231 persones de ≥ 18 anys participants en l'ESB, duta a terme per l'Agència de Salut de Barcelona l'any 2006 [137]. En finalitzar l'enquesta, realitzada a més de 3000 participants, a tots aquells que tenien ≥ 15 anys se'ls oferia la possibilitat de participar en l'estudi de determinació de CTPs, bàsicament aportant una mostra de sang. La visita corresponent a l'estudi de determinació de CTPs es realitzava en una data posterior –prèvia citació via telefònica– a les instal·lacions de l'IMIM. Es van contactar 532 persones (del total de les persones enquestades a l'ESB que havien mostrat interès); un 44% d'aquestes, 231 persones, van participar finalment en l'estudi. L'anàlisi detallada de la taxa de resposta i dels factors sociodemogràfics que van influenciar en la participació van ser publicats en forma d'article científic (*Article A3* de l'*Annex A* de la present tesi) [69].

La visita a l'IMIM era realitzada per personal d'infermeria i consistia –prèvia signatura del corresponent consentiment informat– en una breu entrevista complementària, en la mesura del pes, talla i circumferència de la cintura i malucs, i en l'obtenció de la mostra de sang. Un cop processada la mostra, les alíquotes de sèrum eren emmagatzemades a -80ºC.

Les anàlisis de laboratori es van dur a terme, l'any 2008, en el mateix laboratori que l'estudi a nivell de Catalunya, és a dir, en el Departament de Química Ambiental de l'Institut de Diagnòstic Ambiental i Estudis de l'Aigua (IDÆA-CSIC). Els compostos analitzats van ser els mateixos 19 compostos: cinc PCBs *non-dioxin like* (congèneres 52, 101, 138, 153 i 180), dos PCBs *dioxin like* (congèneres 28 i 118), i 12 plaguicides organoclorats i els seus metabòlits: o,p'-DDT, p,p'-DDT, o,p'-DDE, p,p'-DDE, o,p'-DDD, p,p'-DDD, α-HCH, β-HCH, γ-HCH, δ-HCH, PeCB i HCB. Els nivells de colesterol total i de triglicèrids per al càlcul de les concentracions de CTPs corregides pels lípids totals van ser analitzats pel Grup de Recerca en Risc Cardiovascular i Nutrició de l'IMIM.

Per tal de mantenir la representativitat de la submostra de 231 participants pel que fa al sexe i l'edat de la població general de Barcelona a data 1 de gener de 2006, es van assignar pesos mostrals alhora de realitzar les anàlisis estadístiques. En el càlcul de les ponderacions no es va poder tenir en compte el lloc de residència, en aquest cas el districte de la ciutat, ja que la mostra no era suficientment gran.

3.3. Estudi '*National Health and Nutrition Examination Survey* (NHANES)', Estats Units

Part de la recerca que forma part de la present tesi es basa en dades obtingudes de la *National Health and Nutrition Examination Survey* (NHANES) que es realitza periòdicament als Estats Units. Es tracta d'una enquesta representativa a nivell nacional i que recull informació de salut i nutrició de la població general d'aquest país, incloent dades de biomonitorització a través de l'anàlisi de compostos químics ambientals en mostres de sang i orina [89,138]. Les dades anonimitzades de la NHANES estan disponibles públicament.

La NHANES es duta a terme pels *Centers for Disease Control and Prevention* (CDC), consta de l'aprovació del *National Center for Health Statistics (NCHS) Instituional Review Board* i s'organitza en cicles de dos anys. Tots els participants signen el corresponent consentiment informat. La població d'estudi en que es basa part de la tesi per analitzar el 'nombre de compostos detectats a altes concentracions' consta de 4.739 participants de ≥ 20 anys del període 2003-2004. Durant aquest període es van entrevistar personalment 10.122 persones no institucionalitzades i a 9.643 d'aquestes se'ls va realitzar un examen de salut (incloent persones de totes les edats). L'anàlisi de les

concentracions en sang de compostos químics ambientals es va realitzar en tres submostres dels participants de l'examen de 20 o més anys. En cada una de les submostres es va analitzar un grup diferent de substàncies. El nombre exacte de participants en cada submostra va ser de 1.610, 1.585 i 1.544 individus [89].

Per realitzar l'entrevista i l'examen de salut, un equip format per un metge, tècnics sanitaris i entrevistadors especialitzats en salut i nutrició es desplaçaven al domicili dels participants. L'entrevista es realitzava personalment al domicili, amb algunes parts sobre informació sensible autoadministrades. L'examen físic i l'obtenció de les mostres de sang –i altres mostres biològiques– s'efectuaven en centres mòbils degudament equipats (*mobile examination centers*). Les mostres eren processades i aliquotades en el propi centre mòbil, refrigerades o congelades a -20ºC segons el cas i enviades als corresponents laboratoris [138].

Les anàlisis de laboratori dels compostos químics ambientals es van realitzar en el *CDC's Environmental Health Laboratory*. Per l'anàlisi del 'nombre de compostos detectats a altes concentracions' es van considerar els 91 compostos analitzats en mostres de sèrum [90]. Concretament, aquests compostos eren: *a)* 12 compostos perfluorats (PFCs / PFASs) –analitzats en la submostra de 1.610 participants–; *b)* 13 plaguicides organoclorats (OCs), 10 èters difenílics polibromats (PBDEs) i el bifenil polibromat PBB 153 –analitzats en la submostra de 1.585 participants–; i *c)* 29 PCBs *non-dioxin like*, 9 PCBs *dioxin like* i 17 dibenzodioxines i dibenzofurans policlorats (PCDDs/Fs) –analitzats en la submostra de 1.544 participants–. En cada submostra es van imputar els valors dels compostos no analitzats a partir de la mediana de cada compost en funció del grup d'edat, sexe, raça/ètnia, IMC, nivell d'ingressos i, en dones, nombre d'embarassos.

En la següent pàgina es presenta una taula comparativa de les principals característiques dels tres estudis en els que es basa la tesi.

Taula 1. Característiques dels tres estudis de determinació de compostos tòxics persistents (CTPs) en els que es basa la recerca duta a terme en la tesi.

Característiques	Enquesta de Salut de Catalunya	Enquesta de Salut de Barcelona	NHANES (Estats Units)
Tipus d'estudi	Transversal	Transversal	Transversal
Període d'estudi	2002	2006	2003-2004
Número de participants	919 (399 homes, 520 dones)	231 (94 homes, 137 dones)	4.739 (2.272 homes, 2.467 dones)
Població d'estudi	Població general	Població general	Població general
Localització	Catalunya	Barcelona ciutat	Estats Units
Edat	De 18 a 74 anys (mediana: 45 anys)	≥ 18 anys (mediana: 45 anys)	≥ 20 anys (mediana: 49 anys)
Entrevista de l'enquesta de salut	Entrevista personal, al domicili	Entrevista personal, al domicili	Entrevista personal, al domicili
Responsable de l'enquesta de salut	Departament de Salut (Generalitat de Catalunya)	Agència de Salut Pública de Barcelona	Centers for Disease Control and Prevention (NCHS-CDC)
Entrevista de l'examen de salut	Entrevista personal, al Centre d'Atenció Primària més proper al domicili	Entrevista personal, a l'IMIM	Entrevista personal, amb algunes parts autoadministrades, al domicili
Responsable de l'examen de salut	Departament de Salut (Generalitat de Catalunya)	GRECMC - IMIM	Centers for Disease Control and Prevention (NCHS-CDC)
Qüestionari específic per estudi CTPs	No	Sí (Personal, a l'IMIM)	No
Tipus de mostra biològica	Sèrum	Sèrum	Sèrum
Lloc d'obtenció mostra biològica	Centre d'Atenció Primària més proper al domicili	IMIM	Centres mòbils equipats
Emmagatzematge	-80ºC (Departament de Salut)	-80ºC (IMIM)	-20ºC
Temps d'emmagatzematge	4-6 anys (de 2002 a 2006/08)	2 anys (de 2006 a 2008)	No especificat (< 5 anys)
Número de compostos analitzats	19	19	91
Compostos analitzats	OCs, PCBs	OCs, PCBs	OCs, PCBs, PBDEs, PBB, PCDDs/Fs, PFCs
Laboratori anàlisis CTPs	Departament de Química Ambiental (IDAEA-CSIC)	Departament de Química Ambiental (IDAEA-CSIC)	CDC's Environmental Health Laboratory

4. RESULTATS

En aquest capítol s'inclouen els tres articles que formen part del compendi de publicacions. Tots ells han estat publicats en revistes internacionals de reconegut prestigi. Juntament amb els articles inclosos en l'*Annex A*, serveixen per presentar els resultats obtinguts del treball realitzat per tal d'assolir els objectius i verificar o rebutjar les hipòtesis plantejades inicialment.

Les referències dels tres articles són les següents:

Article 1 [72]:
– Gasull M, Pallarès N, Salcedo N, Pumarega J, Alonso J, Porta M. Self-rated health and chronic conditions are associated with blood concentrations of persistent organic pollutants in the general population of Catalonia, Spain. Environ Res. 2015; 143: 211-220.

Article 2 [74]:
– Gasull M, Castell C, Pallarès N, Miret C, Pumarega J, Téllez-Plaza M, López T, Salas-Salvadó J, Lee DH, Goday A, Porta M. Blood concentrations of persistent organic pollutants and unhealthy metabolic phenotypes in normal-weight, overweight and obese individuals. Am J Epidemiol. 2018; 187: 494-506.

Article 3 [91]:
– Pumarega J, Gasull M, Lee DH, López T, Porta M. Number of Persistent Organic Pollutants Detected at High Concentrations in Blood Samples of the United States Population. PLoS One. 2016; 11: e0160432.

Article 1

Títol: Self-rated health and chronic conditions are associated with blood concentrations of persistent organic pollutants in the general population of Catalonia, Spain.

Autors: Gasull M, Pallarès N, Salcedo N, Pumarega J, Alonso J, Porta M.

Revista: Environmental Research. 2015 Nov;143:211-220.

Factor d'impacte:
Any 2014, últim disponible en el moment de publicació: 4.373 (Q1, D1 Public, Environmental & Occupational Health, Q1, D1 Environmental Sciences).
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Self-rated health and chronic conditions are associated with blood concentrations of persistent organic pollutants in the general population of Catalonia, Spain

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ABSTRACT

Background: Self-rated health (SRH) is a powerful predictor of mortality, morbidity, and need for health services. SRH generally increases with educational level, and decreases with age, number of chronic conditions, and body mass index (BMI). Because human concentrations of most persistent organic pollutants (POPs) also vary by age, education, and BMI, and because of the physiological and clinical effects of POPs, we hypothesized that body concentrations of POPs are inversely associated with SRH.
Objectives: To analyze the relation between serum concentrations of POPs and SRH in the general population of Catalonia, Spain, taking into account sociodemographic factors and BMI, as well as chronic health conditions and mental disorders, measured by the General Health Questionnaire-12 (GHQ-12).
Methods: POP serum concentrations were measured by gas chromatography with electron-capture detection in 919 participants of the Catalan Health Interview Survey.
Results: Individuals with higher concentrations of POPs had significantly poorer SRH; e.g., the median concentration of HCB in subjects with poor SRH was twice as high as in subjects with excellent SRH (366 ng/g vs. 169 ng/g, respectively; p-value < 0.001). In crude models and in models adjusted for sex and BMI, the POPs-SRH association was often dose-dependent, and the likelihood of poor or regular SRH was 2 to 4-times higher in subjects with POP concentrations in the top quartile. In models adjusted for age or for chronic conditions virtually all ORs were near unity. No associations were found between POP levels and GHQ-12.
Conclusions: Individuals with higher concentrations of POPs had significantly poorer SRH, an association likely due to age and chronic conditions, but not to sex, education, social class, BMI, or mental disorders.

1. Introduction

Most persistent organic pollutants (POPs) are known or reasonably suspected to harm relevant aspects of human health, and some probably even do so at low doses (Department of Health and Human Services, 2009; Faroon and Ruiz, 2015; Lee et al., 2014; Litwack, 2014; National Research Council, 2006; Patterson et al., 2009; Porta et al., 2008, 2012; Prüss-Ustün et al., 2011; Vandenberg et al., 2012; World Health Organization, 2013). Even though they have not been manufactured in developed countries for several decades, in the global and highly intertwined economies of today many POPs remain detectable in animal and human food webs, and in virtually all human beings, commonly at low and high concentrations (Aylward et al., 2014; Den Hond et al., 2015; Department of Health and Human Services, 2009; Litwack, 2014;

Abbreviations: ANOVA, analysis of variance; β, regression coefficient; BMI, body mass index; CC, chronic conditions; CHIS, Catalan Health Interview Survey; CI, confidence interval; DDD, dichlorodiphenyldichloroethane; DDE, dichlorodiphenyldichloroethene; DDT, dichlorodiphenyltrichloroethane; GHQ-12, Goldberg's General Health Questionnaire-12; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; OR, odds ratio; ≥P75, equal or above the 75th percentile (top quartile); PCBs, polychlorinated biphenyls; PeCB, pentachlorobenzene; POPs, persistent organic pollutants; SD, standard deviation; SRH, self-rated health; TL, total lipids

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Porta et al., 2010, 2012; Prüss-Ustün et al., 2011; World Health Organization, 2013).

Self-rated health (SRH) does not just capture the individual's subjective well-being: decades of research have shown that it is also a simple and powerful predictor of morbidity and mortality (Baron-Epel, 2004; Bjorner et al., 2005; Brunström and Fredlund, 2001; DeSalvo et al., 2006; Diehr et al., 2001, 2002; Eriksson et al., 2001; Idler and Benyamini, 1997, Idler et al., 2000). SRH is most commonly rated using a five-point scale ranging from excellent health to poor health. Its validity, ease of collection and assessment, and all-inclusive nature, make it a useful tool for measuring the health impact of various chronic conditions (Alonso, 2000; Baron-Epel, 2004; Tarlov et al., 1989). Women tend to have worse perceived health than men, although in studies that corrected for medical indicators gender differences disappeared, and women tended to assess their health more favorably than men (Crimmins et al., 2010; Malmusi et al., 2012; Undén and Elofsson, 2006). SRH generally increases with educational level, decreases with age, and is lower in individuals underweight and obese (Dowd and Zajacova, 2010; Imai et al., 2008; Jiménez-Garcia et al., 2008; Molarius et al., 2006).

In principle, SRH could be influenced by some environmental pollutants, and could thus be helpful to assess the health impacts of environmental exposures (Carrasco et al., 2007; Nakata et al., 2009; Sala et al., 1999; Ushijima et al., 2004; Van Larebeke et al., 2015). Human concentrations of most POPs generally increase with age and body mass index (BMI), though some compounds (as PCBs) may be inversely associated with BMI; birth cohort effects also exist (Gasull et al., 2013; Porta et al., 2008). POP levels often increase with decreasing social class and educational level, particularly when age and birth cohort effects are not accounted for (Gasull et al., 2013). Because of these associations, and because of the physiological and clinical effects of POPs, it is reasonable to hypothesize that POP concentrations are associated with SRH. An ensuing question is whether any putative associations between POPs and SRH will hold once the effects of sex, age, occupational social class, educational level, and BMI are taken into account. Furthermore, a POPs–SRH association might partly be due to chronic health conditions or to mental disorders (Fig. 1). Surprisingly, virtually no studies have analyzed the relationships between body concentrations of POPs or other environmental chemicals, and SRH.

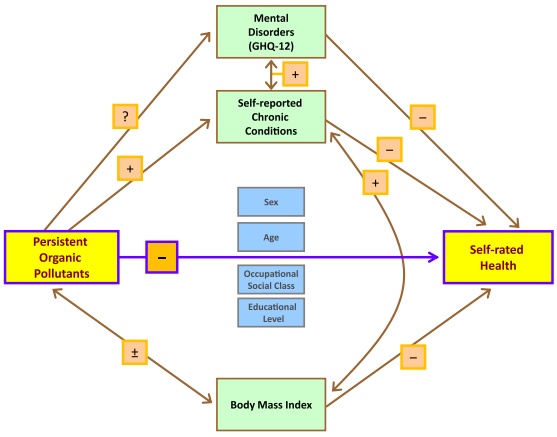

Fig. 1. Diagram summarizing the main study hypotheses. Footnote: Plus signs (+) indicate a positive association (e.g., higher concentrations of persistent organic pollutants are associated to a higher number of self-reported chronic conditions), whereas negative signs (−) indicate an inverse association (e.g., a higher body mass index is associated with a poorer self-rated health, higher concentrations of persistent organic pollutants are associated to a poorer self-rated health).

The aim of the present study was to analyze the relation between serum concentrations of POPs and SRH, taking into account sociodemographic factors and BMI, as well as chronic health conditions and mental disorders, in the non-institutionalized, adult, general population of Catalonia, Spain.

2. Materials and methods

2.1. Study population

The study population has been described in detail elsewhere (Porta et al., 2010). Briefly, in 2002, the Department of Health of the regional Government of Catalonia conducted a new health interview survey (CHIS) to obtain information on perceived health, health-related behaviors, and use of health services (Departament de Salut, 2002; Porta et al., 2010, 2012). The interviews were conducted face to face by trained staff at the home of the interviewee. To achieve a representative sample of the non-institutionalized population of residents in Catalonia a multi-stage random sampling strategy was applied (Departament de Salut, 2002; Juncà et al., 2003).

Once the CHIS interview was finalized, participants 18–74 years old were asked if they wanted to take part in a health examination, which included a supplementary interview, physical examination, and blood and urine samples. Participation was voluntary and had no economic compensation. A random sample was selected amongst those who consented to participate and, of these, 1374 individuals participated during 2002 in the health examination; in such examination, trained nurses measured weight and height, and blood samples were drawn after twelve hours of fasting (Porta et al., 2010, 2012). Information on blood concentrations of lipids and at least 1 mL of serum were available from 919 participants. There were no significant differences between the 919 participants and the remaining participants in the health examination with respect to age, sex, BMI, social class, and educational level (Porta et al., 2010, 2012).

2.2. Health outcomes and socioeconomic variables

As in other similar surveys (Dowd and Zajacova, 2010; Ho et al., 2007; Jiménez-Garcia et al., 2008; Molarius et al., 2006), in the CHIS self-rated health (SRH) status was measured by the question 'How would you rate your overall health?'. The question had five possible answers: 'excellent', 'very good', 'good', 'regular', and 'poor' (Brugulat et al., 2003). For part of the analyses we grouped SRH into two categories, with 'regular' and 'poor' in one group ('poor'), and the remainder in the other ('good'). In other parts of the analyses the variable was analyzed using all five categories.

CHIS interviewers gathered information about 26 chronic conditions (CC). We categorized the number of CC per person in quartiles (Table 1). We also selected two different subgroups of CC based on their possible relationships with POP concentrations (Department of Health and Human Services, 2009; Lee et al., 2014; World Health Organization, 2013). A third subgroup was created including the ten CC that were found to be most correlated with POP concentrations in the study participants.

The lower educational category of subjects without formal studies included the illiterate. To assign the occupational social class we used the Spanish classification, based on Goldthorpe's scheme; the current or last occupation of the head of the household was thus used (Porta et al., 2010). The presence of mental disorders was assessed with Goldberg's General Health Questionnaire (GHQ-12): individuals with a score ≥ 4 were considered likely to have a mental disorder (Sabes-Figuera et al., 2012).

Over 56% of the participants were women, and the average age

Table 1
Sociodemographic and health characteristics of the study population by self-rated health status.

	Self-rated health												*P*
	Total		Excellent		Very good		Good		Regular		Poor		
	N	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)	*N*	(%)	
Number of participants	919	(100)	62	(6.7)	147	(16.0)	470	(51.1)	203	(22.1)	37	(4.0)	
Sex													
Male	399	(43.4)	23	(37.1)	71	(48.3)	215	(45.7)	76	(37.4)	14	(37.8)	0.143[a]
Female	520	(56.6)	39	(62.9)	76	(51.7)	255	(54.3)	127	(62.6)	23	(62.2)	
Age (years)													
Mean ± SD	45.2 ± 15.0		40.5 ± 13.7		38.3 ± 15.3		44.3 ± 14.3		52.0 ± 14.0		54.7 ± 11.9		< 0.001[b]
Median	45.0		37.0		36.0		44.0		52.0		57.0		< 0.001[c]
18–29	175	(19.1)	17	(27.4)	50	(34.0)	93	(19.8)	14	(6.9)	1	(2.7)	< 0.001[d]
30–44	272	(29.6)	25	(40.3)	53	(36.1)	144	(30.6)	44	(21.7)	6	(16.2)	
45–59	288	(31.3)	12	(19.4)	25	(17.0)	158	(33.6)	75	(36.9)	18	(48.6)	
60–74	184	(20.0)	8	(12.9)	19	(12.9)	75	(16.0)	70	(34.5)	12	(32.4)	
Body mass index (kg/m^2)													
Mean ± SD	26.4 ± 4.6		25.5 ± 4.7		25.1 ± 4.6		26.3 ± 4.2		27.5 ± 4.8		28.9 ± 5.7		< 0.001[b]
Median	25.9		24.6		24.6		25.7		27.0		28.0		< 0.001[c]
Underweight (< 18.5)	10	(1.1)	2	(3.2)	4	(2.7)	2	(0.4)	2	(1.0)	0	(0.0)	< 0.001[d]
Normal weight (18.5-24.9)	381	(41.4)	31	(50.0)	77	(52.4)	198	(42.1)	63	(31.0)	12	(32.4)	
Overweight (25.0-29.9)	348	(37.9)	17	(27.4)	50	(34.0)	190	(40.4)	83	(40.9)	8	(21.6)	
Obese (≥ 30)	180	(19.6)	12	(19.4)	16	(10.9)	80	(17.0)	55	(27.1)	17	(45.9)	
Self-reported chronic conditions (No.)													
Mean ± SD	2.9 ± 3.0		1.1 ± 1.5		1.4 ± 1.8		2.3 ± 2.4		5.0 ± 3.0		8.6 ± 3.7		< 0.001[b]
Median	2.0		0.5		1.0		2.0		5.0		9.0		< 0.001[c]
0	224	(24.4)	31	(50.0)	63	(42.9)	122	(26.0)	8	(3.9)	0	(0.0)	< 0.001[d]
1–2	286	(31.1)	23	(37.1)	48	(32.7)	174	(37.0)	39	(19.2)	2	(5.4)	
3–4	188	(20.5)	5	(8.1)	26	(17.7)	107	(22.8)	46	(22.7)	4	(10.8)	
≥ 5	221	(24.0)	3	(4.8)	10	(6.8)	67	(14.3)	110	(54.2)	31	(83.8)	
General Health Questionnaire (GHQ-12)													
0–3	810	(88.1)	58	(93.5)	139	(94.6)	425	(90.4)	168	(82.8)	20	(54.1)	< 0.001[a]
≥ 4	109	(11.9)	4	(6.5)	8	(5.4)	45	(9.6)	35	(17.2)	17	(45.9)	
Birth place													< 0.001[d]
Catalonia	656	(71.8)	51	(83.6)	117	(80.1)	344	(73.3)	125	(62.2)	19	(51.4)	
Rest of Spain	231	(25.3)	9	(14.8)	24	(16.4)	116	(24.7)	68	(33.8)	14	(37.8)	
Abroad	27	(2.9)	1	(1.6)	5	(3.4)	9	(1.9)	8	(4.0)	4	(10.8)	
Educational level													< 0.001[a]
Without formal education	140	(15.3)	10	(16.4)	10	(6.8)	48	(10.3)	58	(28.9)	14	(37.8)	
Primary schooling (1st stage)	242	(26.5)	6	(9.8)	26	(17.7)	131	(28.1)	68	(33.8)	11	(29.7)	
Primary schooling (2nd stage)	227	(24.9)	17	(27.9)	36	(24.5)	127	(27.2)	39	(19.4)	8	(21.6)	
Secondary schooling	192	(21.0)	21	(34.4)	43	(29.3)	98	(21.0)	26	(12.9)	4	(10.8)	
University	111	(12.2)	7	(11.5)	32	(21.8)	63	(13.5)	9	(4.5)	0	(0.0)	
Occupational social class													0.001[a]
V (less affluent)	75	(8.4)	3	(4.8)	8	(5.6)	39	(8.5)	20	(10.4)	5	(13.5)	
IV	420	(47.1)	27	(43.5)	58	(40.3)	206	(45.1)	106	(55.2)	23	(62.2)	
III	229	(25.7)	18	(29.0)	45	(31.3)	114	(24.9)	47	(24.5)	5	(13.5)	
II	94	(10.5)	10	(16.1)	11	(7.6)	59	(12.9)	12	(6.3)	2	(5.4)	
I (most affluent)	74	(8.3)	4	(6.5)	22	(15.3)	39	(8.5)	7	(3.6)	2	(5.4)	

[a] Fisher's exact test (two-tail).
[b] ANOVA test (two-tail).
[c] Kruskal–Wallis test (two-tail).
[d] Pearson Chi-Square test (two-tail).

was 45 years. About 20% were obese and almost 40% overweight, 15% had no formal education, and 55% were from occupational social classes IV or V (Table 1). 75% of participants had one or more CC, and 45% had three or more CC. 12% of subjects had a GHQ-12 score ≥ 4 (14% of women and 9% of men). There were no significant differences in the distribution of birth place, educational level and social class by sex (data not shown). Women were on average 3 years younger than men, tended to report a higher number of CC, and had a lower BMI. These differences were accounted for in multivariate analyses. About 74% of participants rated their health as excellent, very good or good. SRH was significantly inversely associated with age, BMI, number of CC, and having a mental disorder, and positively associated with educational level and social class (Table 1). Birth place was also

associated with SRH, with those born in Catalonia reporting a better health status.

2.3. Analytical chemical methods

A detailed account of laboratory methods has previously been published (Porta et al., 2010, 2012). Serum concentrations of the following persistent organic pollutants were analyzed in the Department of Environmental Chemistry (IIQAB-CSIC, Barcelona): o,p′-DDT, p,p′-DDT, o,p′-DDE, p,p′-DDE, o,p′-DDD, p,p′-DDD, PCBs 28, 52, 101, 118, 138, 153, and 180, PeCB, HCB, α-HCH, β-HCH, γ-HCH and δ-HCH (Porta et al., 2010). Gas chromatography (GC) analyses were performed with an Agilent Technologies model GC-6890N provided with an ECD and a 60 m, 0.25 mm i.d. DB-5 column (film thickness 0.25 μm). Main statistical analyses were limited to compounds that were above the detection limit in 85% of participants. Limits of quantification ranged from 0.0069 ng/mL for PCB 101 to 0.0706 ng/mL for γ-HCH (Porta et al., 2010). When a sample had a concentration of a compound below the detection threshold, it was assigned the mid-value of this limit; when a compound was detected but under the quantification threshold, the mid-value between detection and quantification limits was used (Porta et al., 2010, 2012).

Total serum lipids (TL) were calculated by the Standard formula 2, based on total cholesterol and triglycerides (Bernert et al., 2007; Phillips et al., 1989; Porta et al., 2009), which were determined enzymatically (Txad-Pap and CIN-UV methods, respectively) in serum obtained in the health examination (Departament de Salut, 2002; Porta et al., 2010). POP concentrations were individually corrected for TL by dividing the crude serum POP concentration by TL, and are expressed in nanograms per gram lipid (ng/g). Among the 919 individuals, mean (standard deviation) serum concentrations of total cholesterol, triglycerides and TL were, respectively, 196.5 (40.2), 96.8 (64.2) and 605.1 (130.5) mg/dl.

2.4. Statistical analyses

Univariate statistics were computed as customary (Armitage et al., 2002; Kleinbaum et al., 1998). ANOVA and Kruskal–Wallis test were used to analyze normally and non-normally distributed quantitative variables. Chi-square test was only used when Fisher's exact test could not be computed to assess the relationship between two categorical variables. Density plots (Porta et al., 2010) were used to chart the distribution of POP serum concentrations in SRH groups. To estimate the magnitude of the associations between POPs and SRH, multivariate adjusted odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were computed by unconditional logistic regression (Kleinbaum et al., 1998). Final models were chosen coherently with the study objectives and the nature of the variables (Fig. 1). POP concentrations were introduced in the models as quartile categories. We also computed the number of POPs detected per person with concentrations in the upper quartile (Porta et al., 2012), and this variable was introduced in the models as tercile categories. We assessed linear dose–response relations through the multivariate analog of Mantel's extension test for linear trend; when a linear trend was not apparent, the probability test was used. Unconditional logistic regression was used when studying the association between sociodemographic and health characteristics and SRH. To evaluate correlations between POPs and chronic conditions, the Spearman's correlation coefficient was used. The influence of POP concentrations on the number of CC was assessed through General Linear Models (McCulloch et al., 2008). For each subgroup of selected CC (see Section 2.2.), ORs of having one or more CC and their corresponding 95% CIs were also computed.

The level of statistical significance was set at 0.05 and all tests were two tailed. Analyses were conducted using SPSS version 18.0.0 (SPSS, Chicago, IL, USA, 2009) and R version 3.1.3 (R Core Team, 2015).

3. Results

Serum concentrations of 11 of the 19 POPs analyzed were statistically significantly higher in subjects with poor SRH than in subjects with good SRH (p,p′-DDT, p,p′-DDE, o,p′-DDD, HCB, β-HCH, δ-HCH, and PCB congeners 52, 118, 138, 153 and 180) (data not shown). In the unadjusted results shown in Table 2 and Fig. 2, concentrations of the 8 most commonly detected POPs all tended to increase linearly as SRH decreased from excellent to poor, with the exception of very good SRH, a subgroup in which POP levels were always lowest. Not just the statistical significance, but the magnitude of the differences was also substantial; e.g., for β-HCH and PCB 153 median concentrations were 40% greater in subjects with poor health than in subjects with good health. The corresponding medians for p,p′-DDE and HCB in poor SRH were twice as high than in excellent SRH (792 ng/g vs. 376 ng/g and 366 ng/g vs. 169 ng/g, respectively) (Table 2 and Fig. 2). Similar results for the 8 most commonly detected POPs were found when men and women were considered separately.

As an illustration, Fig. 3 shows the population distribution of serum concentrations of p,p′-DDE for subjects with good (excellent, very good, or good) and poor (regular or poor) SRH: the latter is more skewed to the right (i.e., they have higher concentrations) than the distribution in subjects with good SRH. The shapes of the distributions of all other 7 most prevalent POPs were similar.

In the crude (unadjusted) model, individuals with poor SRH had significantly higher concentrations of all 8 most prevalent POPs; the association was often dose-dependent, and the likelihood of poor health was generally between 2 and 4-times higher in participants with POP concentrations in the top quartile (Table 3). When adjusted for BMI, most such ORs were weakened, but still (except p,p′-DDT) of a substantial magnitude (i.e., ≥ 2) and statistical significance (Table 3, adjusted model A); e.g. individuals with HCB levels in the top quartile had 3.3-times the risk of having poor SRH than individuals in the lower quartile, whereas the corresponding figure from the crude model was 4.2 (Table 3). Also, individuals with 3 or more POPs each at concentrations in the top quartile (vs. individuals with 0 such POPs) had 2.4-times the risk of having poor SRH vs. 2.8-times in the crude model. A similar attenuation and significance of the ORs occurred when we further adjusted for sex (models not shown). However, when we incorporated age (Table 3, models B and C) virtually all ORs were near unity and statistically nonsignificant. Further adjusting for educational level, social class or birth place did not materially change the results (data not shown). Stratifying by sex, in the crude models for men p,p′-DDE, PCB 118, HCB, and β-HCH were inversely associated with SRH, whereas in women all eight POPs were so (all $p < 0.05$). Again, the associations did not hold when age was taken into account.

Multivariate analyses showed that sex (women), age, BMI and number of CC were associated with poor SRH (Supplementary material, Table 1). When these four variables were included in the same model simultaneously, age and CC remained independently and statistically significantly associated with poor SRH; the OR for ≥ 5 CC vs. 1 or 2 was 9.1 ($p < 0.001$).

In the unadjusted results shown in Fig. 2, concentrations of all 8 most commonly detected POPs tended to increase linearly as the number of CC increased. Linear regression models assessing the influence of POP concentrations on the number of CC showed that individuals with higher concentrations of all 8 most prevalent POPs had a significant higher number of CC (Table 4); e.g. subjects

Table 2
Serum concentrations of persistent organic pollutants (POPs) by self-rated health status.

Compound (ng/g lipid)	**Self-rated health**					***P***
	Excellent	**Very good**	**Good**	**Regular**	**Poor**	
p,p′-DDT						
Mean ± SD	37.95 ± 38.67	40.66 ± 65.14	50.93 ± 69.34	63.90 ± 111.3	55.54 ± 72.35	0.045[a]
Median	27.25	25.51	30.21	35.19	40.62	0.009[b]
Min–Max	1.54–190.9	0.83–572.5	0.92–535.2	1.13–1253	1.21–399.8	
p,p′-DDE						
Mean ± SD	630.3 ± 744.5	520.7 ± 652.7	776.4 ± 1031	935.6 ± 1038	1068 ± 859.1	< 0.001[a]
Median	375.6	296.5	435.1	638.3	792.0	< 0.001[b]
Min–Max	40.57–4289	49.95–4383	43.15–9036	1.17–5978	115.9–3577	
HCB						
Mean ± SD	247.5 ± 266.0	222.0 ± 298.0	299.8 ± 322.6	455.7 ± 511.2	471.4 ± 382.5	< 0.001[a]
Median	169.4	114.9	195.9	317.3	366.2	< 0.001[b]
Min–Max	1.11–1269	0.81–1931	0.89–2352	0.79–4799	14.16–1391	
β-HCH						
Mean ± SD	144.4 ± 200.3	122.3 ± 188.8	186.9 ± 215.7	264.2 ± 301.0	300.4 ± 336.3	< 0.001[a]
Median	88.35	69.37	109.5	185.9	153.6	< 0.001[b]
Min–Max	2.03–1323	1.46–1609	1.35–1865	1.60–2716	14.26–1455	
PCB 118						
Mean ± SD	23.89 ± 18.75	22.32 ± 21.81	29.04 ± 34.56	35.79 ± 32.44	42.94 ± 35.30	< 0.001[a]
Median	23.00	16.33	21.46	28.48	33.85	< 0.001[b]
Min–Max	1.23–108.5	0.70–161.9	0.84–465.0	0.73–195.6	1.01–176.0	
PCB 138						
Mean ± SD	79.77 ± 52.93	81.05 ± 96.21	94.88 ± 116.2	111.8 ± 107.8	150.9 ± 176.9	0.002[a]
Median	71.58	59.58	74.15	84.78	110.6	< 0.001[b]
Min–Max	1.38–288.6	0.95–885.9	1.01–1830	0.71–935.0	19.13–1045	
PCB 153						
Mean ± SD	115.3 ± 77.70	112.7 ± 130.2	126.4 ± 101.5	161.4 ± 165.3	237.5 ± 326.4	< 0.001[a]
Median	103.3	87.35	104.0	117.0	143.5	< 0.001[b]
Min–Max	5.62–445.7	0.97–1417	1.09–847.3	0.72–1377	29.95–1912	
PCB 180						
Mean ± SD	97.42 ± 69.41	97.88 ± 130.7	102.5 ± 82.74	128.0 ± 124.7	191.8 ± 337.8	< 0.001[a]
Median	83.83	72.84	83.80	94.73	107.5	0.001[b]
Min–Max	23.26–415.7	4.08–1483	2.56–738.7	11.06–909.2	18.21–2047	

[a] ANOVA test (two tail).
[b] Kruskal–Wallis test (two-tail).

with concentrations of HCB in the upper quartile had on average 3 chronic conditions more than subjects in the lowest quartile (*p*-value <0.001), and individuals who had concentrations of ≥ 3 POPs in the upper quartile had over 2 CC more than individuals without any compound at such concentrations. When models were adjusted for sex and age (model A), or further adjusted for BMI (model B), the associations only remained statistically significant for HCB and PCB 118.

We also assessed the influence of POP concentrations on selected CC (Supplementary material, Table 2). When we considered diabetes, high cholesterol, hypertension and thyroid problems, the likelihood of having one or more of these CC was between 1.8 and 6.2-times higher in participants with POP concentrations in the top quartile than in participants with POP concentrations in the lowest quartile, in models adjusted for BMI. The ORs were somewhat attenuated when arthritis, rheumatoid arthritis, chronic allergies, asthma and malignant tumors were also considered. The ORs for the associations between POP concentrations and having ≥ 1 of the ten CC most related to POP concentrations in the study participants ranged between 2.4 for p,p′-DDT and 7.8 for HCB (*p*-values <0.001) (Supplementary material, Table 2, model C).

The null adjusted estimates previously found for poor SRH by quartiles of POP concentrations (Table 3, model C) were not materially altered when models were further adjusted for the number of CC (Table 3, model D). The significant and positive crude estimates previously found for poor SRH by quartiles of POP concentrations (Table 3, crude model) became null when adjusted for number of CC.

Participants at risk of suffering mental disorders (GHQ-12 ≥ 4) were more likely to have poor SRH (multivariate-adjusted OR = 2.3, 95% CI 1.4–3.7). Serum POP concentrations were not associated with mental disorders, neither in crude models nor in age-adjusted models (data not shown). Models stratified by sex or age also showed no association. POP concentrations were also not associated with the prevalence of self-reported depression or anxiety disorder.

4. Discussion

Individuals with higher concentrations of POPs had significantly poorer SRH. In crude models and in models adjusted for sex and BMI, the POPs–SRH association was often dose-dependent, and the likelihood of poor or regular SRH was 2 to 4-times higher in subjects with POP concentrations in the top quartile. However, in models adjusted for age or for chronic conditions virtually all

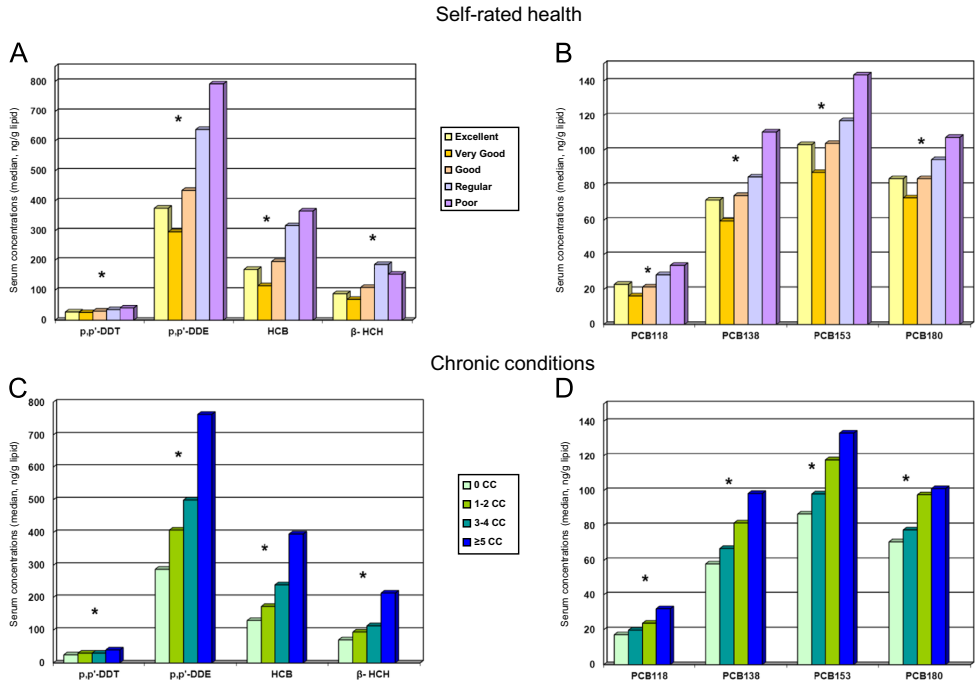

Fig. 2. Crude, unadjusted associations between serum concentrations of individual POPs and self-rated health (A and B), and number of chronic conditions (CC) (C and D). * p-value derived from Kruskal-Wallis' test. All $p < 0.01$.

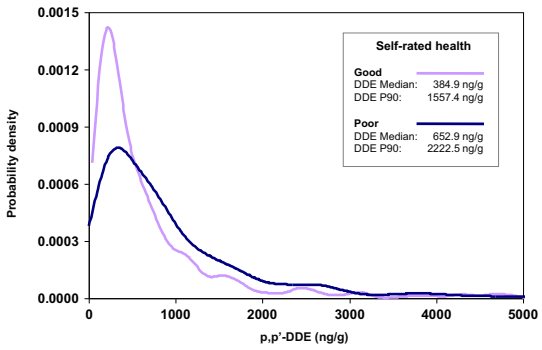

Fig. 3. Distribution of serum concentrations of p,p′-DDE by self-rated health. Footnote: Good: excellent, very good, or good self-rated health. Poor: regular or poor self-rated health.

ORs were near unity. No associations were found between POP levels and GHQ-12. Thus, the POPs–SRH association was most likely due to age and chronic conditions, but not to sex, education, social class, BMI, or mental disorders (Fig. 1).

Although in older ages the expectations of what is considered "good health" decrease, and at any given level of SRH more health problems are tolerated than in younger ages (Idler, 1993; Orfila et al., 2000), in many studies, including ours, SRH worsens with increasing age. In our study the inverse association between age and SRH remained significant even once chronic conditions (CC) were included in the model. Concentrations of many POPs often increase with age, which reflects years of exposure, birth cohort effects, and perhaps changes in metabolic functions related to ageing (such as a putative lower capacity to excrete xenobiotics) (Porta et al., 2008, 2010, 2012). Clearly, relative to younger individuals older citizens had more years to accumulate POPs and lived in periods when use of some POPs (e.g., DDT, HCB, PCBs) was more extensive. In the study population age was also strongly associated with POP concentrations (Porta et al., 2010), and it explained to some extent the effect of POPs on SRH (Table 3, and Supplementary Material, Table 1).

Individuals with higher concentrations of all 8 most prevalent POPs had a significantly higher number of CC (Table 4); and the significant and positive crude estimates for poor SRH by quartiles of POP concentrations became null when adjusted for number of CC. Estimates for the separate and joint effects of age and CC on SRH (Supplementary Material, Table 1) further suggest that the POPs–SRH association could largely operate through CC (Fig. 1).

Are POPs causally related to SRH through CC? The answer largely depends on whether we consider that the available evidence supports the causal nature of the POPs–CC associations, since the CC–SRH associations can be deemed causal (Alonso et al., 2013; Wilson and Cleary, 1995). Many such pollutants are known to alter significantly a range of physiological functions, and known or reasonably suspected to contribute to cause severe clinical effects, as well as a substantial burden of disease. Indeed, some highly prevalent POP mixtures have immunosuppressive, oxidative, proinflammatory, neuroendocrine, metabolic, non-genotoxic or epigenetic effects (Faroon and Ruiz, 2015; Henkler and Luch, 2011; Lee et al., 2014; Litwack, 2014; National Research Council, 2006; Porta, 2012; Stein, 2012; Prüss-Ustün et al., 2011; World Health Organization, 2013).

Nevertheless, in this cross-sectional study the objective was not etiologic (Porta, 2014), but to quantify the magnitude of the association between POP concentrations and SRH. Such analysis is of interest both adjusted for other variables (as CC) and unadjusted;

Table 3
Associations between serum concentrations of POPs and self-rated health status*.

Compound (ng/g lipid)	Crude model			Adjusted model A[a]			Adjusted model B[b]			Adjusted model C[c]			Adjusted model D[d]		
	OR	(CI 95%)	P[1]	OR	(CI 95%)	P[1]	OR	(CI 95%)	P[1]	OR	(CI 95%)	P[1]	OR	(CI 95%)	P[1]
p,p′-DDT															
≤ 13.68	1.0		0.017[2]	1.0		0.423	1.0		0.674	1.0		0.605	1.0		0.909
13.69–30.02	1.0	(0.6 – 1.5)		0.9	(0.6–1.4)		0.8	(0.5–1.3)		0.8	(0.5–1.2)		0.8	(0.5–1.4)	
30.03–57.72	1.1	(0.7–1.8)		1.0	(0.7–1.6)		0.8	(0.5–1.2)		0.7	(0.5–1.2)		0.9	(0.5–1.5)	
> 57.72	1.6	(1.1–2.4)		1.3	(0.8–2.0)		0.9	(0.6–1.4)		0.8	(0.5–1.3)		0.9	(0.5-1.5)	
p,p′-DDE															
≤ 222.6	1.0		< 0.001[2]	1.0		< 0.001[2]	1.0		0.941	1.0		0.855	1.0		0.742
222.7–433.7	1.3	(0.8–2.1)		1.2	(0.8–2.0)		1.0	(0.6–1.6)		1.0	(0.6–1.6)		0.9	(0.5–1.6)	
433.8-910.9	2.0	(1.3–3.1)		1.8	(1.1–2.8)		1.1	(0.7–1.7)		1.0	(0.6–1.7)		0.9	(0.5–1.5)	
> 910.9	2.6	(1.7–4.0)		2.1	(1.3–3.3)		0.9	(0.6–1.6)		0.9	(0.5–1.4)		0.7	(0.4–1.3)	
HCB															
≤ 86.39	1.0		< 0.001[2]	1.0		< 0.001[2]	1.0		0.427[2]	1.0		0.958	1.0		0.498
86.40–200.9	1.8	(1.1–2.9)		1.7	(1.0–2.7)		1.2	(0.7–2.0)		1.1	(0.7–1.9)		1.2	(0.7–2.1)	
201.0–415.1	2.4	(1.5–3.8)		2.1	(1.3–3.4)		1.2	(0.7–2.1)		1.1	(0.6–1.8)		1.1	(0.6–1.9)	
> 415.1	4.2	(2.6–6.6)		3.3	(2.0–5.4)		1.3	(0.7–2.4)		1.0	(0.5–1.9)		0.8	(0.4–1.6)	
β-HCH															
≤ 52.20	1.0		< 0.001[2]	1.0		< 0.001[2]	1.0		0.833	1.0		0.189[2]	1.0		0.132[2]
52.21–110.7	1.2	(0.8–2.0)		1.2	(0.7–1.9)		0.9	(0.5–1.4)		0.9	(0.5–1.4)		0.8	(0.4–1.3)	
110.8–251.4	2.2	(1.4–3.4)		1.9	(1.2–3.0)		1.0	(0.6–1.6)		0.9	(0.5–1.5)		0.8	(0.4–1.4)	
> 251.4	3.1	(2.0–4.7)		2.4	(1.5–3.8)		0.8	(0.5–1.4)		0.7	(0.4–1.2)		0.6	(0.3–1.1)	
PCB 118															
≤ 10.43	1.0		< 0.001[2]	1.0		< 0.001[2]	1.0		0.419[2]	1.0		0.836	1.0		0.930
10.44–22.99	1.2	(0.8–1.9)		1.1	(0.7–1.8)		1.0	(0.6–1.6)		1.0	(0.6–1.6)		0.9	(0.5–1.5)	
23.00–38.24	1.6	(1.1–2.6)		1.5	(0.9–2.3)		1.0	(0.6–1.6)		0.9	(0.6–1.5)		0.9	(0.5–1.5)	
> 38.24	2.7	(1.8–4.2)		2.2	(1.4–3.5)		1.2	(0.8–2.0)		1.1	(0.7–1.9)		0.8	(0.5–1.5)	
PCB 138															
≤ 43.98	1.0		< 0.001	1.0		0.002	1.0		0.287	1.0		0.253	1.0		0.050
43.99–74.09	1.7	(1.1–2.6)		1.6	(1.0–2.5)		1.1	(0.7–1.7)		1.1	(0.7–1.8)		1.2	(0.7–2.0)	
74.10–118.5	1.4	(0.9–2.3)		1.3	(0.8–2.0)		0.7	(0.4–1.2)		0.7	(0.4–1.2)		0.6	(0.3–1.0)	
> 118.5	2.5	(1.6–3.9)		2.2	(1.4–3.5)		0.9	(0.6–1.5)		0.9	(0.6–1.6)		0.7	(0.4–1.3)	
PCB 153															
≤ 64.97	1.0		< 0.001	1.0		0.001	1.0		0.172	1.0		0.179	1.0		0.052
64.98–104.1	1.7	(1.1–2.7)		1.7	(1.1–2.6)		1.1	(0.7–1.7)		1.1	(0.7–1.8)		1.2	(0.7–2.0)	
104.2–162.3	1.4	(0.9–2.2)		1.3	(0.8–2.0)		0.7	(0.4–1.1)		0.7	(0.4–1.1)		0.6	(0.3–1.1)	
> 162.3	2.5	(1.6–3.9)		2.3	(1.5–3.6)		0.9	(0.5–1.5)		0.9	(0.5–1.6)		0.8	(0.4–1.4)	
PCB 180															
≤ 54.96	1.0		0.001[2]	1.0		0.001[2]	1.0		0.760	1.0		0.909	1.0		0.520
54.97–85.34	1.3	(08–2.1)		1.2	(0.8–2.0)		0.8	(0.5–1.3)		0.9	(0.5–1.4)		0.8	(0.5–1.4)	
85.35–126.6	1.5	(1.0–2.4)		1.5	(1.0–2.4)		0.8	(0.5–1.3)		0.8	(0.5–1.4)		0.7	(0.4–1.2)	
> 126.6	2.0	(1.3–3.1)		2.0	(1.3–3.0)		0.8	(0.5–1.3)		0.9	(0.5–1.5)		0.7	(0.4–1.3)	
Number of POPs at high concentrations (≥ P75)															
0	1.0		< 0.001[2]	1.0		< 0.001[2]	1.0		0.830	1.0		0.932	1.0		0.948
1–2	1.6	(1.1–2.5)		1.5	(1.0–2.3)		1.1	(0.7–1.7)		1.1	(0.7–1.7)		0.9	(0.6–1.5)	
≥ 3	2.8	(2.0–4.0)		2.4	(1.7–3.4)		1.1	(0.7–1.8)		1.1	(0.7–1.7)		1.0	(0.6–1.6)	

OR: odds ratio of having regular or poor self-rated health (vs. excellent, very good, or good) by POP quartiles.

* Excellent, very good, and good vs. regular, and poor.
[1] Unless otherwise specified, *p* value derived from Wald test.
[2] Multivariate analog of Mantel's extension test for linear trend.
[a] Adjusted for BMI.
[b] Adjusted for sex and age.
[c] Adjusted for sex, age, and BMI.
[d] Adjusted for sex, age, BMI, and number of CC.

the unadjusted estimates describe the association as it exists in individuals living under real conditions. Hence, while the POPs–SRH association may or may not be partly causal, it is real; from a pragmatic perspective (Porta, 2014) it is relevant to note the fact that people with poorer SRH will often have higher levels of POPs.

Some POPs have adverse neurologic and mental effects (Faroon and Ruiz, 2015; Kim et al., 2015a, b; Lee et al., 2007; Singh et al., 2013; Richardson et al., 2009). Thus, mental disorders might also have a function in the pathway between POPs and SRH. However, in the present study we did not observe an association between POP concentrations and psychological distress / mental disorders, measured with the GHQ-12. We also did not observe an

Table 4
Influence of serum concentrations of POPs on the number of chronic conditions.

Compound	Crude model			Adjusted model A[a]			Adjusted model B[b]		
(ng/g lipid)	β	P^1	P^2	β	P^1	P^2	β	P^1	P^2
p,p′-DDT									
≤ 13.68	Ref.		< 0.001	Ref.		0.472	Ref.		0.432
13.69–30.02	0.13	0.638		−0.17	0.497		−0.20	0.419	
30.03–57.72	0.31	0.264		−0.38	0.136		−0.42	0.100	
> 57.72	1.00	< 0.001		−0.09	0.746		−0.19	0.479	
p,p′-DDE									
≤ 222.6	Ref.		< 0.001	Ref.		0.397	Ref.		0.464
222.7–433.7	0.51	0.060		−0.07	0.776		−0.10	0.699	
433.8–910.9	1.54	< 0.001		0.35	0.197		0.30	0.265	
> 910.9	2.14	< 0.001		0.19	0.532		0.09	0.766	
HCB									
≤ 86.39	Ref.		< 0.001	Ref.		0.011	Ref.		0.050
86.40–200.9	0.58	0.028		−0.18	0.492		−0.24	0.364	
201.0–415.1	1.20	< 0.001		−0.08	0.784		−0.20	0.489	
> 415.1	2.98	< 0.001		0.71	0.040		0.48	0.199	
β-HCH									
≤ 52.20	Ref.		< 0.001	Ref.		0.924	Ref.		0.997
52.21–110.7	0.68	0.011		0.07	0.773		0.04	0.879	
110.8–251.4	1.54	< 0.001		0.09	0.748		−0.01	0.963	
> 251.4	2.63	< 0.001		0.23	0.500		0.03	0.940	
PCB 118									
≤ 10.43	Ref.		< 0.001	Ref.		0.016	Ref.		0.032
10.44–22.99	0.48	0.077		0.12	0.624		0.10	0.688	
23.00–38.24	1.10	< 0.001		0.12	0.650		0.09	0.745	
> 38.24	2.27	< 0.001		0.80	0.005		0.72	0.010	
PCB 138									
≤ 43.98	Ref.		< 0.001	Ref.		0.271	Ref.		0.229
43.99–74.09	0.70	0.011		−0.09	0.729		−0.07	0.775	
74.10–118.5	1.30	< 0.001		0.14	0.618		0.14	0.605	
> 118.5	2.15	< 0.001		0.43	0.148		0.47	0.116	
PCB 153									
≤ 64.97	Ref.		< 0.001	Ref.		0.305	Ref.		0.220
64.98–104.1	0.64	0.020		−0.21	0.430		−0.18	0.493	
104.2–162.3	1.17	< 0.001		−0.09	0.752		−0.04	0.873	
> 162.3	2.08	< 0.001		0.28	0.355		0.36	0.228	
PCB 180									
≤ 54.96	Ref.		< 0.001	Ref.		0.801	Ref.		0.525
54.97–85.34	0.76	0.006		−0.03	0.920		0.01	0.961	
85.35–126.65	1.36	< 0.001		0.19	0.478		0.30	0.273	
> 126.65	1.75	< 0.001		0.17	0.570		0.32	0.282	
Number of POPs at high concentrations (≥ P75)									
0	Ref.		< 0.001	Ref.		0.268	Ref.		0.334
1–2	1.06	< 0.001		0.35	0.138		0.34	0.155	
≥ 3	2.04	< 0.001		0.33	0.198		0.27	0.295	

β: change in number of chronic conditions.
[1] *p* value of each category of the variable when compared with the reference category.
[2] *p*-value for the variable in the model.
[a] Adjusted for sex and age.
[b] Adjusted for sex, age, and BMI.

association between POPs and self-reported depression or anxiety disorders, in accordance with results in NHANES (Berk et al., 2014).

Studies that assessed the effects of environmental exposures on SRH or mental health (e.g., Carrasco et al., 2007; Nakata et al., 2009; Ushijima et al., 2004) seldom used biomarkers of human exposure or were conducted in a representative sample of the general population; specifically, no studies have analyzed the relation between body concentrations of POPs and GHQ, and only one analyzed POP concentrations and SRH: in agreement with our results, Van Larebeke et al. (2015) found no association—when different confounders were considered—between body levels of PCBs, HCB or p,p′-DDE and SRH in subjects aged 50–65 years from Flanders, Belgium. No association was observed between HCB and CC in a specific population highly-exposed to this POP in Catalonia (Sala et al., 1999); the association between HCB serum levels and SRH was not reported. In the field of health-related quality of life, no studies on factors affecting SRH used biomarkers of human contamination by POPs.

The CHIS survey used as the basis of our study has several limitations: it is cross-sectional, it excluded institutionalized

individuals (in whom findings might differ), and we studied a small number of chemicals. However, the study includes a large sample of the general population aged 18–74 years, and methods were state-of-the-art (Brugulat et al., 2003; Porta et al., 2010, 2012).

Beyond uses of SRH as a measure of people's perception of health (Huisman and Deeg, 2010), SRH is also used as a proxy for objective health based on its established association with morbidity and mortality (Alonso, 2000; Baron-Epel, 2004; Bjorner et al., 2005; Brunström and Fredlund, 2001; DeSalvo et al., 2006; Diehr et al., 2001, 2002; Eriksson et al., 2001; Idler and Benyamini, 1997; Idler et al., 2000). SRH is also extensively applied in the analysis of need for and access to health care services (Valderas and Alonso, 2008; Wilson and Cleary, 1995).

In conclusion, in this sample of the general population of Catalonia we found that individuals with higher concentrations of POPs had significantly poorer SRH. The association was most likely due to age and chronic conditions, but not to sex, education, social class, BMI, or mental disorders.

Conflict of interest

The authors declare they have no competing financial interests.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2015.10.005.

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SUPPLEMENTARY MATERIAL

Table 1. Associations between sociodemographic characteristics of the study population and self-rated health status*.

	Four different crude models[a]					Three age-adjusted models[b]					Fully adjusted model[c]				
	OR	(CI 95%)	P[1]	P[2]	R^2	OR	(CI 95%)	P[1]	P[2]	R^2	OR	(CI 95%)	P[1]	P[2]	R^2
Age															
18-29	1.0			<0.001	0.120						1.0			0.027	0.362
30-44	2.4	(1.3-4.4)	0.005								1.5	(0.7-2.9)	0.272		
45-59	5.1	(2.8-9.1)	<0.001								2.3	(1.2-4.5)	0.014		
60-74	8.6	(4.7-15.7)	<0.001								2.4	(1.2-4.9)	0.016		
Sex (women vs. men)	1.4	(1.0-1.9)	0.032		0.007	1.6	(1.1-2.2)	0.005		0.128	0.9	(0.6-1.3)	0.530		
BMI															
Normal weight	1.0			<0.001	0.040	1.0			0.075	0.126	1.0			0.450	
Underweight	1.0	(0.2-4.9)	0.980			1.1	(0.2-5.6)	0.914			2.2	(0.4-13.3)	0.403		
Overweight	1.4	(1.0-2.0)	0.038			0.9	(0.6-1.4)	0.744			1.1	(0.7-1.6)	0.750		
Obese	2.7	(1.8-4.0)	<0.001			1.6	(1.0-2.4)	0.039			1.4	(0.9-2.3)	0.167		
Chronic conditions (No.)															
1-2	1.0			<0.001	0.342	1.0			<0.001	0.354	1.0			<0.001	
0	0.2	(0.1-0.5)	<0.001			0.2	(0.1-0.5)	<0.001			0.3	(0.1-0.6)	0.001		
3-4	2.2	(1.4-3.4)	0.001			1.9	(1.2-3.1)	0.006			2.0	(1.2-3.2)	0.004		
≥5	10.5	(6.9-16.2)	<0.001			8.7	(5.6-13.6)	<0.001			9.1	(5.7-14.3)	<0.001		

* Excellent, very good, and good vs. regular, and poor.

[1] p value of each category of the variable when compared with the reference category.

[2] p-value for the variable in the model.

[a] Each of the four models is completely unadjusted. [b] Each of the three models is adjusted for age only. [c] Age, sex, BMI and chronic conditions are mutually adjusted for.

OR: odds ratio of having regular or poor self-rated health (vs. excellent, very good, or good) by sociodemographic characteristics of the study population.

Table 2. Associations between serum concentrations of persistent organic pollutants (POPs) and selected chronic conditions.

Compound (ng/g lipid)	Adjusted model A[a]			Adjusted model B[b]			Adjusted model C[c]		
	OR	(CI 95%)	P[1]	OR	(CI 95%)	P[1]	OR	(CI 95%)	P[1]
p,p'-DDT									
≤ 13.68	1.0		0.002	1.0		0.002	1.0		<0.001
13.69-30.02	1.3	(0.8-2.0)		1.2	(0.8-1.8)		1.1	(0.7-1.6)	
30.03-57.72	1.5	(1.0-2.4)		1.4	(1.0-2.0)		1.2	(0.8-1.8)	
> 57.72	1.9	(1.3-3.0)		1.8	(1.3-2.7)		2.4	(1.6-3.6)	
p,p'-DDE									
≤ 222.6	1.0		<0.001	1.0		<0.001	1.0		<0.001
222.7-433.7	1.8	(1.1-2.9)		1.3	(0.9-2.0)		1.6	(1.1-2.4)	
433.8-910.9	3.0	(1.8-4.7)		1.9	(1.3-2.8)		2.6	(1.8-3.9)	
> 910.9	4.0	(2.5-6.4)		3.3	(2.2-4.9)		4.6	(3.0-7.2)	
HCB									
≤ 86.39	1.0		<0.001	1.0		<0.001	1.0		<0.001
86.40-200.9	2.2	(1.3-3.6)		1.2	(0.8-1.8)		1.4	(1.0-2.0)	
201.0-415.1	2.8	(2.8-4.7)		1.6	(1.1-2.3)		2.5	(1.7-3.8)	
> 415.1	5.9	(5.9-9.9)		4.9	(3.1-7.5)		7.8	(4.7-12.9)	
β-HCH									
≤ 52.20	1.0		<0.001	1.0		<0.001	1.0		<0.001
52.21-110.7	2.0	(1.2-3.5)		1.5	(1.0-2.2)		1.6	(1.1-2.3)	
110.8-251.4	3.5	(2.1-5.8)		2.6	(1.8-3.9)		2.3	(1.6-3.4)	
> 251.4	6.2	(3.7-10.3)		4.8	(3.1-7.3)		6.3	(3.9-10.0)	
PCB 153									
≤ 64.97	1.0		<0.001	1.0		<0.001	1.0		<0.001
64.98-104.1	1.8	(1.1-2.9)		1.6	(1.1-2.3)		1.8	(1.2-2.6)	
104.2-162.3	2.9	(1.8-4.6)		2.3	(1.6-3.4)		2.2	(1.5-3.3)	
> 162.3	5.3	(3.3-8.5)		3.7	(2.5-5.6)		4.6	(3.0-7.0)	
Number of POPs at high concentrations (≥P75)									
0	1.0		<0.001	1.0		<0.001	1.0		<0.001
1-2	1.6	(1.1-2.5)		1.5	(1.1-2.2)		1.8	(1.3-2.6)	
≥3	3.7	(2.6-5.3)		3.1	(2.2-4.3)		4.3	(3.0-6.2)	

All models adjusted for BMI.

[1] Multivariate analog of Mantel's extension test for linear trend.

[a] CC considered: diabetes, high cholesterol, hypertension, thyroid problems.

[b] CC considered: diabetes, high cholesterol, hypertension, thyroid problems, arthritis or rheumatoid arthritis, chronic allergies, asthma, malignant tumors.

[c] CC considered: diabetes, hypertension, thyroid problems, arthritis or rheumatoid arthritis, varicose veins in legs, chronic cervical back pain, chronic lumbar or dorsal back pain, cataract, depression and/or anxiety disorders, osteoporosis.

OR: odds ratio of having ≥1 CC from the specified list by POP quartiles.

Article 2

Títol: Blood concentrations of persistent organic pollutants and unhealthy metabolic phenotypes in normal-weight, overweight and obese individuals.

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Original Contribution

Blood Concentrations of Persistent Organic Pollutants and Unhealthy Metabolic Phenotypes in Normal-Weight, Overweight, and Obese Individuals

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Factors underlying metabolic phenotypes, such as the metabolically healthy but obese phenotype, remain unclear. Differences in metabolic phenotypes—particularly, among individuals with a similar body mass index—could be related to concentrations of persistent organic pollutants (POPs). To our knowledge, no studies have analyzed POPs and metabolic phenotypes in normal-weight persons. We investigated the relationships between serum concentrations of POPs and metabolic phenotypes in 860 normal-weight, overweight, and obese participants in the 2002 Catalan Health Interview Survey (Spain). POP concentrations were significantly higher in metabolically unhealthy than in metabolically healthy individuals. In models adjusting for body mass index and other confounders, hexachlorobenzene, β-hexachlorocyclohexane, and polychlorinated biphenyls were associated with the unhealthy metabolic phenotype and metabolic syndrome. Among normal-weight individuals, the adjusted prevalence ratio of having an unhealthy phenotype for the upper category of the sum of orders of the 6 mentioned POPs (all individually associated with metabolic phenotypes) was 4.1 (95% confidence interval: 1.7, 10.0). Among overweight and obese individuals, the corresponding prevalence ratio for the sum of polychlorinated biphenyls was 1.4 (95% confidence interval: 1.0, 1.8). Our results supported the hypothesis that POP concentrations are associated with unhealthy metabolic phenotypes, not only in obese and overweight individuals but also (and probably more strongly) in normal-weight individuals.

environmental exposure/adverse effects; environmental pollutants/toxicity; health survey; human biomonitoring; metabolic phenotype; metabolic syndrome; metabolically healthy obese; persistent organic pollutants

Abbreviations: ATPIII, National Cholesterol Education Program—Third Adult Treatment Panel; BMI, body mass index; CI, confidence interval; DDE, dichlorodiphenyldichloroethene; DDT, dichlorodiphenyltrichloroethane; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; HDL, high-density lipoprotein; IDF, International Diabetes Federation; MetS, metabolic syndrome; MONO, metabolically obese nonobese; PCB, polychlorinated biphenyl; POP, persistent organic pollutant.

Recent studies have revealed factors that appear to protect obese individuals from cardiometabolic disturbances (1, 2). Such studies used body size–metabolic phenotypes to classify individuals according to body mass index (BMI) and the presence or absence of cardiometabolic complications including hypertension, dyslipidemia, or insulin resistance. One such phenotype, "metabolically healthy obese," consists of individuals who remain free of metabolic abnormalities despite being obese. Another metabolic phenotype comprises normal-weight but metabolically unhealthy individuals (i.e., individuals who present cardiometabolic abnormalities despite having a normal BMI), also called "metabolically obese nonobese" (MONO) (3). Some studies found factors such as visceral fat accumulation, adipose cell size, and behavioral characteristics (such as physical activity and alcohol intake) to be related to metabolic phenotypes (1, 4–6). However, it remains unclear what underlying factors and mechanisms explain the normal metabolic profile of metabolically healthy, obese individuals (1, 2).

Similar to metabolically healthy obesity, the understanding of the MONO individual is important because an abnormal metabolic profile, rather than adiposity itself, is associated with a higher risk for cardiovascular diseases (7). While regional fat distribution and body composition could partly

explain differences in the metabolic profile among nonobese individuals (8), some environmental contaminants, such as persistent organic pollutants (POPs), might also play a role, as they probably do in obese individuals (9, 10).

POPs are synthetic chemicals highly lipophilic and resistant to degradation; virtually all humans accumulate POP mixtures throughout the life course, with wide interindividual differences in concentrations (10–12). Most POPs are endocrine disruptors (13), and several prospective studies have reported positive relationships between POP concentrations and type 2 diabetes, insulin resistance, hypertension, and other cardiometabolic disorders (9, 10, 12, 14–17). Additionally, other studies have reported positive associations between POPs and metabolic syndrome (MetS) (18–21). Therefore, differences among metabolic phenotypes—which take into account not only the components of MetS but also such other factors as insulin resistance and biomarkers of inflammation—could be related to differences in POP concentrations.

To our knowledge, only 2 previous studies have analyzed the association between POPs and metabolic phenotypes. One study was performed in 76 nondiabetic, obese postmenopausal women (22), and the other selected 184 overweight and obese patients visiting a weight-management clinic (23). It appears that no studies have analyzed POPs and unhealthy metabolic phenotypes in normal-weight persons. We analyzed, for the first time, the relationship between body POP concentrations and metabolic phenotypes in a sample of the general population (n = 860). Our sample included: 1) men and women; 2) a wide range of ages (18–74 years); 3) normal-weight, overweight, and obese individuals; and 4) diabetic and nondiabetic individuals. Of potential importance, Catalonia (in Spain) is a Mediterranean region with dietary patterns generally protective against several cardiometabolic risk factors (24).

The aim of the present study was to analyze the relationship between POP serum concentrations and metabolic phenotypes in normal-weight, overweight, and obese individuals in the general adult population of Catalonia, Spain. Additionally, we analyzed the relationship between POPs and MetS.

METHODS

Study population

The study population has been described in detail elsewhere (25, 26). Briefly, participants in the Catalan Health Interview Survey, aged 18–74 years, were offered the option to take part in a health examination that included a physical examination, a supplementary interview, and the collection of urine and blood samples. A total of 1,374 individuals, who gave specific written informed consent, participated during 2002 in the health examination (27).

Trained nurses recorded the weight and height; the corresponding BMI was computed (measured weight (kg) divided by measured height squared (m^2)) and grouped into 4 categories: underweight (<18.50), normal weight (18.50–24.99), overweight (25.00–29.99), and obese (≥30.00). Waist circumference was measured at the level of the umbilicus. Systolic and diastolic blood pressures were measured twice, and the average was used in the statistical analyses. Blood samples were drawn after 12 hours of fasting (27). A capillary blood sample was also obtained during the health examination and used to determine glucose concentration in whole blood (26). Information on blood concentrations of lipids and at least 1 mL of serum (for POP analyses) was available for 919 participants.

Ten underweight participants were excluded from the statistical analyses. In the present report, analyses of metabolic phenotypes were based on 860 participants with data available on POP serum concentrations and on metabolic phenotype. There were no statistically significant differences between the 860 individuals and the remaining participants in the health examination with respect to age, sex, BMI, educational level, or occupational social class. Analyses of MetS were based on 858 and 881 participants with information on MetS status according to the definitions of the International Diabetes Federation (IDF) (28) and the National Cholesterol Education Program–Third Adult Treatment Panel (ATPIII) (29), respectively.

Body size–metabolic phenotypes

Body size–metabolic phenotypes were defined using criteria previously described by Wildman et al. (6). Individuals were classified as having an unhealthy metabolic phenotype if they had 2 or more of the following cardiometabolic abnormalities: hypertension (systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg, or current use of antihypertensive medication); hypertriglyceridemia (fasting triglyceride level ≥150 mg/dL; no information on triglyceride-lowering medication was available); low high-density lipoprotein (HDL) cholesterol (<40 mg/dL in men, <50 mg/dL in women, or current use of cholesterol-lowering medication); hyperglycemia (fasting glucose level ≥100 mg/dL, current use of insulin or oral antidiabetic medication, or previous diagnosis of diabetes); insulin resistance (homeostatic model assessment of insulin resistance of >4.66, the 90th percentile); and systemic inflammation (high-sensitivity C-reactive protein level of >7.35 mg/L, the 90th percentile). Distributions are shown in Table 1.

Metabolic syndrome

MetS status was assigned to participants following the IDF and ATPIII definitions. According to IDF (28), participants were considered to have MetS if they had abdominal obesity (waist circumference of ≥94 cm for men or ≥80 cm for women) and also 2 or more of the following cardiometabolic abnormalities (as previously defined): hypertriglyceridemia, low HDL cholesterol, hypertension, or hyperglycemia. According to the ATPIII definition (29), participants were considered to have MetS if they had 3 or more of these 5 components: abdominal obesity (waist circumference of ≥102 cm for men or ≥88 cm for women), hypertriglyceridemia, low HDL cholesterol, hypertension, or hyperglycemia (fasting glucose level of ≥100 mg/dL or current use of insulin or oral antidiabetic medication).

Analytical chemical methods

Serum POP concentration assays. A detailed account of laboratory methods has previously been published (25) (details are also provided in Web Appendix 1 (available at

Table 1. Metabolic Phenotype and Its Component Cardiometabolic Abnormalities in Participants According to Body Mass Index[a], Catalan Health Interview Survey, Spain, 2002

Component	No. of Participants	%	Normal Weight		Overweight		Obese		*P* Value[b]
			No.	%	No.	%	No.	%	
Study population	860	100	364	42.3	325	37.8	171	19.9	
Metabolic phenotype									<0.001
Healthy (≤1 abnormalities)	483	56.2	293	80.5	151	46.5	39	22.8	
Unhealthy (≥2 abnormalities)	377	43.8	71	19.5	174	53.5	132	77.2	
Hypertension[c]	393	45.8	89	24.5	176	54.2	128	75.3	<0.001
Hypertriglyceridemia[d]	115	13.5	13	3.6	58	18.0	44	26.2	<0.001
Low HDL cholesterol[e]	300	34.9	89	24.5	128	39.4	83	48.5	<0.001
Hyperglycemia[f]	315	37.2	69	19.1	138	43.4	108	64.7	<0.001
HOMA-IR[g]	81	10.2	6	1.7	29	9.6	46	31.5	<0.001
hsCRP[h]	82	10.0	24	6.8	24	7.8	34	21.7	<0.001

Abbreviations: HOMA-IR, homeostatic model assessment of insulin resistance; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein.

[a] Body mass index was computed from measurements as weight (kg) divided by height squared (m^2) and grouped into 4 categories: underweight (<18.50), normal weight (18.50–24.99), overweight (25.00–29.99), and obese (≥30.00).

[b] Fisher's exact test.

[c] Defined as ≥130/85 mm Hg or medication use.

[d] Defined as ≥150 mg/dL; 14 nonfasting subjects with triglyceride levels ≥150 mg/dL were excluded.

[e] Defined as <40 mg/dL in men, <50 mg/dL in women, or medication use.

[f] Defined as ≥100 mg/dL or medication use; we excluded 7 subjects missing blood-glucose concentrations, 6 subjects with blood-glucose concentration ≤60 mg/dL, 16 nonfasting subjects with blood-glucose concentration ≥100 mg/dL and no medication use, and 4 pregnant women.

[g] Defined as above the 90th percentile (4.66); we excluded 43 subjects reporting a current use of insulin or oral antidiabetic medication, 32 nonfasting subjects, 7 subjects missing blood glucose concentrations, 5 subjects with blood glucose concentration ≤60 mg/dL, and 4 pregnant women.

[h] Defined as above the 90th percentile (7.35 mg/L).

https://academic.oup.com/aje)). Serum concentrations of 19 POPs were analyzed by gas chromatography with electron-capture detection. Main statistical analyses were limited to the 8 compounds that were above the detection limit in >85% of participants: p,p′-dichlorodiphenyltrichloroethane (DDT); p,p′-dichlorodiphenyldichloroethene (DDE); polychlorinated biphenyl (PCB) congeners 118, 138, 153, and 180; hexachlorobenzene (HCB); and β-hexachlorocyclohexane (HCH) (25). Lipid correction (division of individual crude serum POP concentrations by total lipids) is not appropriate when studying metabolic phenotypes (10, 30, 31), and thus in the present study POP concentrations are expressed in nanograms per milliliter (ng/mL).

Clinical bioassays. Cholesterol and triglycerides were determined enzymatically (Roche Diagnostics, Basel, Switzerland) in serum obtained in the health examination (25, 27). Serum concentrations of high-sensitivity C-reactive protein were measured with a high-sensitivity turbidimetric assay (Quantex CRP Ultra Sensitive; Biokit SA, Barcelona, Spain) (32). Fasting insulin was determined by radioimmunoassay, using commercial kits (Amersham, Little Chalfont, United Kingdom), and the homeostasis model assessment was used to calculate insulin resistance applying the following formula: (fasting insulin (mU/L) × fasting glucose (mg/dL) × 0.0555)/22.5 (33).

Statistical analyses

Univariate statistics were computed as customary (34). Fisher's exact test for homogeneity was applied to assess the relationship between 2 categorical variables. To assess differences on age, BMI, and POP concentrations according to metabolic phenotype and MetS status, Student's *t* test and the Mann-Whitney *U* test were used.

To estimate the magnitude of the associations between POPs and an unhealthy metabolic phenotype (≥2 cardiometabolic abnormalities), prevalence ratios and their 95% confidence intervals were computed by Poisson regression models with robust variance (35). Statistically significant interactions were found between BMI and POP concentrations (*P* for interaction ≤0.005 for all); thus, analyses were stratified by BMI (dichotomized as normal-weight and overweight/obese). Prevalence ratios were also estimated from logistic models as the ratio of the predicted probabilities for each outcome comparing the 3 highest quartiles with the lowest one, and 95% confidence intervals were generated by the bootstrap percentile method using 1,000 resamples (36). Prevalence ratios were also computed by Poisson regression to estimate the magnitude of the associations between POPs and MetS.

POP concentrations were entered in the models as quartile categories. To assess exposure to multiple compounds, we

computed the sum of PCBs, the sum of orders of the 8 most prevalent POPs mentioned, and the sum of orders of the 6 POPs individually associated with metabolic phenotypes (11, 26) (see Web Appendix).

In models with adjustments, the following potential confounders were included: age, sex, BMI, cigarette smoking, alcohol consumption, physical activity, occupational social class, and educational level. We assessed linear dose-response relationships through the multivariate analogue of Mantel's extension test for linear trend; when a linear trend was not apparent, the probability test was used.

General linear regression models were used to assess the relationship between number of cardiometabolic abnormalities (as a continuous variable, instead of the binary outcome "healthy / unhealthy metabolic phenotype," Table 1) and concentrations of POPs. Results are expressed as adjusted geometric means with their corresponding 95% confidence intervals (34).

The level of statistical significance was set at 0.05 and all tests were 2-tailed. Analyses were conducted using SPSS, version 22.0.0 (SPSS Inc., Chicago, Illinois), and R, version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The prevalence of the metabolically healthy phenotype in the study population was 56.2% (Table 1). Of the 860 participants, 39 (4.5%) were obese yet metabolically healthy, 151 (17.6%) were overweight yet metabolically healthy, and 71 (8.3%) had normal weight but were metabolically unhealthy (≥2 cardiometabolic abnormalities; i.e., MONO). The percentages of individuals with a healthy metabolic phenotype among overweight and obese participants were 46.5 and 22.8, respectively, whereas 19.5% of the normal-weight participants were metabolically unhealthy (Table 1).

Among both normal-weight participants and overweight/obese participants, individuals with an unhealthy metabolic phenotype were older and had a higher BMI and higher waist circumference than individuals with a healthy metabolic phenotype (Table 2). Concentrations of all POPs were significantly higher in metabolically unhealthy individuals than in metabolically healthy subjects (Figure 1 and Web Table 1). For example, among normal-weight individuals, the median concentration of HCB and PCB 118 was 2 times higher in metabolically unhealthy individuals than in metabolically healthy subjects. The corresponding values among overweight and obese individuals were 1.8 and 1.7 for HCB and PCB 118, respectively ($P < 0.001$). The differences in POP concentrations between metabolically healthy and unhealthy individuals (Figure 1) show patterns strikingly similar among normal-weight and overweight/obese participants.

Among normal-weight individuals, multivariate analyses showed that concentrations of all 4 PCBs were positively associated with having an unhealthy (vs. healthy) metabolic phenotype—the so-called MONO—after adjusting for age, sex, BMI, cigarette smoking, alcohol consumption, and physical activity, in a nonlinear dose-response manner. Prevalence ratios for the upper quartile of PCBs ranged between 1.1 and 1.9, whereas prevalence ratios for the third quartile ranged between 2.5 and 3.2 (P values <0.01) (Table 3, model 1). When the sum of PCBs was considered, normal-weight individuals in the third quartile had 3 times the risk of having an unhealthy metabolic phenotype compared with individuals in the lowest quartile of the sum of PCBs (95% confidence interval (CI): 1.4, 6.3) ($P \leq 0.001$). HCB and β-HCH were also significantly associated with having an unhealthy metabolic phenotype, in this case in a linear dose-response manner; prevalence ratios for the upper quartile of HCB and β-HCH were 2.0 (95% CI: 0.8, 4.9) and 2.4 (95% CI: 1.0, 5.9), respectively (P for linear trend < 0.1) (Table 3, model 1). Among normal-weight individuals, the unhealthy metabolic phenotype was also associated with mixtures of POPs: Individuals in the upper category of the sum of orders of the 6 mentioned POPs had 3.7 times the risk of having an unhealthy metabolic phenotype compared with subjects in the lowest category. The prevalence ratios for the second and third categories were 2.6 and 3.0, respectively (P trend = 0.003). Associations were also found between the sum of orders of all 8 POPs and the unhealthy phenotype (prevalence ratios for the second, third, and fourth categories = 2.4, 2.9, and 3.0, respectively; P trend = 0.008). When model 1 further adjusted for occupational social class (Table 3, model 2), all above-mentioned associations remained statistically significant and the magnitude of the prevalence ratios increased slightly (e.g., the prevalence ratio for the third quartile of PCB 180 became 3.6 (95% CI: 1.6, 7.9)). Adding adjustment for education to model 1 did not materially change the estimates.

Among overweight and obese individuals, models with adjustments showed that individuals with concentrations of PCBs in the upper quartile were more likely to have an unhealthy metabolic phenotype than individuals in the lower quartile. Prevalence ratios for individuals in the upper quartile of PCBs ranged between 1.2 and 1.4 (P for trend <0.005 for all) (Table 4, model 1). For HCB this prevalence ratio was also 1.4 (95% CI: 1.0, 1.9) ($P = 0.023$). The unhealthy metabolic phenotype was also associated with the sum of orders of the 6 mentioned POPs and with the sum of orders of all 8 POPs: The prevalence ratio of having an unhealthy phenotype for individuals in the each upper category was 1.2 (95% CI: 0.9, 1.7 and $P \leq 0.020$ for both) (Table 4, model 1). Further adjusting for occupational social class (Table 4, model 2) or for education did not materially change the estimates. No significant interactions were observed between POP concentrations and sex or age in overweight/obese individuals or in normal-weight subjects. As compared with previously shown prevalence ratios (computed by Poisson regression), prevalence ratios estimated from logistic models were slightly larger (Web Table 2).

The sum of concentrations of the 6 POPs tended to increase as the number of cardiometabolic abnormalities increased (P trend = 0.001) (Web Figure 1). The association was similarly observed among normal-weight and overweight/obese individuals.

The prevalence of MetS was 25.2% (216 of 858 participants) when using the IDF definition and 23.0% (203 of 881) when using the ATPIII definition (Web Table 3). Adjusted prevalence ratios of having MetS according to POP concentrations are shown in Figure 2 and Web Tables 4 and 5. Similar to what was observed for metabolic phenotypes, no associations with MetS were observed for DDT and DDE. By contrast, HCB was positively associated with MetS using either definition. The risk of having MetS was 2.7 (IDF definition) and 2.8 (ATPIII

Table 2. Characteristics of Study Participants According to Body Mass Index[a] and Metabolic Phenotype, Catalan Health Interview Survey, Spain, 2002

Characteristic	Total		Normal Weight					Overweight or Obese				
			Metabolically Healthy		Metabolically Unhealthy		*P* Value[b]	Metabolically Healthy		Metabolically Unhealthy		*P* Value[b]
	No.	%	No.	%	No.	%		No.	%	No.	%	
Study population	860	100	293	80.5	71	19.5		190	38.3	306	61.7	
Sex							0.024[c]					0.053[c]
Men	375	43.6	88	30.0	32	45.1		87	45.8	168	54.9	
Women	485	56.4	205	70.0	39	54.9		103	54.2	138	45.1	
Age, years[d]	45.3 (15.2)		35.7 (12.3)		49.4 (14.9)		<0.001	44.2 (12.9)		54.3 (13.2)		<0.001
Body mass index[a,d]	26.5 (4.6)		22.4 (1.7)		23.0 (1.6)		0.003	28.2 (3.1)		30.1 (4.0)		<0.001
Waist circumference, cm[d]	87.0 (12.8)		75.9 (7.9)		82.0 (9.1)		<0.001	90.0 (9.2)		96.7 (10.3)		<0.001
Occupational social class[e]							0.008[c]					0.161[c]
V (less affluent)	54	6.4	15	5.2	6	8.5		9	4.8	24	8.1	
IV	358	42.5	101	35.1	39	54.9		80	42.8	138	46.5	
III	238	28.2	79	27.4	15	21.1		54	28.9	90	30.3	
II	115	13.6	54	18.8	5	7.0		28	15.0	28	9.4	
I (most affluent)	78	9.3	39	13.5	6	8.5		16	8.6	17	5.7	
Educational level[e]							0.001[c]					<0.001[c]
Without formal education	136	15.9	15	5.2	12	16.9		29	15.3	80	26.6	
Primary schooling (1st stage)	219	25.7	50	17.2	21	29.6		48	25.3	100	33.2	
Primary schooling (2nd stage)	216	25.3	91	31.3	16	22.5		55	28.9	54	17.9	
Secondary schooling	179	21.0	85	29.2	16	22.5		32	16.8	46	15.3	
University	103	12.1	50	17.2	6	8.5		26	13.7	21	7.0	
Smoking status[e]							0.153[c]					0.635[c]
Never	421	49.6	135	46.7	30	42.9		92	49.2	164	54.1	
Other (past, occasionally)	56	6.6	18	6.2	2	2.9		13	7.0	23	7.6	
Past	117	13.8	24	8.3	12	17.1		32	17.1	49	16.2	
Current	255	30.0	112	38.8	26	37.1		50	26.7	67	22.1	
Alcohol drinking[e]							0.056[c]					0.472[c]
Nondrinker	391	45.7	120	41.2	39	55.7		89	47.1	143	46.7	
Regular drinker	421	49.2	154	52.9	26	37.1		89	47.1	152	49.7	
Heavy drinker	44	5.1	17	5.8	5	7.1		11	5.8	11	3.6	
Physical activity[e]							0.855[c]					0.293[c]
Very active	32	3.9	14	4.9	2	2.9		7	3.8	9	3.1	
Active	72	8.7	24	8.5	7	10.3		22	12.1	19	6.5	
Moderately active	411	49.8	142	50.2	37	54.4		87	47.8	145	49.5	
Moderately inactive	149	18.0	53	18.7	13	19.1		29	15.9	54	18.4	
Inactive	162	19.6	50	17.7	9	13.2		37	20.3	66	22.5	

[a] Body mass index was computed from measurements as weight (kg) divided by height squared (m^2) and grouped into 4 categories: underweight (<18.50), normal weight (18.50–24.99), overweight (25.00–29.99), and obese (≥30.00).
[b] Unless otherwise specified, *P* derived from Student's *t* test.
[c] Fisher's exact test.
[d] Values are expressed as the mean (standard deviation).
[e] There were 17, 7, 11, 4, and 34 participants with missing values for occupational social class, educational level, smoking status, alcohol drinking, and physical activity, respectively.

definition) times higher for individuals with HCB concentrations in the top quartile than for those in the lower quartile. β-HCH and all 4 PCBs were also associated with at least 1 definition of MetS (Figure 2 and Web Tables 4 and 5). Sensitivity analyses excluding participants with type 2 diabetes yielded similar results.

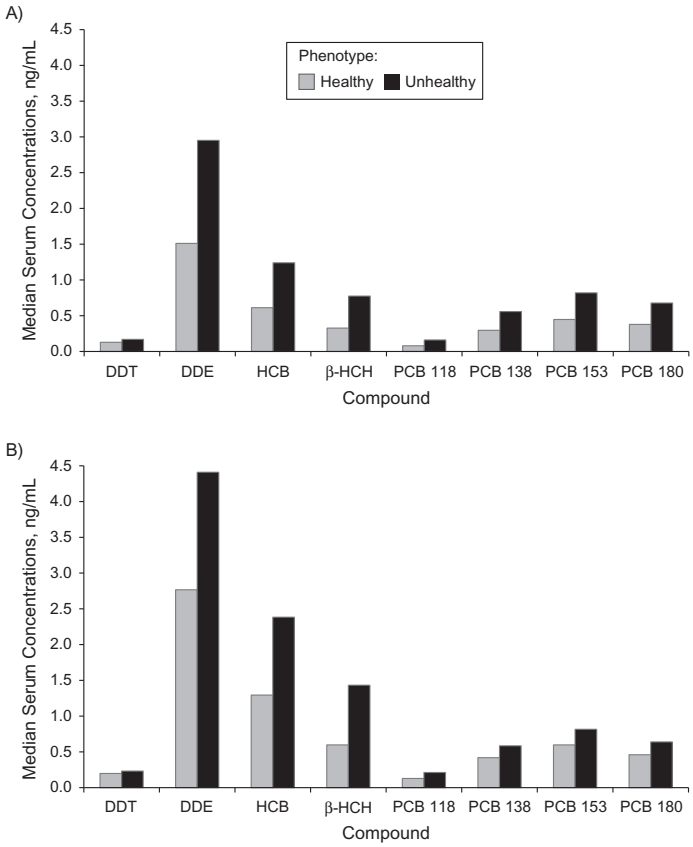

Figure 1. Serum concentrations of persistent organic pollutants according to metabolic phenotypes among normal-weight participants (A) and among overweight and obese participants (B), Catalan Health Interview Survey, Spain, 2002. Differences between pairs of medians were all statistically significant ($P < 0.001$ for all except for p,p′-DDT: $P = 0.013$ for normal-weight and 0.027 for overweight/obese participants; Mann-Whitney *U* test, 2-tail). DDE, dichlorodiphenyldichloroethene; DDT, dichlorodiphenyltrichloroethane; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; PCB, polychlorinated biphenyl.

DISCUSSION

Metabolically healthy individuals—obese, overweight, or normal weight—had significantly lower serum concentrations of POPs than individuals with 2 or more cardiometabolic abnormalities. In obese/overweight individuals and normal-weight individuals, lower concentrations of HCB, β-HCH, and PCBs were also generally associated with a healthy metabolic phenotype even when adjusting for age, sex, BMI, cigarette smoking, alcohol consumption, physical activity, occupational social class, and education. The magnitude of the associations was stronger in normal-weight individuals than in the obese/overweight. The sum of orders of the 6 POPs individually associated with metabolic phenotypes and the sum of orders of all 8 POPs showed linear dose-response relationships among normal-weight individuals and were also associated with the metabolic phenotype in obese/overweight individuals.

Similarly, a positive linear association was observed between the sum of POP concentrations and the number of cardiometabolic abnormalities. Thus, the observed POP–metabolic phenotype relationship appears to be independent of the cutoff number of abnormalities used to classify the unhealthy phenotype. Multiple criteria have been applied to define metabolic phenotypes (1, 2, 37); we used information on not just the components of MetS but also on homeostatic model assessment–measured insulin resistance and inflammation, which are some of the possible mechanisms of action or effects of POPs along with endocrine disruption (9, 13, 16). POPs might also increase the risk of obesity (38), the main risk factor for unhealthy metabolic phenotypes, and they have also been associated with an increased risk for some of the cardiometabolic abnormalities considered when defining the unhealthy phenotype, such as hyperglycemia or hypertension (9, 14, 17).

Table 3. Association of Serum Concentrations of Persistent Organic Pollutants With the Unhealthy Metabolic Phenotype (≥2 Cardiometabolic Abnormalities) Among Normal-Weight Participants, Catalan Health Interview Survey, Spain, 2002

Compound and Concentration, ng/mL	Crude Model (n = 364)			Model 1[a] (n = 349)			Model 2[b] (n = 344)		
	PR	95% CI	*P* Value[c]	PR	95% CI	*P* Value[c]	PR	95% CI	*P* Value[c]
p,p′-DDT			0.043			0.469			0.443
≤0.086	1.0	Referent		1.0	Referent		1.0	Referent	
0.087–0.178	1.2	0.6, 2.1		1.1	0.6, 1.9		1.0	0.6, 1.8	
0.179–0.349	1.6	0.9, 2.8		1.3	0.7, 2.2		1.2	0.7, 2.1	
>0.349	1.7	0.9, 3.1		1.2	0.6, 2.1		1.2	0.6, 2.2	
p,p′-DDE			<0.001			0.181			0.194
≤1.24	1.0	Referent		1.0	Referent		1.0	Referent	
1.25–2.63	1.5	0.8, 2.9		1.3	0.7, 2.3		1.3	0.7, 2.4	
2.64–5.56	2.4	1.3, 4.5		1.6	0.9, 3.2		1.7	0.9, 3.4	
>5.56	3.2	1.8, 5.8		1.5	0.8, 2.9		1.5	0.8, 2.8	
HCB			<0.001			0.082			0.118
≤0.509	1.0	Referent		1.0	Referent		1.0	Referent	
0.510–1.193	1.7	0.9, 3.3		1.6	0.9, 3.1		1.8	0.9, 3.4	
1.194–2.610	2.5	1.4, 4.7		2.0	1.0, 3.9		2.1	1.0, 4.3	
>2.610	4.0	2.2, 7.3		2.0	0.8, 4.9		2.0	0.8, 5.1	
β-HCH			<0.001			0.047			0.031
≤0.288	1.0	Referent		1.0	Referent		1.0	Referent	
0.289–0.670	1.8	0.9, 3.6		1.6	0.8, 3.3		1.7	0.9, 3.4	
0.671–1.547	3.7	2.0, 6.9		1.9	0.9, 4.1		1.9	0.9, 4.2	
>1.547	4.9	2.6, 9.4		2.4	1.0, 5.9		2.8	1.1, 6.7	
PCB 118			<0.001[d]			0.001[d]			0.001[d]
≤0.060	1.0	Referent		1.0	Referent		1.0	Referent	
0.061–0.135	1.2	0.6, 2.6		1.6	0.9, 3.1		1.2	0.6, 2.3	
0.135–0.242	3.7	2.0, 6.7		2.5	1.5, 4.3		2.6	1.5, 4.5	
>0.242	3.0	1.5, 6.0		1.1	0.6, 2.2		1.6	0.8, 3.0	
PCB 138			<0.001[d]			0.001[d]			<0.001[d]
≤0.258	1.0	Referent		1.0	Referent		1.0	Referent	
0.259–0.451	1.6	0.7, 3.7		1.2	0.5, 2.7		1.2	0.5, 2.8	
0.452–0.722	5.6	2.8, 11.3		2.9	1.4, 6.1		3.3	1.6, 7.0	
>0.722	5.2	2.6, 10.7		1.9	0.9, 4.3		1.9	0.8, 4.4	
PCB 153			<0.001[d]			0.003[d]			0.001[d]
≤0.361	1.0	Referent		1.0	Referent		1.0	Referent	
0.362–0.626	1.9	0.8, 4.4		1.3	0.6, 3.1		1.3	0.6, 3.2	
0.627–0.978	5.9	2.8, 12.2		3.0	1.3, 6.8		3.3	1.5, 7.5	
>0.978	5.6	2.6, 11.8		1.9	0.8, 4.3		2.0	0.8, 4.6	
PCB 180			<0.001[d]			<0.001[d]			<0.001[d]
≤0.314	1.0	Referent		1.0	Referent		1.0	Referent	
0.315–0.503	1.2	0.5, 3.2		0.8	0.3, 2.0		0.8	0.3, 2.1	
0.504–0.783	5.9	2.9, 12.3		3.2	1.4, 7.0		3.6	1.6, 7.9	
>0.783	6.3	3.0, 13.1		2.0	0.9, 4.7		2.3	1.0, 5.4	
Sum of PCBs			<0.001[d]			<0.001[d]			<0.001[d]
≤1.03	1.0	Referent		1.0	Referent		1.0	Referent	
1.04–1.76	1.4	0.6, 3.3		0.9	0.4, 2.2		1.0	0.4, 2.4	
1.76–2.72	5.6	2.8, 11.1		3.0	1.4, 6.3		3.3	1.6, 7.1	
>2.73	5.8	2.9, 11.8		1.9	0.9, 4.1		2.0	0.9, 4.6	

Table continues

Table 3. Continued

Compound and Concentration, ng/mL	Crude Model ($n = 364$)			Model 1[a] ($n = 349$)			Model 2[b] ($n = 344$)		
	PR	95% CI	*P* Value[c]	PR	95% CI	*P* Value[c]	PR	95% CI	*P* Value[c]
Sum of orders, 6 POPs[e]			<0.001			0.003			0.003
6–10	1.0	Referent		1.0	Referent		1.0	Referent	
11–15	3.3	1.5, 7.2		2.6	1.1, 5.9		3.0	1.3, 6.8	
16–19	5.4	2.5, 11.7		3.0	1.2, 7.2		3.5	1.4, 8.7	
20–24	8.6	4.1, 17.8		3.7	1.5, 9.1		4.1	1.7, 10.0	
Sum of orders, all POPs			<0.001			0.008			0.034[d]
8–14	1.0	Referent		1.0	Referent		1.0	Referent	
15–20	3.8	1.9, 7.9		2.4	1.1, 5.2		2.6	1.2, 5.5	
21–26	5.0	2.4, 10.3		2.9	1.3, 6.5		3.4	1.5, 7.8	
27–32	7.7	3.7, 15.9		3.0	1.3, 6.8		3.1	1.3, 7.3	

Abbreviations: CI, confidence interval; DDE, dichlorodiphenyldichloroethene; DDT, dichlorodiphenyltrichloroethane; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; PCB, polychlorinated biphenyl; POP: persistent organic pollutant; PR, prevalence ratio.

[a] Model 1 adjusted for age, sex, body mass index, cigarette smoking, alcohol consumption, and physical activity.

[b] Model 2 adjusted for age, sex, body mass index, cigarette smoking, alcohol consumption, physical activity, and occupational social class.

[c] Unless otherwise specified, *P* was derived from the multivariate analogue of Mantel's extension test for linear trend.

[d] Wald test.

[e] HCB, β-HCH, and PCB congeners 118, 138, 153, and 180.

Table 4. Association of Serum Concentrations of Persistent Organic Pollutants With the Unhealthy Metabolic Phenotype (≥2 Cardiometabolic Abnormalities) Among Overweight and Obese Participants, Catalan Health Interview Survey, Spain, 2002

Compound and Concentration, ng/mL	Crude Model ($n = 496$)			Model 1[a] ($n = 472$)			Model 2[b] ($n = 462$)		
	PR	95% CI	*P* Value[c]	PR	95% CI	*P* Value[c]	PR	95% CI	*P* Value[c]
p,p′-DDT			0.101			0.454[d]			0.333[d]
≤0.086	1.0	Referent		1.0	Referent		1.0	Referent	
0.087–0.178	1.2	0.9, 1.5		1.1	0.9, 1.4		1.1	0.9, 1.4	
0.179–0.349	1.1	0.9, 1.4		1.0	0.8, 1.2		0.9	0.7, 1.2	
>0.349	1.3	1.0, 1.6		1.0	0.8, 1.3		1.0	0.8, 1.3	
p,p′-DDE			<0.001			0.624[d]			0.710[d]
≤1.24	1.0	Referent		1.0	Referent		1.0	Referent	
1.25–2.63	1.4	1.0, 1.9		1.1	0.8, 1.5		1.1	0.8, 1.4	
2.64–5.56	1.4	1.0, 1.8		1.0	0.8, 1.3		1.0	0.7, 1.3	
>5.56	1.8	1.3, 2.3		1.1	0.8, 1.4		1.1	0.8, 1.4	
HCB			<0.001			0.023[d]			0.028[d]
≤0.509	1.0	Referent		1.0	Referent		1.0	Referent	
0.510–1.193	1.4	1.0, 2.0		1.1	0.8, 1.5		1.1	0.8, 1.5	
1.194–2.610	1.4	1.0, 2.0		1.1	0.8, 1.5		1.1	0.8, 1.5	
>2.610	2.0	1.5, 2.8		1.4	1.0, 1.9		1.4	1.0, 1.9	
β-HCH			<0.001			0.030[d]			0.031[d]
≤0.288	1.0	Referent		1.0	Referent		1.0	Referent	
0.289–0.670	0.9	0.6, 1.2		0.7	0.5, 1.0		0.7	0.5, 1.0	
0.671–1.547	1.4	1.1, 1.9		1.0	0.7, 1.3		1.0	0.7, 1.3	
>1.547	1.7	1.3, 2.2		1.0	0.8, 1.4		1.0	0.8, 1.4	

Table continues

Table 4. Continued

Compound and Concentration, ng/mL	Crude Model (n = 496)			Model 1[a] (n = 472)			Model 2[b] (n = 462)		
	PR	95% CI	P Value[c]	PR	95% CI	P Value[c]	PR	95% CI	P Value[c]
PCB 118			<0.001			0.046			0.074
≤0.060	1.0	Referent		1.0	Referent		1.0	Referent	
0.061–0.135	1.0	0.8, 1.4		1.0	0.8, 1.3		1.0	0.8, 1.3	
0.135–0.242	1.2	0.9, 1.6		1.0	0.8, 1.3		1.0	0.8, 1.3	
>0.242	1.6	1.3, 2.0		1.2	1.0, 1.6		1.2	0.9, 1.5	
PCB 138			<0.001			0.045			0.040
≤0.258	1.0	Referent		1.0	Referent		1.0	Referent	
0.259–0.451	1.2	0.9, 1.6		1.0	0.7, 1.3		1.0	0.7, 1.3	
0.452–0.722	1.5	1.1, 2.0		1.1	0.8, 1.4		1.1	0.8, 1.4	
>0.722	1.8	1.4, 2.3		1.2	0.9, 1.6		1.2	0.9, 1.6	
PCB 153			<0.001			0.027			0.026
≤0.361	1.0	Referent		1.0	Referent		1.0	Referent	
0.362–0.626	1.4	1.0, 1.9		1.2	0.9, 1.7		1.2	0.9, 1.6	
0.627–0.978	1.7	1.3, 2.2		1.2	0.9, 1.7		1.2	0.9, 1.7	
>0.978	1.9	1.5, 2.5		1.4	1.0, 1.9		1.4	1.0, 1.8	
PCB 180			<0.001			0.029			0.027
≤0.314	1.0	Referent		1.0	Referent		1.0	Referent	
0.315–0.503	1.4	1.0, 1.8		1.1	0.8, 1.4		1.0	0.8, 1.4	
0.504–0.783	1.7	1.3, 2.2		1.3	1.0, 1.7		1.3	1.0, 1.7	
>0.783	1.8	1.4, 2.4		1.3	1.0, 1.7		1.3	1.0, 1.7	
Sum of PCBs			<0.001			0.007			0.007
≤1.03	1.0	Referent		1.0	Referent		1.0	Referent	
1.04–1.76	1.4	1.0, 1.9		1.1	0.8, 1.5		1.1	0.8, 1.4	
1.76–2.72	1.7	1.3, 2.3		1.2	0.9, 1.6		1.2	0.9, 1.6	
>2.73	2.0	1.5, 2.6		1.4	1.0, 1.8		1.4	1.0, 1.8	
Sum of orders, 6 POPs[e]			<0.001			0.020[d]			0.028[d]
6–10	1.0	Referent		1.0	Referent		1.0	Referent	
11–15	1.3	0.9, 1.7		1.0	0.7, 1.4		1.0	0.7, 1.4	
16–19	1.4	1.0, 1.9		0.9	0.7, 1.3		1.0	0.7, 1.3	
20–24	1.9	1.5, 2.5		1.2	0.9, 1.7		1.2	0.9, 1.7	
Sum of orders, all POPs			<0.001			0.009[d]			0.012[d]
8–14	1.0	Referent		1.0	Referent		1.0	Referent	
15–20	1.4	1.0, 1.9		1.1	0.8, 1.5		1.0	0.8, 1.4	
21–26	1.3	1.0, 1.8		0.9	0.7, 1.3		0.9	0.7, 1.3	
27–32	2.0	1.5, 2.6		1.2	0.9, 1.7		1.2	0.9, 1.7	

Abbreviations: CI, confidence interval; DDE, dichlorodiphenyldichloroethene; DDT, dichlorodiphenyltrichloroethane; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; PCB, polychlorinated biphenyl; POP: persistent organic pollutant; PR, prevalence ratio.

[a] Model 1 adjusted for age, sex, body mass index, cigarette smoking, alcohol consumption, and physical activity.

[b] Model 2 adjusted for age, sex, body mass index, cigarette smoking, alcohol consumption, physical activity, and occupational social class.

[c] Unless otherwise specified, P was derived from the multivariate analogue of Mantel's extension test for linear trend.

[d] Wald test.

[e] HCB, β-HCH, and PCB congeners 118, 138, 153, and 180.

To our knowledge, only 2 studies have analyzed associations between POP concentrations and metabolic phenotypes, and these studies did not include normal-weight individuals. Our results agree with Gauthier et al. (22) and Dirinck et al. (23), who reported positive associations between PCB concentrations and unhealthy metabolic phenotypes in overweight and obese individuals. Remarkably, we also observed the association in normal-weight individuals. The lack of association that

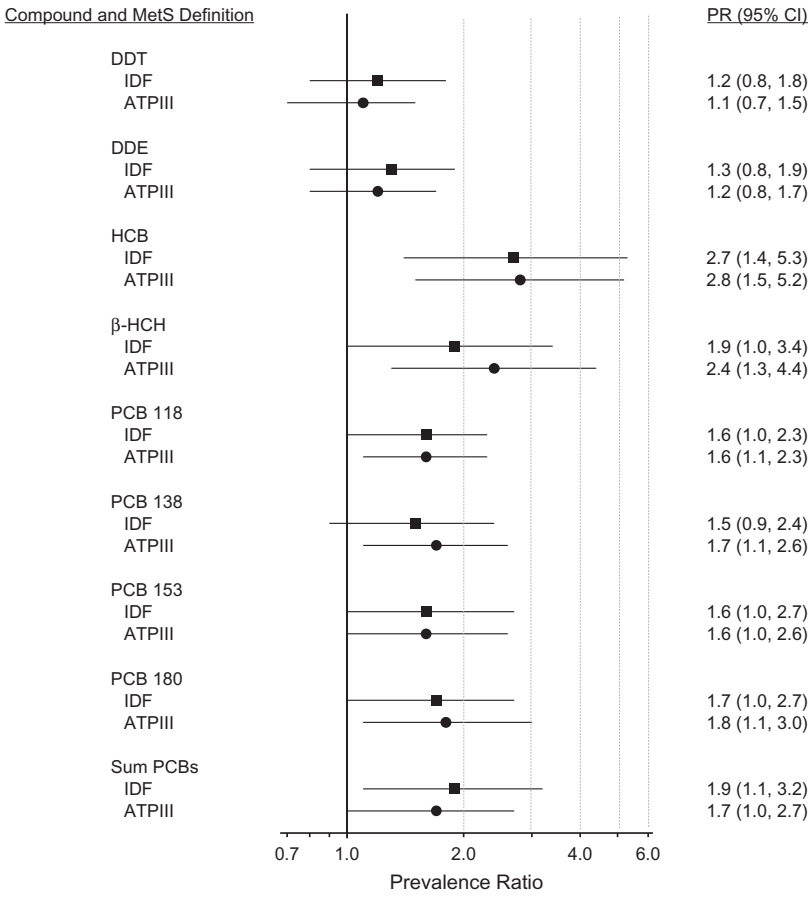

Figure 2. The association between metabolic syndrome and concentrations of persistent organic pollutants (POPs), Catalan Health Interview Survey, Spain, 2002. Prevalence ratios (PRs) and 95% confidence intervals (CIs) of metabolic syndrome for the upper quartile (vs. lower quartile) of POP concentrations, adjusted for age, body mass index, sex, cigarette smoking, alcohol consumption, and physical activity. Metabolic syndrome was defined according to National Cholesterol Education Program—Third Adult Treatment Panel (ATPIII) and International Diabetes Federation (IDF) definitions. DDE, dichlorodiphenyldichloroethene; DDT, dichlorodiphenyltrichloroethane; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; PCB, polychlorinated biphenyl.

we noted between DDE concentrations and metabolic phenotypes is also consistent with results reported by Gauthier et al. (22); Dirinck et al. (23) studied only PCBs. We believe ours is the first study to analyze associations of DDT, HCB, and β-HCH with metabolic phenotypes (including C-reactive protein and homeostatic model assessment). It is also the first report on the relationship between POP concentrations and metabolic phenotypes in a sample of the general population. In contrast with previous studies, ours included diabetic and nondiabetic individuals, both sexes, a wide age range, and a much larger number of individuals.

Our observation that in normal-weight participants the association with the unhealthy metabolic phenotype was stronger with PCB concentrations in the third quartile than in the fourth quartile is coherent with evidence that endocrine-disrupting chemicals such as POPs can have nonmonotonic effects (10, 39). Some previous studies of POPs also reported nonmonotonic associations with outcomes as type 2 diabetes and MetS (9, 10, 14, 19, 39, 40). However, confirmation of the nonlinear dose-responses in larger populations is needed.

Our results agree with previous studies that also found positive associations between PCBs and some organochlorine pesticides, such as β-HCH, and MetS (18–21), but not with DDT and DDE (20). In a prospective nested case-control study based on the general population in Korea (with 64 cases of MetS and 182 controls followed during 4 years), serum concentrations of PCBs and organochlorine pesticides at baseline were associated with an increased risk of MetS (19). Although random sampling variation cannot be discarded, the different results for specific POPs might reflect different mechanisms of action or different target organs.

The main limitation of our study is its cross-sectional design, which prevents inferring causal relationships: Theoretically, individuals who developed an unhealthy metabolic phenotype might have accumulated POPs at a higher rate than individuals who retained a healthy phenotype. However, empirical evidence in support of such possibility is scant, and the putative mechanisms have not been elucidated; for example, few if any human studies have shown that the underlying pathophysiological processes that eventually lead to clinical type 2 diabetes or other metabolic disorders also induce a higher accumulation of POPs (10). Furthermore, the study findings are in accordance with results of experimental animal studies (10, 13, 16) and human prospective studies (9, 10, 14, 15, 19), which were able to rule out "reverse causation" and disease progression bias. Also because of its cross-sectional design, and because dyslipidemia was one of the abnormalities considered when defining phenotypes, lipid correction of POP concentrations would entail an overadjustment (31). A relatively high number of comparisons were made; hence, false positives might have occurred. Nonetheless, associations with the unhealthy phenotype were largely consistent for normal-weight and overweight/obese individuals and for groups of highly correlated compounds (for example, among PCBs). Study limitations also included the lack of information on changes in body weight (23) and the use of capillary blood instead of venous blood to define hyperglycemia (26).

Our findings support the hypothesis that exposure to POPs is associated with unhealthy metabolic phenotypes, not only in obese and overweight individuals but also in normal-weight individuals. POPs might also contribute to increase the risk of MetS. These results should be refuted or confirmed by prospective longitudinal studies assessing a larger number of potentially obesogenic environmental and individual factors. Nevertheless, they add to the existing evidence supporting policies to decrease human exposure to POPs (12, 41, 42). Considering that, in the majority of the general population, POP exposure occurs largely through the ingestion of fatty parts of animal foods (43–45), results might also support existing dietary guidelines to prevent cardiometabolic disorders.

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WEB MATERIAL

Web Appendix 1. Methods, additional information.

Sampling methods of the Catalan Health Interview Survey

The target population of the Catalan Health Interview Survey (CHIS) was all non-institutionalized residents in Catalonia (Spain) in 2001.The selection of a representative sample of the non-institutionalized population followed a complex design, including a multiple-stage random sampling strategy. In the first sampling stage, municipalities (for the city of Barcelona, districts) were selected from the eight health areas of Catalonia, according to their population size (eight strata). Based on the size of the municipality (or district), at the second sampling stage a random sample from the Census was used to select individuals using proportional probabilities. Face to face interviews were conducted at home by trained staff from October 2001 to April 2002 (1- 5).

Sociodemographic and life style characteristics

Sociodemographic and life style variables (smoking, alcohol consumption, physical activity, occupational social class and educational level) were obtained from the CHIS. Occupational social class was assigned through the current or last occupation of the participant or, if he/she had a less privileged social class than the head of the household, through the current or last occupation of the latter. Occupations were coded using the four-digit Spanish 'Clasificación Nacional de Ocupaciones' (CNO94), which is closely related to the international ISCO88 coding system (5, 6). Educational level was classified according to the highest completed level of education in five categories: without formal education (WFE), primary schooling (1st stage), primary schooling (2nd stage), secondary, and university studies. WFE included the illiterate.

Serum POP concentrations assays

Serum concentrations of the following persistent organic pollutants were analyzed in the Department of Environmental Chemistry (IIQAB-CSIC, Barcelona) (3, 4): o,p'-DDT (dichlorodiphenyltrichloroethane), p,p'-DDT, o,p'-DDE (dichlorodiphenyldichloroethene), p,p'-DDE, o,p'-DDD (dichlorodiphenyldichloroethane), p,p'-DDD, PCB (polychlorinated biphenyl) congeners 28, 52, 101, 118, 138, 153, and 180, PeCB (pentachlorobenzene), HCB (hexachlorobenzene), α-HCH (hexachlorocyclohexane), β-HCH, γ-HCH, and δ-HCH. Gas chromatography (GC) analyses were performed with an Agilent Technologies model GC-6890N provided with an ECD and a 60 m, 0.25 mm i.d. DB-5 column (film thickness 0.25 μm). Limits of detection ranged from 0.0023 ng/mL for PCB 101 to 0.0235 ng/mL for γ-HCH.

Limits of quantification ranged from 0.0069 ng/mL for PCB 101 to 0.0706 ng/mL for γ-HCH. When a sample had a concentration of a compound below the detection threshold, it was assigned the mid-value of this limit; when a compound was detected but under the quantification threshold, the mid-value between detection and quantification limits was used (3, 4).

Exposure to multiple compounds

To assess the effect of exposure to multiple compounds, we computed *a)* the sum of PCBs for each participant by adding the serum concentration of the 4 most prevalent PCBs, and then assigning each participant to one quartile of the new variable (sum of PCBs) (7). We also computed *b)* the sum of orders or sum of category ranking of the 8 most prevalent POPs mentioned above by categorizing each POP in quartiles and adding for each participant the category number of each POP (7, 8). Similarly, we calculated *c)* the sum of orders of the 6 POPs that were found individually associated with metabolic phenotypes.

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Web Table 1. Serum Concentrations of Persistent Organic Pollutants (POPs) by Body Mass Index and Metabolic Phenotype, Catalan Health Interview Survey, 2002.

		Normal-weight			Overweight and Obese		
Compound	**Total**	**Metabolically Healthy**	**Metabolically Unhealthy**	***P***	**Metabolically Healthy**	**Metabolically Unhealthy**	***P***
p,p'-DDT [a]	0.149	0.098	0.152	0.012	0.163	0.211	0.030
(95% CI)	(0.137-0.163)	(0.084-0.114)	(0.114-0.202)		(0.136-0.195)	(0.182-0.244)	
Median	0.177	0.128	0.169		0.198	0.232	
p,p'-DDE [a]	2.729	1.686	3.327	<0.001	2.713	4.150	<0.001
(95% CI)	(2.540-2.932)	(1.515-1.876)	(2.609-4.241)		(2.348-3.133)	(3.681-4.678)	
Median	2.634	1.511	2.951		2.767	4.410	
HCB [a]	1.088	0.554	1.091	<0.001	1.090	2.072	<0.001
(95% CI)	(0.997-1.187)	(0.479-0.641)	(0.802-1.484)		(0.909-1.307)	(1.850-2.321)	
Median	1.210	0.612	1.240		1.294	2.383	
β-HCH [a]	0.628	0.315	0.704	<0.001	0.602	1.218	<0.001
(95% CI)	(0.576-0.685)	(0.273-0.363)	(0.514-0.965)		(0.514-0.705)	(1.077-1.378)	
Median	0.684	0.327	0.774		0.598	1.432	
PCB 118 [a]	0.100	0.059	0.124	<0.001	0.095	0.163	<0.001
(95% CI)	(0.092-0.109)	(0.051-0.069)	(0.094-0.162)		(0.080-0.113)	(0.143-0.186)	
Median	0.137	0.079	0.161		0.128	0.212	
PCB 138 [a]	0.392	0.251	0.552	<0.001	0.379	0.565	<0.001
(95% CI)	(0.366-0.419)	(0.221-0.286)	(0.471-0.646)		(0.335-0.428)	(0.513-0.623)	
Median	0.451	0.296	0.558		0.419	0.585	
PCB 153 [a]	0.564	0.378	0.786	<0.001	0.518	0.808	<0.001
(95% CI)	(0.530-0.602)	(0.338-0.424)	(0.665-0.931)		(0.455-0.590)	(0.735-0.888)	
Median	0.628	0.447	0.820		0.598	0.816	
PCB 180 [a]	0.488	0.362	0.685	<0.001	0.433	0.648	<0.001
(95% CI)	(0.464-0.514)	(0.333-0.393)	(0.582-0.807)		(0.389-0.481)	(0.599-0.700)	
Median	0.499	0.378	0.677		0.460	0.639	

[a] ng/mL, geometric mean.
Differences between pairs of medians were all statistically significant (all *P* <0.001, except for p,p'-DDT: *P* = 0.013 and 0.027 for normal-weight and overweight/obese, respectively) (Mann-Whitney's *U*-test, two-tail).
Unless otherwise specified, *P* derived from Student's *t*-test.

Web Table 2. Association Between Serum Concentrations of Persistent Organic Pollutants and the Unhealthy Metabolic Phenotype (≥2 Cardiometabolic Abnormalities), Catalan Health Interview Survey, 2002. Prevalence Ratio Estimated from Logistic Models.

	Normal-weight			Overweight/Obese		
	Adjusted model (N=344)			Adjusted model (N=462)		
Compounds (ng/mL)	**PR**	**95% CI**	***P***	**PR**	**95% CI**	***P***
p,p'-DDT						
≤ 0.086	1.0		0.472	1.0		0.340[a]
0.087-0.178	1.1	0.4, 2.8		1.4	0.7. 3.0	
0.179-0.349	1.3	0.5, 3.1		0.8	0.4, 1.7	
> 0.349	1.4	0.5, 4.6		1.0	0.5, 2.1	
p,p'-DDE						
≤ 1.24	1.0		0.261	1.0		0.569[a]
1.25-2.63	1.3	0.4, 3.5		1.0	0.4, 2.1	
2.64-5.56	2.0	0.6, 6.7		0.7	0.3, 1.4	
> 5.56	1.6	0.4, 5.7		0.9	0.4, 2.0	
HCB						
≤ 0.509	1.0		0.026	1.0		0.062[a]
0.510-1.193	2.4	0.8, 7.9		1.1	0.5, 2.3	
1.194-2.610	3.5	1.1, 15.8		1.0	0.4, 2.2	
> 2.610	4.1	0.8, 22.3		2.4	0.9, 7.2	
β-HCH						
≤ 0.288	1.0		0.007	1.0		0.006[a]
0.289-0.670	1.8	0.6, 5.5		0.4	0.1, 0.7	
0.671-1.547	2.4	0.7, 8.4		0.8	0.3, 1.8	
> 1.547	6.6	1.3, 30.2		1.0	0.4, 2.8	
PCB 118						
≤ 0.060	1.0		0.002[a]	1.0		0.060
0.060-0.135	1.4	0.5, 4.4		0.9	0.5, 1.9	
0.135-0.242	4.7	2.1, 16.8		0.9	0.4, 1.9	
> 0.242	1.9	0.6, 8.7		1.9	0.9, 4.2	
PCB 138						
≤ 0.258	1.0		0.003[a]	1.0		0.103
0.259-0.451	1.1	0.3, 4.3		0.8	0.4, 1.6	
0.452-0.722	5.4	1.9, 24.8		1.0	0.5, 2.1	
> 0.722	2.0	0.5, 8.8		1.6	0.8, 4.0	
PCB 153						
≤ 0.361	1.0		0.004[a]	1.0		0.056
0.362-0.626	1.3	0.4, 5.9		1.1	0.6, 2.6	
0.627-0.978	5.3	1.8, 24.9		1.4	0.6, 3.0	
> 0.978	1.9	0.5, 9.7		2.0	0.9, 4.6	
PCB 180						
≤ 0.314	1.0		<0.001[a]	1.0		0.079
0.315-0.503	0.6	0.0, 2.8		0.8	0.4, 1.7	
0.504-0.783	5.5	1.7, 24.2		1.4	0.7, 3.2	
> 0.783	2.6	0.8, 12.4		1.6	0.7, 3.7	
Sum of PCBs						
≤ 1.03	1.0		0.001[a]	1.0		0.014
1.04-1.76	0.7	0.2, 3.2		0.8	0.4, 1.8	
1.76-2.72	5.1	1.9, 18.7		1.3	0.6, 3.0	
> 2.73	2.0	0.6, 9.0		2.1	1.0, 5.2	
Sum of orders 6 POPs[b]						
6-10	1.0		0.002	1.0		0.027[a]
11-15	3.8	1.1, 15.7		0.8	0.4, 1.8	
16-19	5.3	1.3, 28.0		0.7	0.3, 1.6	
20-24	7.1	1.6, 37.0		1.7	0.7, 4.4	
Sum of orders all POPs						
8-14	1.0		0.036[a]	1.0		0.005[a]
15-20	3.1	1.1, 12.0		0.9	0.4, 1.9	
21-26	4.8	1.4, 24.2		0.6	0.3, 1.3	
27-32	4.4	1.0, 25.7		1.9	0.8, 4.9	

Abbreviations: CI, confidence interval; PR, prevalence ratio, estimated from logistic models as the ratio of the predicted probabilities for each outcome comparing the 3 highest quartiles with the lowest one (see Methods); POP: persistent organic pollutant.

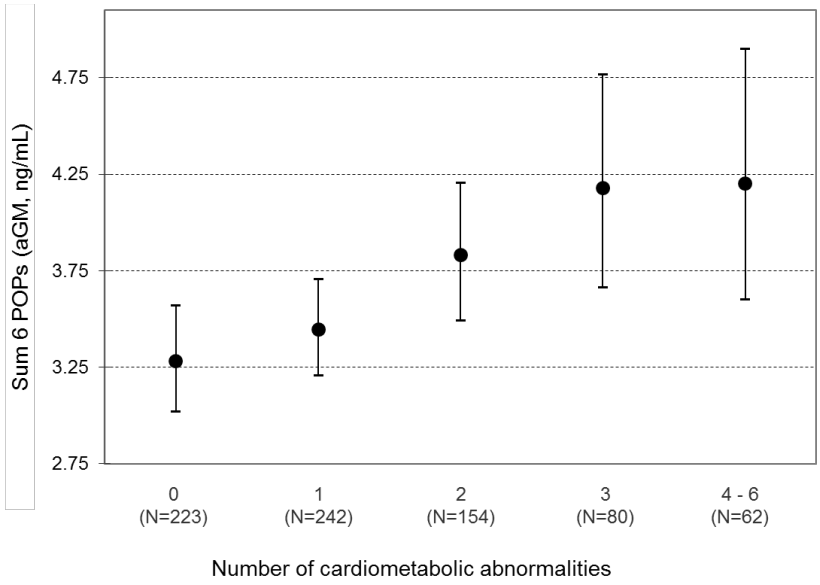
Adjusted model: adjusted for age, sex, body mass index, cigarette smoking, alcohol consumption, physical activity and occupational social class.

Unless otherwise specified, *P* derived from the multivariate analogue of Mantel's extension test for linear trend.

[a] Wald test.

[b] HCB, β-HCH, and PCB congeners 118, 138, 153, and 180.

Web Figure 1. Sum of Concentrations of 6 POPs (ng/mL) by Number of Cardiometabolic Abnormalities. Adjusted Geometric Mean and 95% Confidence Intervals of the Sum of Concentrations. Catalan Health Interview Survey, 2002.



P for linear trend: 0.001.

Sum 6 POPs: sum of serum concentrations (ng/mL) of HCB, β-HCH, and PCB congeners 118, 138, 153, and 180.

aGM: Geometric mean adjusted for age, sex, body mass index, cigarette smoking, alcohol consumption, and physical activity.

Web Table 3. Prevalence of the Metabolic Syndrome and of Each of its Five Components in the Study Participants by Sex, Catalan Health Interview Survey, 2002.

	Total		Men		Women		
	N	(%)	N	(%)	N	(%)	*P* [c]
Total	919	(100)	399	(43.4)	520	(56.6)	
Metabolic Syndrome							
IDF	216	(25.2)	96	(26.6)	120	(24.1)	0.426
ATPIII	203	(23.0)	96	(25.6)	107	(21.1)	0.125
Abdominal obesity							
IDF (≥94 cm, men / ≥80 cm, women)	403	(51.1)	153	(45.4)	250	(55.4)	0.006
ATPIII (≥102 cm, men / ≥88 cm, women)	204	(25.9)	60	(17.8)	144	(31.9)	<0.001
Hypertriglyceridemia							
(≥150 mg/dL)[a]	115	(12.7)	73	(18.7)	42	(8.2)	<0.001
Low HDL cholesterol							
a. (<40 mg/dL, men / <50 mg/dL, women)	260	(28.3)	113	(28.3)	147	(28.3)	
b. Medication use	64	(7.0)	29	(7.3)	35	(6.7)	
Total (a &/or b)	304	(33.1)	136	(34.1)	168	(32.3)	0.572
Hypertension							
a. (≥130 mmHg SBP / ≥ 85 mmHg DBP)	402	(43.8)	197	(49.4)	205	(39.5)	
b. Medication use	111	(12.1)	53	(13.3)	58	(11.2)	
Total (a &/or b)	414	(45.1)	203	(50.9)	211	(40.7)	0.002
Hyperglycemia							
IDF							
a. (≥100 mg/dL)[b]	319	(36.1)	172	(45.3)	147	(29.2)	
b. Type II diabetes	61	(6.6)	31	(7.8)	30	(5.8)	
Total (a &/or b)	327	(36.9)	173	(45.5)	154	(30.4)	<0.001
ATPIII							
a. (≥100 mg/dL)[b]	319	(36.1)	172	(45.3)	147	(29.2)	
b. Medication use	43	(4.7)	24	(6.0)	19	(3.7)	
Total (a &/or b)	325	(36.7)	173	(45.5)	152	(30.0)	<0.001

Abbreviations: ATPIII, National Cholesterol Education Program - Third Adult Treatment Panel; IDF, International Diabetes Federation.

[a] Non-fasting subjects with triglyceride levels ≥150 mg/dL were excluded (N = 14).

[b] 7 subjects missing blood glucose concentrations, 6 subjects with whole blood glucose concentration ≤55 mg/dL, 18 non-fasting subjects with whole blood glucose concentration ≥100 mg/dL, and 4 pregnant women, were excluded.

[c] Fisher's exact test.

Web Table 4. Association Between Serum Concentrations of Persistent Organic Pollutants and Metabolic Syndrome (International Diabetes Federation, IDF) (N=858), Catalan Health Interview Survey, 2002.

Compound (ng/mL)	**Metabolic Syndrome (IDF)**								
	Crude model			**Model 1**			**Model 2**		
	PR	**95% CI**	***P***	**PR**	**95% CI**	***P***	**PR**	**95% CI**	***P***
p,p'-DDT									
≤ 0.086	1.0		<0.001	1.0		0.130 [a]	1.0		0.537 [a]
0.087-0.178	1.9	1.2, 2.9		1.5	1.0, 2.3		1.3	0.9, 2.0	
0.179-0.349	2.1	1.4, 3.3		1.3	0.9, 2.1		1.2	0.8, 1.8	
> 0.349	3.1	2.1, 4.6		1.6	1.1, 2.4		1.2	0.8, 1.8	
p,p'-DDE									
≤ 1.24	1.0		<0.001	1.0		0.219 [a]	1.0		0.423 [a]
1.25-2.63	2.3	1.4, 3.6		1.5	0.9, 2.4		1.3	0.8, 2.0	
2.64-5.56	2.9	1.8, 4.5		1.3	0.8, 2.1		1.1	0.7, 1.6	
> 5.56	4.7	3.1, 7.3		1.6	1.0, 2.5		1.3	0.8, 1.9	
HCB									
≤ 0.509	1.0		<0.001	1.0		<0.001	1.0		0.001
0.510-1.193	3.1	1.7, 5.9		2.3	1.2, 4.4		1.8	1.0, 3.3	
1.194-2.610	4.9	2.7, 8.9		3.1	1.7, 5.8		2.1	1.1, 3.8	
> 2.610	10.2	5.8, 17.9		4.9	2.5, 9.5		2.7	1.4, 5.3	
β-HCH									
≤ 0.288	1.0		<0.001	1.0		<0.001	1.0		0.010
0.289-0.670	1.7	0.9, 3.0		1.3	0.7, 2.3		1.1	0.6, 1.9	
0.671-1.547	4.3	2.6, 7.2		2.3	1.3, 4.0		1.7	1.0, 2.9	
> 1.547	7.6	4.6, 12.4		3.1	1.7, 5.7		1.9	1.0, 3.4	
PCB 118									
≤ 0.060	1.0		<0.001	1.0		0.001	1.0		0.016
0.060-0.135	1.2	0.8, 2.0		1.2	0.8, 2.0		1.1	0.7, 1.8	
0.135-0.242	2.3	1.5, 3.5		1.5	0.9, 2.3		1.2	0.8, 1.9	
> 0.242	4.2	2.8, 6.2		1.9	1.3, 3.0		1.6	1.0, 2.3	
PCB 138									
≤ 0.258	1.0		<0.001	1.0		0.248	1.0		0.140
0.259-0.451	2.0	1.2, 3.2		1.5	0.9, 2.4		1.4	0.9, 2.3	
0.452-0.722	3.3	2.1, 5.1		1.5	0.9, 2.6		1.4	0.9, 2.3	
> 0.722	4.2	2.7, 6.4		1.5	0.9, 2.5		1.5	0.9, 2.4	
PCB 153									
≤ 0.361	1.0		<0.001	1.0		0.211	1.0		0.307 [a]
0.362-0.626	2.0	1.2, 3.2		1.5	0.9, 2.6		1.5	0.9, 2.5	
0.627-0.978	3.2	2.0, 4.9		1.5	0.9, 2.6		1.4	0.9, 2.4	
> 0.978	4.2	2.8, 6.5		1.6	0.9, 2.7		1.6	1.0, 2.7	
PCB 180									
≤ 0.314	1.0		<0.001	1.0		0.056 [a]	1.0		0.036 [a]
0.315-0.503	2.0	1.2, 3.2		1.2	0.7, 2.0		1.2	0.7, 2.0	
0.504-0.783	3.7	2.4, 5.8		1.7	1.0, 2.8		1.7	1.1, 2.8	
> 0.783	4.2	2.7, 6.5		1.4	0.8, 2.3		1.7	1.0, 2.7	
Sum of PCBs									
≤ 1.03	1.0		<0.001	1.0		0.232 [a]	1.0		0.072 [a]
1.04-1.76	2.7	1.6, 4.5		1.8	1.0, 3.1		1.6	0.9, 2.7	
1.76-2.72	3.8	2.3, 6.1		1.7	0.9, 3.0		1.5	0.9, 2.5	
> 2.73	5.3	3.3, 8.4		1.8	1.0, 3.2		1.9	1.1, 3.2	

Abbreviations: CI, confidence interval; PR, prevalence ratio.

Model 1: adjusted for age, sex, cigarette smoking, alcohol consumption and physical activity.

Model 2: further adjusted for body mass index.

Unless otherwise specified, *P* derived from multivariate analogue of Mantel's extension test for linear trend.

[a] Wald test.

Web Table 5. Association Between Serum Concentrations of Persistent Organic Pollutants and Metabolic Syndrome (National Cholesterol Education Program - Third Adult Treatment Panel, ATPIII) (N=881), Catalan Health Interview Survey, 2002.

Compound (ng/mL)	**Metabolic Syndrome (ATPIII)**								
	Crude model			**Model 1**			**Model 2**		
	PR	**95% CI**	***P***	**PR**	**95% CI**	***P***	**PR**	**95% CI**	***P***
p,p'-DDT									
≤ 0.086	1.0		<0.001	1.0		0.062	1.0		0.742
0.087-0.178	1.4	0.9, 2.1		1.1	0.7, 1.7		1.0	0.7, 1.5	
0.179-0.349	1.8	1.2, 2.7		1.1	0.7, 1.7		1.0	0.6, 1.4	
> 0.349	2.7	1.8, 3.9		1.4	1.0, 2.1		1.1	0.7, 1.5	
p,p'-DDE									
≤ 1.24	1.0		<0.001	1.0		0.029	1.0		0.316
1.25-2.63	1.6	1.0, 2.7		1.1	0.7, 1.8		1.0	0.6, 1.5	
2.64-5.56	2.5	1.6, 4.0		1.2	0.7, 1.9		1.0	0.6, 1.5	
> 5.56	4.4	2.8, 6.7		1.5	1.0, 2.4		1.2	0.8, 1.7	
HCB									
≤ 0.509	1.0		<0.001	1.0		<0.001	1.0		<0.001
0.510-1.193	2.2	1.2, 4.2		1.8	0.9, 3.3		1.3	0.7, 2.5	
1.194-2.610	3.8	2.1, 6.9		2.6	1.4, 4.8		1.8	1.0, 3.2	
> 2.610	9.0	5.3, 15.6		5.4	2.9, 9.9		2.8	1.5, 5.2	
β-HCH									
≤ 0.288	1.0		<0.001	1.0		<0.001	1.0		<0.001
0.289-0.670	1.4	0.7, 2.6		1.1	0.6, 2.1		1.0	0.5, 1.7	
0.671-1.547	3.9	2.2, 6.6		2.3	1.3, 4.2		1.7	1.0, 3.0	
> 1.547	7.9	4.8, 13.1		4.2	2.3, 7.6		2.4	1.3, 4.4	
PCB 118									
≤ 0.060	1.0		<0.001	1.0		<0.001	1.0		0.007
0.060-0.135	1.1	0.7, 1.9		1.0	0.6, 1.7		1.0	0.6, 1.6	
0.135-0.242	1.9	1.2, 3.0		1.2	0.7, 1.9		1.0	0.7, 1.6	
> 0.242	4.3	2.9, 6.3		2.1	1.4, 3.1		1.6	1.1, 2.3	
PCB 138									
≤ 0.258	1.0		<0.001	1.0		0.009	1.0		0.001 [a]
0.259-0.451	1.4	0.8, 2.4		1.0	0.6, 1.7		0.8	0.5, 1.4	
0.452-0.722	3.0	1.9, 4.8		1.4	0.9, 2.4		1.3	0.8, 2.0	
> 0.722	4.6	3.0, 7.1		1.7	1.0, 2.7		1.7	1.1, 2.6	
PCB 153									
≤ 0.361	1.0		<0.001	1.0		0.016	1.0		0.005 [a]
0.362-0.626	1.3	0.8, 2.2		1.0	0.6, 1.6		0.9	0.5, 1.5	
0.627-0.978	3.0	1.9, 4.6		1.4	0.8, 2.4		1.2	0.7, 1.9	
> 0.978	4.3	2.8, 6.6		1.6	0.9, 2.6		1.6	1.0, 2.6	
PCB 180									
≤ 0.314	1.0		<0.001	1.0		0.195 [a]	1.0		0.003 [a]
0.315-0.503	1.9	1.1, 3.3		1.1	0.7, 2.0		1.0	0.6, 1.7	
0.504-0.783	3.5	2.2, 5.7		1.6	0.9, 2.7		1.7	1.0, 2.7	
> 0.783	4.5	2.9, 7.2		1.4	0.8, 2.5		1.8	1.1, 3.0	
Sum of PCBs									
≤ 1.03	1.0		<0.001	1.0		0.019	1.0		0.001 [a]
1.04-1.76	1.7	1.0, 2.8		1.1	0.6, 1.9		0.9	0.6, 1.6	
1.76-2.72	3.0	1.9, 4.8		1.3	0.8, 2.2		1.0	0.6, 1.7	
> 2.73	4.8	3.1, 7.6		1.6	1.0, 2.8		1.7	1.0, 2.7	

Abbreviations: CI, confidence interval; PR, prevalence ratio.

Model 1: adjusted for age, sex, cigarette smoking, alcohol consumption and physical activity.

Model 2: further adjusted for body mass index.

Unless otherwise specified, *P* derived from multivariate analogue of Mantel's extension test for linear trend.

[a] Wald test.

Article 3

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RESEARCH ARTICLE

Number of Persistent Organic Pollutants Detected at High Concentrations in Blood Samples of the United States Population

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Abstract

Human exposure to environmental chemicals as persistent organic pollutants (POPs) is usually assessed considering each pollutant individually, with little attention to concentrations of mixtures in individuals or social groups. Yet, it may be relatively common for humans to have low and high concentrations of numerous POPs. The study objectives were to analyze the number of POPs detected per person at high concentrations in the U.S. population, and the associations between such type of indicators and socioeconomic factors as gender, race / ethnicity, education, and poverty level. From 91 POPs analyzed in serum samples of 4,739 individuals in three subsamples of the National Health and Nutrition Examination Survey (NHANES) 2003–2004 (the last period with valid updated individual data for the compounds considered in the present study), we computed the number of POPs whose serum concentrations were above selected cutoff points. POPs included were 13 organochlorine compounds (OCs), 10 polybrominated diphenyl ethers (PBDEs), the polybrominated biphenyl (PBB) 153, 38 polychlorinated biphenyls (PCBs), 17 polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDDs/Fs), and 12 perfluorinated compounds (PFCs). Over 13% of participants had ≥10 of the 37 most detected POPs each at a concentration in the top decile (P90). Over 30% of subjects with total toxic equivalency (TEQ) ≥P75, had ≥10 of 24 POPs not included in TEQ calculations at concentrations ≥P90. Compared to non-Hispanic whites, the adjusted odds ratio of having ≥10 of the 37 POPs at P90 was 9.2 for non-Hispanic blacks and 0.18 for Mexican Americans. Poverty, body mass index, age, and gender were also independently associated with having ≥10 POPs in the top decile. More than one tenth of the US population may have ≥10 POPs each at concentrations in the top decile. Such pattern is nine times more frequent in Non-Hispanic blacks and four times less frequent in Mexican Americans than in non-Hispanic whites.

Competing Interests: The authors have declared that no competing interests exist.

Abbreviations: β-HCH, β-hexachlorocyclohexane; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CI, confidence interval; GM, geometric mean; HBM, Human Biomonitoring; LOD, limit of detection; NHANES, National Health and Nutrition Examination Survey; nPhc, number of POPs detected per person at high concentrations; PBBs, polybrominated biphenyls; PBDEs, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzo-*p*-dioxins; PCDFs, polychlorinated dibenzofurans; PFCs, perfluorinated compounds; Phc, POPs at high concentrations; PIR, family's total income divided by the family size-specific poverty threshold income; POP, persistent organic pollutant; OCs, organochlorine compounds; OR, odds ratio; TEQ, total toxic equivalency.

Introduction

There is abundant evidence worldwide on lifelong human contamination from mixtures of environmental chemicals as persistent organic pollutants (POPs) [1–7]; yet, the vast majority of studies report each pollutant individually, with little attention to concentrations of mixtures in individual persons or social groups. Thus, the complex features of such internal, body contamination remain unsatisfactorily characterized. Biomonitoring surveys, for instance, do not integrate the number of compounds detected per person and the concentration of each compound [1,4–6,8–12]. Possible health effects of POPs include a variety of developmental, metabolic, neurodegenerative, and neoplastic disorders [5,8,9,10,12–24]. Reasonable concerns exist about such effects at low concentrations; such issues can be integrated with the fact that it is common for humans to have mixtures of POPs at low and high concentrations [6,8,12].

Approaches to these issues include 'Environment-Wide Association Studies' (EWAS), and analyses of concentrations of POPs combined, using estimates of total body burden, or different sums of concentrations [24–27]. Efforts to improve exposure assessment must continue: not only to advance etiologic studies and risk assessment, but also to foster knowledge on the characteristics of human chemical contamination itself. Such knowledge is a recognized right of citizens in democratic societies; it is also essential to evaluate the impacts of health, industrial, and related policies [1,5,8,10,28,29]. Indeed, the sources and pathways of exposure to pollutants are socioeconomic and cultural. Thus, strong relationships exist between concentrations of individual POPs and social factors, including income, education, and race / ethnicity [1,30–39]. Unfortunately, such relationships have seldom been analyzed integrating several compounds and their concentrations.

Recently, a set of indicators that integrate the number of compounds detected per person and their corresponding concentrations was proposed, including the number of compounds detected at high concentrations. The analyses were based on the general population of Catalonia, Spain [12]. Because studies in the U.S. on combinations of POPs and other chemicals raised relevant questions about the levels and effects of such mixtures [8,9,16,40–44], and because of the relatively large size of the U.S. population, we aimed at applying the methodology [8] to the U.S. general population.

Therefore, the objectives of the present study were to analyze the number of POPs detected per person at high concentrations (nPhc) in the U.S. National Health and Nutrition Examination Survey (NHANES), and to analyze the associations between such indicator and main socioeconomic factors. Our main hypotheses were that most of the U.S. population would have POPs at low and high concentrations, and that sociodemographic factors (such as age, gender, body mass index (BMI), parity, or income) that are often related with POP concentrations when each compound is analyzed individually [2,12,13,30,34,35] would continue to show similar relationships when the POPs are jointly analyzed [12].

Materials and Methods

Data

Conducted by the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS), the National Health and Nutrition Examination Survey (NHANES) collects nationally representative environmental biomonitoring data from about 5,000 annual participants in each two-year cycle [2,45–48]. NHANES is a publicly available data set, and all participants provide written informed consent, consistent with approval by the NCHS Institutional Review Board. Ethical approval for use of NHANES data is not required as it is anonymized. We examined data from NHANES laboratory and demographic files corresponding to

2003–2004, which is the last period with valid updated individual data for compounds considered in the present study [45,47]. Except for perfluorinated compounds (PFCs), in NHANES 2005–2006 and 2007–2008 serum concentrations of POPs were measured using weighted pooled-samples, and no data for POPs have been published for NHANES 2009–2010 and 2011–2012 [47]. Therefore, it is not possible to calculate the number of POPs detected per person at high concentrations in more recent periods.

In each NHANES, most chemicals or their metabolites were measured in serum samples from random subsamples of about 2,500 participants aged 12 years and older. The chemicals' concentrations were analyzed by CDC's Environmental Health Laboratory using mass spectrometry and related methods [2,46]. Data for 91 POPs were analyzed, including: 13 organochlorine compounds (OCs) and their respective metabolites; 10 polybrominated diphenyl ethers (PBDEs); the polybrominated biphenyl (PBB) 153; 29 non-dioxin-like polychlorinated biphenyls (PCBs); 3 dioxin-like coplanar PCBs; 6 dioxin-like mono-ortho-substituted PCBs; 10 polychlorinated dibenzofurans (PCDFs); 7 polychlorinated dibenzo-p-dioxins (PCDDs); and 12 PFCs [46] (S1 Table). Thus, serum concentrations of lipophilic chemicals (e.g., dioxins and PCBs) are presented per gram of total lipid (better reflecting the amount stored in body fat) [1,2,12,31,46]; results of analyses per whole weight of serum were similar and are not presented. Concentrations of PFCs, non-lipophilic POPs, are shown per liter of serum. Limits of detection (LOD) for whole weight POP concentrations were different for each serum sample of each person [45,46], while LODs for lipid-adjusted concentrations were the same values for all samples and individuals (values ranged from 3.8 pg/g of lipid and 7.8 ng/g of lipid) [2,45,46]. Finally, LODs for PFCs ranged from 0.1 to 1.0 μg/L [46].

We considered important covariates as age, sex, race/ethnicity (non-Hispanic white, henceforth 'White'; Mexican American; non-Hispanic black, henceforth 'Black'; other Hispanic; and other), education (categorized to less than high school diploma, high school diploma, and greater than high school diploma), and body mass index (BMI) in kg/m^2. To estimate the participants' income we used the family's total income divided by the family size-specific poverty threshold income ratio (PIR), with two categories: "Low" income (PIR < 2), and "High" income (PIR ≥ 2) [43,45]. In women, we also considered the number of pregnancies resulting in live births, and the number of children breastfed $\geq$1 month (henceforth, 'breastfeeding') [45].

Statistical analyses

The present study included 4,739 participants $\geq$20 years old (for all adults 85 years and older, age was coded at 85 years to reduce the risk of disclosure) [45]. They came from three subsamples (S2 Table). There were no significant differences between the 1,610, 1,585 and 1,544 participants of each subsample in a broad range of sociodemographic variables (including sex, race/ethnicity, educational level, PIR, BMI, number of pregnancies or breastfeeding) (S2 Table).

We imputed the unmeasured POP values by the median serum concentration of each POP according to age, sex, race/ethnicity, PIR, BMI, and, in women, number of pregnancies [49,50]. In 79 POPs the imputation was performed using concentrations adjusted by lipids, and in 12 PFCs, in μg/L. We calculated the total toxic equivalency (TEQ) [51,52] for 26 POPs: 3 dioxin-like coplanar PCBs, 6 dioxin-like mono-*ortho*-substituted PCBs, 10 PCDFs, and 7 PCDDs [45,46]. To compare POP concentrations in the present study and pooled concentrations in NHANES 2005–2006 and 2007–2008 we computed concentrations of POPs by sex, race/ethnicity and age groups [46,47]. We also compared PFC serum concentrations in the present study and concentrations in NHANES of 2005–2006, 2007–2008, 2009–2010 and 2011–2012 [46,47]. Descriptive values for POP concentrations imputed are summarized in S1 Table, sorted from the highest to the lowest percentage of detection.

Based on previous work by Porta et al. (2012) [12], we calculated the number of POPs detected in each person at high concentrations (nPhc) as follows: for each subject we added the number of POPs whose serum concentrations were equal to or greater than a selected cutoff point [12]. To be conservative, in the main analyses we included only 37 POPs that had been detected (each) in >85% of the study subjects (henceforth called the most prevalent POPs). Such 37 POPs were: 2 OCs, 3 PBDEs, PBB 153, 23 non-dioxin-like PCBs, 3 dioxin-like PCBs, one PCDD [1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin (HpCDD)], and 4 PFCs (S1 Table). Ancillary analyses included 50 compounds detected in >50% of subjects. Finally, other analyses included all 91 POPs, with quartiles, quintiles and deciles defined after the imputation of concentrations (S1 Table) [12]. As usual, serum concentrations of POPs did not follow a normal distribution [31], and the increment of concentrations in the highest percentiles was very strong (e.g., for *p*,*p*'-DDE the increment of concentrations between P75 and P90 was of 2.14 times, and between P90 and the maximum it was 14.5 times; for PCB 153 the corresponding figures were 53% and 12.36 times, respectively) (S1 Table).

We defined 'high concentrations' using compound- and population-specific percentiles, based on actual POP distributions, as cutoff points [12,43,44]. In the main statistical analyses the cutoff point used was percentile 90 (P90), the upper decile (S1 Table).

Univariate statistics were computed as customary [53,54]. The highest correlations were observed between PCB congeners 170 and 180, 138 and 153, 146 and 153 (all Spearman's $\rho > 0.982$ and p's < 0.001). Fisher's exact test for homogeneity was applied to assess the relationship between two categorical variables. For comparisons between continuous variables ANOVA, Kruskal-Wallis, and Mann-Whitney's *U* tests were used. When a tendency was observed, Mantel–Haenszel's χ^2 test and Jonckheere-Terpstra test for linear trend were used.

To estimate the magnitude of associations between the socioeconomic factors and the number of most prevalent POPs with concentrations in the upper decile, multivariate-adjusted odds ratios (ORs) and their corresponding 95% confidence intervals (CI) were calculated by unconditional logistic regression with progressive degrees of adjustment [55]. The main effects of all predictors were independently explored in the base models, and final models were adjusted for age, gender, BMI, race/ethnicity and poverty income, in accordance with the nature of the variables and the study objectives. The number of POPs with concentrations in the upper decile was tested in different regression models using 3 different categorizations (all dichotomous): ≥1 POP (vs. no Phc), ≥6 POPs (vs. <6 POPs) and ≥10 POPs (vs. <10 POPs). Categorical ordinal variables were analyzed for a linear dose–response relation through the multivariate analogue of Mantel's extension test; when a linear trend was not apparent, the probability test was used. Analyses were conducted using SPSS version 18 (SPSS, Armonk, NY, USA, 2009).

Results

Over 67% of the 4,739 participants (73.8% of men and 61.1% of women) had one or more of the 37 most prevalent POPs at concentrations equal to or greater than the 90th percentile (≥P90), while 38.0% had ≥3 POPs, and over 13% had ≥10 POPs each in such top decile (Table 1 and Table 2). Over 37% of subjects had ≥10 compounds each at concentrations in the top quartile (≥P75) (S3 Table). The number of POPs detected per person ranged between 23 and 74, with an average of 49.7. Over 57% of participants had ≥50 POPs detected (S1 Fig).

In over 45% of participants who had only one POP at high concentrations (Phc) (≥P90), this chemical was an OC, a PBDE or PBB 153. By contrast, among subjects with numerous Phc, the majority of such compounds were PCBs. For instance, when the nPhc was ≥3, more than 40% of these compounds were PCBs and HpCDD.

Table 1. Characteristics of subjects with and without ten or more POPs with concentrations in the upper decile.

			≥10 POPs with concentrations in the upper decile				
Characteristics	**Total**		**Yes**		**No**		
	N (%)		**N (%)**		**N (%)**		***p*-value**
Total	4,739	(100)	619	(13.1)	4,120	(86.9)	
Gender							<0.001
Women	2,467	(52.1)	271	(11.0)	2,196	(89.0)	
Men	2,272	(47.9)	348	(15.3)	1,924	(84.7)	
Age (years)	49.0		70.0		45.0		<0.001[a]
Race/ethnicity							<0.001
Non-Hispanic white	2,539	(53.6)	282	(11.1)	2,257	(88.9)	
Mexican American	951	(20.1)	21	(2.2)	930	(97.8)	
Non-Hispanic black	948	(20.0)	277	(29.2)	671	(70.8)	
Other Hispanic	140	(3.0)	19	(13.6)	121	(86.4)	
Other	161	(3.4)	20	(12.4)	141	(87.6)	
Educational level							<0.001
College or above	2,138	(45.2)	243	(11.4)	1,895	(88.6)	
High school	1,193	(25.2)	140	(11.7)	1,053	(88.3)	
< High school	1,399	(29.6)	232	(16.6)	1,167	(83.4)	
Poverty income ratio							0.036
>2	2,394	(53.6)	289	(12.1)	2,105	(87.9)	
≤2	2,075	(46.4)	295	(14.2)	1,780	(85.8)	
Body mass index (kg/m^2)	27.4		26.7		27.6		0.004[a]
Underweight (<18.5)	70	(1.5)	10	(14.3)	60	(85.7)	<0.001[b]
Normal weight (18.5–24.9)	1,406	(30.3)	193	(13.7)	1,213	(86.3)	
Overweight (25.0–29.9)	1,630	(35.1)	248	(15.2)	1,382	(84.8)	
Obese (≥30)	1,538	(33.1)	154	(10.0)	1,384	(90.0)	
Pregnancy[c]							0.741
No	93	(5.0)	12	(12.9)	81	(87.1)	
Yes	1,768	(95.0)	208	(11.8)	1,560	(88.2)	
No. of pregnancies resulting in live births[c]	2.00		3.00		2.00		<0.001[a]
Breastfeeding[d,e]							0.450
No	78	(7.4)	6	(7.7)	72	(92.3)	
Yes	975	(92.6)	106	(10.9)	869	(89.1)	
No. of children breastfed[d,e]	2.00		2.00		2.00		0.144[a]

Values for age, body mass index, number of pregnancies resulting in live births and number of children breastfed are median.

Unless otherwise specified, *p*-Value derived from Fisher's exact test (two-tail).

[a] Mann-Whitney's *U* test.

[b] Without participants <18.5 kg/m^2 of body mass index.

[c] Women only.

[d] Only women with ≥1 pregnancies resulting in live births.

[e] Breastfed ≥1 month.

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The median age of participants with ≥10 POPs at high concentrations (Phc) was 70 years, while for participants with <10 Phc it was 45 years, and for participants without any Phc, 39 years. Over 11% of Whites, 2.2% of Mexican Americans, and 29.2% of Blacks had ≥10 Phc (p <0.001) (Table 1). Subjects with ≥10 Phc had a slightly lower median BMI than subjects with <10 Phc (26.7 Kg/m^2 and 27.6 Kg/m^2, respectively, p for trend = 0.004) (Table 1).

Table 2. Characteristics of the individuals with one or more POPs with concentrations in the upper decile.

			No. of POPs with concentrations in the upper decile										
Characteristics	**Total**		**≥10**		**6 to 9**		**3 to 5**		**2**		**1**		
	N (%)		**N (%)**		**N (%)**		**N (%)**		**N (%)**		**N (%)**		***p*-value**
Total	3,184	(67.2)	619	(19.4)	375	(11.8)	807	(25.3)	560	(17.6)	823	(25.8)	
(Cumulative %)				(19.4)		(31.2)		(56.6)		(74.2)		(100)	
Gender													<0.001
Women	1,507	(47.3)	271	(18.0)	135	(9.0)	406	(26.9)	272	(18.0)	423	(28.1)	
Men	1,677	(52.7)	348	(20.8)	240	(14.3)	401	(23.9)	288	(17.2)	400	(23.9)	
Age (years)	57.0		70.0		60.0		64.0		46.0		43.0		<0.001[a]
Race/ethnicity													<0.001[b]
Non-Hispanic white	1,780	(55.9)	282	(15.8)	233	(13.1)	530	(29.8)	270	(15.2)	465	(26.1)	
Mexican American	581	(18.2)	21	(3.6)	76	(13.1)	159	(27.4)	154	(26.5)	171	(29.4)	
Non-Hispanic black	629	(19.8)	277	(44.0)	40	(6.4)	76	(12.1)	93	(14.8)	143	(22.7)	
Other Hispanic	79	(2.5)	19	(24.1)	11	(13.9)	17	(21.5)	16	(20.3)	16	(20.3)	
Other	115	(3.6)	20	(17.4)	15	(13.0)	25	(21.7)	27	(23.5)	28	(24.3)	
Educational level													<0.001
College or above	1,403	(44.2)	243	(17.3)	168	(12.0)	339	(24.2)	248	(17.7)	405	(28.9)	
High school	790	(24.9)	140	(17.7)	103	(13.0)	210	(26.6)	144	(18.2)	193	(24.4)	
< High school	984	(31.0)	232	(23.6)	103	(10.5)	256	(26.0)	168	(17.1)	225	(22.9)	
Poverty income ratio													0.002
>2	1,608	(53.4)	289	(18.0)	189	(11.8)	389	(24.2)	295	(18.3)	446	(27.7)	
≤2	1,406	(46.6)	295	(21.0)	175	(12.4)	365	(26.0)	240	(17.1)	331	(23.5)	
Body mass index (kg/m^2)	27.2		26.7		28.1		26.8		27.6		27.8		0.084[a]
Pregnancy[c]													0.447[b]
No	51	(4.4)	12	(23.5)	4	(7.8)	9	(17.6)	8	(15.7)	18	(35.3)	
Yes	1,106	(95.6)	208	(18.8)	97	(8.8)	306	(27.7)	193	(17.5)	302	(27.3)	
No. of pregnancies resulting in live births[c]	3.00		3.00		2.00		3.00		3.00		2.00		<0.001[a]
Breastfeeding[d,e]													0.067
No	47	(7.4)	6	(12.8)	3	(6.4)	11	(23.4)	7	(14.9)	20	(42.6)	
Yes	592	(92.6)	106	(17.9)	42	(7.1)	180	(30.4)	104	(17.6)	160	(27.0)	
No. of children breastfed[d,e]	2.00		2.00		2.00		2.00		2.00		2.00		0.001[a]

Values for age, body mass index, number of pregnancies resulting in live births and number of children breastfed are median.

Unless otherwise specified, *p*-Value derived from Mantel–Haenszel's χ^2 test for linear trend.

[a] Jonckheere-Terpstra test for linear trend.

[b] Fisher's exact test (two-tail).

[c] Women only.

[d] Only women with ≥1 pregnancies resulting in live births.

[e] Breastfed ≥1 month.

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Women with ≥10 Phc had a higher number of pregnancies resulting in live births than women with <10 Phc (age-unadjusted medians: 3.0 and 2.0, respectively, *p* for trend <0.001). There were significant differences in the nPhc by sex, age, BMI, race/ethnicity, educational level, PIR, and, in women, by number of pregnancies, and breastfeeding (Table 2).

Multivariate analyses adjusted by age, gender and BMI showed that, as compared to Whites, Blacks had an odds ratio (OR) = 10.1 of having ≥10 Phc, whilst for Mexican Americans the OR was 0.2 (both *p's* <0.001) (Table 3). When further adjusted by poverty income the OR for Blacks decreased to 9.2, and for Mexican Americans to 0.18 (both *p's* <0.001). Differences

Table 3. Associations between sociodemographic characteristics and having ten or more POPs with concentrations in the upper decile.

	Model 1			Model 2			Model 3		
Characteristics	**OR[a]**	**(95% CI)**		**OR[a]**	**(95% CI)**		**OR[a]**	**(95% CI)**	
Gender									
Women	1.00			1.00			1.00		
Men	1.54***	(1.28,	1.85)	1.74***	(1.42,	2.13)	1.73***	(1.40,	2.13)
Age (years)	1.06***	(1.05,	1.07)	1.08***	(1.07,	1.09)	1.08***	(1.07,	1.09)
Race/ethnicity									
Non-Hispanic white	1.00			--			1.00		
Mexican American	0.22***	(0.14,	0.35)				0.18***	(0.11,	0.30)
Non-Hispanic black	10.11***	(7.82,	13.1)				9.18***	(7.05,	12.0)
Other Hispanic	3.17***	(1.78,	5.63)				2.64**	(1.43,	4.85)
Other	1.94*	(1.11,	3.37)				1.55	(0.84,	2.88)
Educational level									
College or above	1.00			1.00			1.00		
High school	0.91	(0.72,	1.15)	0.96	(0.75,	1.24)	0.96	(0.74,	1.25)
< High school	1.04	(0.84,	1.28)	1.22	(0.95,	1.55)	1.14	(0.88,	1.49)
Poverty income ratio									
>2	1.00			1.00			--		
≤2	1.13	(0.94,	1.37)	1.24*	(1.00,	1.53)			
Body mass index (kg/m^2)									
Normal weight	1.00			1.00			1.00		
Overweight	0.96	(0.77,	1.20)	0.96	(0.75,	1.22)	1.02	(0.79,	1.30)
Obese	0.74*	(0.58,	0.94)	0.57***	(0.44,	0.75)	0.58***	(0.44,	0.77)
Pregnancy[b]									
No	1.00			1.00			1.00		
Yes	0.48*	(0.24,	0.99)	0.57	(0.24,	1.38)	0.60	(0.25,	1.46)
No. of pregnancies resulting in live births[b]	0.99	(0.92,	1.06)	0.97	(0.89,	1.06)	0.97	(0.88,	1.06)
Breastfeeding[c,d]									
No	1.00			1.00			1.00		
Yes	1.15	(0.46,	2.87)	1.36	(0.48,	3.84)	1.30	(0.46,	3.68)
No. of children breastfed[c,d]	0.88	(0.76,	1.01)	0.97	(0.82,	1.14)	0.96	(0.81,	1.13)

Model 1: adjusted by age, gender and body mass index.

Model 2: adjusted by age, gender, body mass index and race/ethnicity.

Model 3: adjusted by age, gender, body mass index, race/ethnicity and poverty income.

[a] *p*-Value derived from Wald's test.

[b] Women only.

[c] Only among women with ≥1 pregnancies resulting in live births and, in the three models, further adjusted by such number of pregnancies.

[d] Breastfed ≥1 month.

* $p \leq 0.05$

** $p \leq 0.01$

*** $p \leq 0.001$.

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between Blacks and Whites were larger in the older age groups / birth cohorts, and null in the younger ones (p for interaction <0.001) (Fig 1).

For PIR ≤2, or "Low" income (vs. PIR>2 or "High" income) the OR of having ≥10 Phc was 1.13 (p >0.05) when the model was adjusted by age, gender and BMI, and 1.24 (p = 0.045) when further adjusted by race/ethnicity. The OR for obesity (vs. normal weight) was 0.74 (p for trend = 0.015) in the model adjusted by age and gender, and, when further adjusting by race/

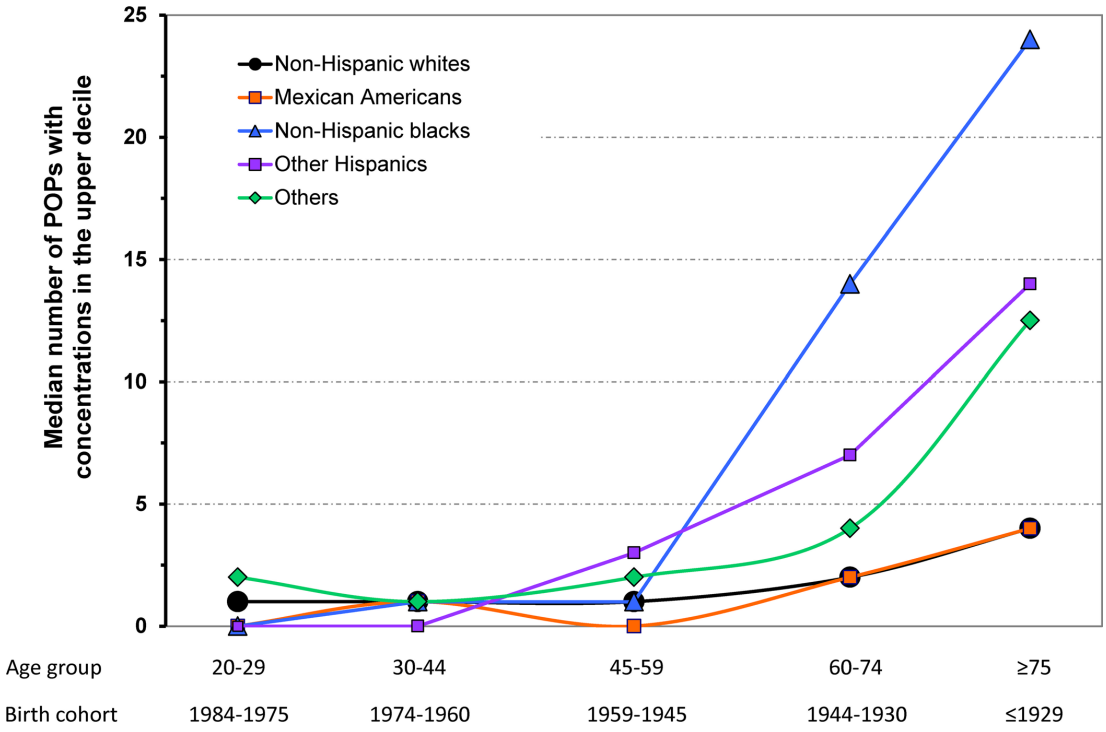

Fig 1. Median number of POPs with concentrations in the upper decile by age/birth cohort and race/ethnicity.

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ethnicity and poverty income, it was 0.58 (p for trend <0.001) (Table 3). In women, pregnancy halved the probability of having ≥10 Phc when adjusting by age and body mass index (OR = 0.48, p = 0.048) (Table 3).

In models assessing the relationship between sociodemographic factors and the probability of having ≥1 POPs at concentrations ≥P90 (vs. not having POPs with concentrations ≥P90), adjusted by age, gender and BMI, the OR for Blacks (vs. Whites) was 1.10 (p = 0.266) and for Mexican Americans, 0.74 (p <0.001). When further adjusted by race/ethnicity, the OR for PIR≤2 (vs. PIR>2) was 1.17 (p = 0.026); and for obesity (vs. normal weight), 0.73 (p for trend <0.001 for BMI) (S4A Table). The corresponding figures for the probability of having ≥6 POPs at concentrations ≥P90 were 3.37 for Blacks and 0.51 for Mexican Americans (both p <0.001), 1.24 for PIR≤2 (p <0.01), and 0.91 for obesity (vs. normal weight) (p for trend = 0.353).

Because of the influence of PCBs in the previous results, we also analyzed associations among sociodemographic factors and the likelihood of having ≥1 of 6 POPs other than PCBs (i.e., OCs, PBDEs, and PBB 153 detected ≥85% of subjects) at high concentrations (S4B Table). Contrary to what was observed when all compound families were considered, for Blacks (vs. Whites) the OR of having ≥1 of such POPs was 0.76, and for Mexican Americans, 1.41, adjusting by age, gender and BMI (both p's <0.01). The corresponding OR for PIR≤2 was 1.19 (p = 0.011), and for obesity, 0.82 (p for trend = 0.013). When further adjusting by race/

ethnicity, the OR for PIR≤2 was 1.15 ($p = 0.038$), and for obesity, 0.80 (p for trend = 0.006) (S4B Table).

The geometric mean (GM) of nPhc doubled when the cutoff P75 was used instead of P90 (see S3 Table). For the cutoff P75 the percentage of subjects with ≥10 Phc was 37.5 for POPs detected in ≥85% of participants, and 45.2 for POPs detected in ≥50% of participants. However, the percentage of subjects without any Phc decreased slightly when the number of POPs included in the analyses increased.

In the 1,183 participants with the highest total TEQ concentrations (≥P75 of the distribution of total TEQ concentrations [i.e., ≥26.68 pg WHO-TEQ/g of lipid]), the percentage of subjects with ≥10 Phc was about twice the corresponding figure observed when all 4,739 participants were considered. Over 90% of the 1,183 subjects had ≥1 POPs a) not included in TEQ calculations, and b) with concentrations ≥P90. Over 30% had ≥10 such POPs, and almost 7% had ≥20 such POPs. Spearman's ρ coefficient between the total TEQ concentration and nPhc (considering the 24 POPs not included in TEQ calculations, and the P90 in all participants for high concentrations) was 0.475 ($p < 0.001$).

Over 43% of participants had TEQ concentrations ≥21 pg WHO-TEQ/g of lipid, a biomonitoring equivalent value (see Discussion). Taking into account health-based guidelines for other compounds, less than 1% of participants had concentrations of hexachlorobenzene ≥47 ng/g of lipid, and concentrations for the sum of *p,p'*-DDT and *p,p'*-DDE ≥5,000 ng/g of lipid. Two subjects had concentrations of BDE 99 ≥520 ng/g of lipid; 2 participants (aged <40 years) had concentrations ≥700 ng/g of lipid for the sum of 35 PCBs (without dioxin-like coplanar PCBs), and 6 participants (aged ≥40 years) had concentrations ≥1,800 ng/g of lipid. 10% of participants had concentrations for the sum of PCBs 138, 153 and 180 ≥216 ng/g of lipid. Only 4 participants had concentrations for the sum of these three PCBs ≥900 ng/g of lipid.

We also compared the concentrations of POPs detected in ≥85% of the participants in the present study (2003–2004), and their respective pooled concentrations for the NHANES periods 2005–2006 and 2007–2008. The concentrations of some POPs in the present study were only slightly higher than in subsequent periods; they were not higher or not statistically significant in the case of *p,p'*-DDE, PBB 153 and some PBDEs compounds (S5A Table). For 3 PFCs, concentrations in 2003–2004 were similar to concentrations in 2005–2010, and slightly higher than concentrations in 2011–2012 (S5B Table).

Discussion

More than half of the study population had concentrations in the top decile of ≥1 of the most commonly detected POPs, 38% had ≥3, and over 13% had ≥10 POPs each in their respective top decile. Findings are thus partly in contrast with the notion that human POP concentrations are low in the vast majority of the population [5,12]: such view holds only when each individual compound is looked at separately, but not when the individual human is of concern.

Median age of participants with ≥10 of most prevalent POPs at high concentrations was 70 years, while median age of participants without any Phc was 39 years. This could be due to biological aging effects or to birth cohort effects. Furthermore, the median age of participants without any Phc was near the median age of participants with 1 or 2 Phc. There were also significant differences in the nPhc by gender, race/ethnicity, educational level, PIR, BMI, parity, and breastfeeding. These results are in accordance with our main hypotheses (most of the U.S. population had POPs at low and high concentrations; sociodemographic factors related with each POP concentration showed similar relationships for the joint analysis of POPs).

Race/ethnicity was the sociodemographic factor most associated with a higher nPhc: Blacks had 9 times a greater chance of having ≥10 Phc than Whites, and Mexican Americans over 4

times a lower chance. The nPhc indicator not only shows that Blacks have higher body concentrations of POPs than Whites (or Mexican Americans lower concentrations), but it also quantifies how many POPs are in a specific high concentration range. The NHANES questionnaires had a large number of sociodemographic items; in this study, we used the sociodemographic factors that were available and related with body concentrations of POPs [12,32,35,39,45,46].

Results of unconditional logistic regression models for ≥1 Phc, ≥6 Phc, and ≥10 Phc (vs. no Phc, <6 Phc, and <10 Phc, respectively) in the subsample without imputations and PCBs, PCDDs/Fs analyzed by the sociodemographic factors (to assess the possible biases of imputations), were similar to results of models with imputations, except in some models for gender, which was not statistically significant, although ORs were similar.

Most studies found an inverse association between PCB levels in blood and BMI [56–58], as in the present analyses for all participants and 37 POPs.

Also rarely if ever noted before: high percentages of subjects with TEQ ≥P75 (≥26.68 pg WHO-TEQ/g of lipid) had numerous POPs not included in TEQ calculations, at high concentrations. Findings suggest that studies using TEQ measures could be even more relevant if they additionally assessed subgroups with high nPhc. Results do not imply that nPhc and related exposure indicators are preferable to other indicators to evaluate associations between POP mixtures and clinical outcomes; nPhc indicators just provide a different and complementary approach to indicators such as the sum of concentrations of PCBs [48,59–64], or the sum of orders of POPs [65].

Our goal was not to evaluate whether individuals have increased health risks due to multiple compounds at high concentrations, nor to assess the role of modes and mechanisms of action, but to propose a new and useful approach for exposure assessment. However, severe adverse health effects have been reported for concentrations similar to or lower than P90 in the present study [5,9,11,15,16,66–69]; e.g., in an NHANES study the OR of having diabetes for a concentration of ≥60.2 ng/g lipid of PCB 153 was 5.9 (95% CI = 3.0–11.9) [66]; in the present study the P90 for PCB 153 was 79.8 ng/g lipid. P90 of concentrations of individual PCBs in NHANES is as high or higher than in other countries with population-based surveys as Canada and Australia [6,70]. For *p,p'*-DDE and *β*-hexachlorocyclohexane (*β*-HCH), it is also as high or higher than in Canada, Australia and Germany [6,70].

In this study, over 43% of participants had TEQ concentrations ≥21 pg WHO-TEQ/g of lipid, which is the biomonitoring equivalent value published for dioxin TEQ, a health-risk based screening guideline [71]. Also, in the present study 10% of participants had concentrations for the sum of PCBs 138, 153 and 180 equal to or greater than the Human Biomonitoring level-I (HBM-I), which is 3 μg/L plasma or, when accounting for lipids, 216 ng/g lipid for the present study. HBM-I is a health-related exposure limit recommended for PCBs by the German Human Biomonitoring Commission [59–62]. For compounds considered in the present study, other biomonitoring equivalents values are only available for hexachlorobenzene, the arithmetic sum of *p,p'*-DDT and *p,p'*-DDE, the sum of 35 PCBs, and BDE 99 [59,71,72]; for these compounds very few subjects had concentrations above the corresponding biomonitoring equivalents in this study. To our knowledge, no current health-related limit values are available for the rest of PBDEs or for PFCs [59–61,71,72]. Although there are regulations and guidelines for other pollutants (e.g. lead, mercury, cadmium and other metals) and for POPs in air, soil, water and food (e.g., tolerable daily intakes), there are hardly any other guidelines for human POP concentrations to define levels of concern than the ones mentioned above [59–62,71].

Beyond findings on concentrations of individual compounds, the indicators illuminate a crucial–and usually overlooked–feature of human contamination by POPs: the frequency of mixtures of POPs at high concentrations. The approach could naturally be developed to integrate other pollutants of concern.

Importantly, 2003–2004 is the last period of NHANES in which the individual concentration of each compound is available for each individual subject. In 2005–2006 and 2007–2008 serum concentrations of POPs (except PFCs) were measured in weighted pooled-samples (not in individual samples); no data were published for 2009–2010 and 2011–2012. Therefore, data to calculate the number of POPs detected per person at high concentrations in more recent periods are not available.

Concentrations of most POPs in 2003–2004 were only slightly higher than in more recent periods (Tables in S5 File). Virtually all major contemporary health effects of POPs will be influenced by concentrations experienced by human cohorts during several decades, not just by recent exposures. Furthermore, the nPhc can be fruitfully applied to analyze data from many periods and settings.

Different POPs were analyzed in participants of the three NHANES 2003–2004 subsamples; even in two of the three subsamples all selected POPs were not analyzed in all participants. Each sample, however, is valid; and it is efficient not to analyze all POPs in all participants [2,46]. For PFCs, the LODs were constant for each sample analyzed [46]. For the other 55 compounds, the LOD for the whole weight concentrations was different for each serum sample of each person [2]. When PCDD/Fs, PCBs, OCs, PBDEs, and PBB 153 concentrations were measured in serum lipid, LOD calculations were performed using the chemical concentration expressed per amount of lipid, and the LOD concentration expressed per amount of lipid was the highest LOD among all the individual samples analyzed [2,46]. LODs for lipid adjusted concentrations were highest compared to the LODs for the whole weight concentrations, and rates of detection were lower, than for whole weight concentrations; as a consequence, lipid adjusted results are more conservative (e.g., because there were less compounds detected in $\geq$85% of participants).

In the present study, some associations between nPhc and sociodemographic factors are quite influenced by the predominance of PCBs and HpCDD at high concentrations among subjects with $\geq$3 nPhc. The cutoff point for nPhc should be chosen with this issue in mind, while also avoiding a too high nPhc (e.g., because of lower detection rates of some POPs) [12].

Serum concentrations of POPs do not follow a normal distribution [31]. Values for P90 can be much higher than the P75 (e.g., for *p,p'*-DDE the P90 value was 2.14 times greater than P75, and for PCB 153 it was 53%). Such differences between highest concentrations minimize a possible misclassification of concentrations in $\geq$P90 or <P90 due to laboratory measurement errors [46]. The minimum percentage of participants with concentrations in the top decile of $\geq$1 POPs will be 10%, but such percentage will not necessarily, linearly, or indefinitely increase (nor approach 100%) as the number of compounds considered increases: the percentage of participants with concentrations of $\geq$1 POPs in the top decile is only partly positively influenced by the number of compounds considered; it is also inversely influenced by the magnitude of the correlations between the pairs of compounds, being highest when POPs are completely uncorrelated (for details see Suppl. Material of Porta et al., 2012) [12]. Therefore, the nPhc follows a distribution that is influenced by all the correlations between the pairs of compounds, and results may not be due to chance. Figure 1 of Supplemental Material of Porta et al., 2012 [12] shows different values for $\geq$1 by the number of POPs considered, and the values when the POPs were completely uncorrelated. For $\geq$10 POPs at high concentrations (rather than $\geq$1 POP) this situation is even more restrictive; when we focused on $\geq$10 POPs at high concentrations, it was statistically possible for the minimum percentage of participants with $\geq$10 POPs at high concentrations to be 0% (i.e., it was not statistically inevitable for that percentage to be 10%), since it is possible that highly-correlated sets of POPs comprise 9 or less POPs. Furthermore, such minimum percentage also depends on the number of POPs analyzed, the number of POPs in the top decile, and the number of participants included.

Conclusion

In summary, more than 13% of the US population may have ≥10 POPs each at concentrations in the top decile. This finding is not to be expected just on statistical grounds. High percentages of subjects with TEQ ≥P75 have numerous POPs not included in TEQ calculations, at high concentrations. The nPhc is related to race/ethnicity, age, and BMI. It is also likely to be related to other relevant social, environmental, and individual factors. The study findings foster knowledge on previously unknown characteristics of human chemical contamination in the US population. Such knowledge is a right of citizens, and could also be considered when evaluating the impacts of relevant public and private policies.

Supporting Information

S1 Fig. Percentage of participants according to number of POPs detected per person. (91 POPs analyzed, n = 4,739)
(PDF)

S1 Table. Limit of detection (LOD) and statistics of concentrations of 91 POPs for the 4,739 participants.
(DOCX)

S2 Table. Population characteristics by survey subsample.
(DOCX)

S3 Table. Frequency of subjects with high concentrations of the most detected POPs according to different definitions of 'high concentration'.
(DOCX)

S4 Table. S4ATable. Associations between sociodemographic characteristics and having one or more POPs with concentrations in the upper decile. S4B Table. Associations between sociodemographic characteristics and having one or more OCs, PBDEs and PBB 153 with concentrations in the upper decile.
(DOCX)

S5 Table. S5A Table. Serum pooled concentrations of POPs most detected for the three most recent NHANES Surveys periods analyzed. S5B Table. Serum concentrations of four perfluorinated compounds (μg/L) most detected for the most recent NHANES Surveys periods analyzed.
(DOCX)

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Author Contributions

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S1 Table. Limit of detection (LOD) and statistics of concentrations of 91 POPs for the 4,739 participants.

Persistent organic pollutant	Units of measurement	% ≥LOD	median	P75	P90	maximum
2,2',3,4,4',5' and 2,3,3',4,4',6-Hexachlorobiphenyl (PCB 138 & 158)	ng/g of lipid	100	23.50	36.30	58.90	773.0
2,3',4,4',5-Pentachlorobiphenyl (PCB 118)	ng/g of lipid	100	6.80	12.96	25.00	354.0
2,2',4,4',5,5'-Hexachlorobiphenyl (PCB 153)	ng/g of lipid	99.9	29.77	51.90	79.76	986.0
2,2',3,4,4',5,5'-Heptachlorobiphenyl (PCB 180)	ng/g of lipid	99.9	25.80	45.18	67.17	627.0
2,2',3,5'-Tetrachlorobiphenyl (PCB 44)	ng/g of lipid	99.9	1.94	2.40	3.30	85.40
2,4,4',5-Tetrachlorobiphenyl (PCB 74)	ng/g of lipid	99.9	5.50	11.60	19.22	180.0
p,p'-Dichlorodiphenyldichloroethene (DDE)	ng/g of lipid	99.9	370.0	737.0	1580.0	22900
2,2',4,4',5-Pentachlorobiphenyl (PCB 99)	ng/g of lipid	99.8	4.80	7.07	12.77	304.0
Perfluorooctane sulfonic acid (PFOS)	µg/L	99.8	20.50	25.50	35.20	435.0
Perfluorooctanoic acid (PFOA)	µg/L	99.8	3.65	4.70	6.20	77.20
2,2',3,3',4,4',5-Heptachlorobiphenyl (PCB 170)	ng/g of lipid	99.7	9.30	15.63	22.18	299.0
2,2',3,4',5,5',6-Heptachlorobiphenyl (PCB 187)	ng/g of lipid	99.6	6.86	12.50	18.95	158.0
Perfluorononanoic acid (PFNA)	µg/L	99.4	0.90	1.25	1.75	11.50
Perfluorohexane sulfonic acid (PFHxS)	µg/L	99.1	1.70	2.20	3.70	27.10
2,4,4'-Trichlorobiphenyl (PCB 28)	ng/g of lipid	99.1	5.02	5.53	7.66	237.0
2,2',4,5'-Tetrachlorobiphenyl (PCB 49)	ng/g of lipid	98.7	1.30	1.60	2.10	54.50
2,2',3,4',5,5'-Hexachlorobiphenyl (PCB 146)	ng/g of lipid	98.6	3.50	5.84	9.23	86.75
Hexachlorobenzene	ng/g of lipid	98.5	15.90	19.00	22.45	174.0
2,2',5,5'-Tetrachlorobiphenyl (PCB 52)	ng/g of lipid	98.0	2.70	3.30	4.55	133.0
2,2',3,3',4,4',5,6' and 2,2',3,4,4',5,5',6-Octachlorobiphenyl (PCB 196 & 203)	ng/g of lipid	97.6	4.57	8.00	12.04	148.0
2,3,3',4,4'-Pentachlorobiphenyl (PCB 105)	ng/g of lipid	97.3	1.32	2.40	4.24	76.82
2,2',4,4'-Tetrabromodiphenyl ether (BDE 47)	ng/g of lipid	97.1	19.70	26.80	56.00	2350.0
2,3,3',4,4',5-Hexachlorobiphenyl (PCB 156)	ng/g of lipid	96.2	4.56	7.76	11.71	367.0
2,2',3,3',4,5,5',6-Octachlorobiphenyl (PCB 199)	ng/g of lipid	96.2	5.63	10.50	16.46	298.0
2,2',3,4,4',5',6-Heptachlorobiphenyl (PCB 183)	ng/g of lipid	96.0	2.30	4.00	6.29	50.74
2,2',4,5,5'-Pentachlorobiphenyl (PCB 101)	ng/g of lipid	95.4	1.64	2.15	3.20	79.30

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S1 Table, continued.

Persistent organic pollutant	Units of measurement	% ≥LOD	median	P75	P90	Maximum
2,2',3,3',4,4',5,5'-Octachlorobiphenyl (PCB 194)	ng/g of lipid	94.7	5.61	10.35	16.57	149.0
2,3',4,4'-Tetrachlorobiphenyl (PCB 66)	ng/g of lipid	93.2	1.40	1.90	2.55	118.0
2,2',3,3',4,5',6'-Heptachlorobiphenyl (PCB 177)	ng/g of lipid	92.8	1.95	3.70	5.70	51.87
1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin (HpCDD)	pg/g of lipid	92.5	29.35	50.10	65.55	456.0
2,2',4,4',6-Pentabromodiphenyl ether (BDE 100)	ng/g of lipid	91.3	3.50	5.20	10.50	339.0
2,2',3,4,5'-Pentachlorobiphenyl (PCB 87)	ng/g of lipid	91.2	0.90	1.10	1.64	39.00
2,2',3,4',5',6-Hexachlorobiphenyl (PCB 149)	ng/g of lipid	89.6	0.60	0.80	1.13	23.90
2,2',4,4',5,5'-Hexabromodiphenyl ether (BDE 153)	ng/g of lipid	88.1	4.40	6.60	16.10	821.0
2,2',4,4',5,5'-Hexabromobiphenyl (BB 153)	ng/g of lipid	87.7	2.70	4.10	8.10	225.0
2,3,3',4',6-Pentachlorobiphenyl (PCB 110)	ng/g of lipid	86.8	1.20	1.51	2.27	59.20
2,2',3,3',4,4',5,5',6-Nonachlorobiphenyl (PCB 206)	ng/g of lipid	85.9	3.30	7.01	11.80	176.0
2,2',3,3',5,5',6-Heptachlorobiphenyl (PCB 178)	ng/g of lipid	82.8	1.72	2.95	4.68	29.76
trans-Nonachlor	ng/g of lipid	82.1	22.70	40.40	54.25	355.0
2,4,4'-Tribromodiphenyl ether (BDE 28)	ng/g of lipid	81.4	1.20	1.65	3.20	65.20
1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin (HxCDD)	pg/g of lipid	79.0	27.20	43.50	54.90	206.0
2,2',3,3',4,5,5'-Heptachlorobiphenyl (PCB 172)	ng/g of lipid	78.2	1.30	2.23	3.10	26.30
2,2',3,3',4,4',5,5',6,6'-Decachlorobiphenyl (PCB 209)	ng/g of lipid	76.9	1.86	5.05	10.20	100.0
2,3,3',4,4',5'-Hexachlorobiphenyl (PCB 157)	ng/g of lipid	75.7	1.07	1.99	3.01	84.00
2,3',4,4',5,5'-Hexachlorobiphenyl (PCB 167)	ng/g of lipid	73.1	1.06	2.20	3.08	50.90
Oxychlordane	ng/g of lipid	66.3	13.90	24.70	34.40	159.0
3,3',4,4',5-Pentachlorobiphenyl (PCB 126)	pg/g of lipid	66.1	18.70	32.20	48.40	721.0
2,2',3,3',4,4',5,6-Octachlorobiphenyl (PCB 195)	ng/g of lipid	63.6	1.20	2.30	3.21	17.20
1,2,3,4,6,7,8,9-Octachlorodibenzo-*p*-dioxin (OCDD)	pg/g of lipid	56.8	256.0	401.5	493.0	3280.0
beta-Hexachlorocyclohexane	ng/g of lipid	56.6	10.80	21.60	42.25	2850.0
1,2,3,7,8-Pentachlorodibenzo-*p*-dioxin (PeCDD)	pg/g of lipid	49.0	<LD	7.70	10.10	36.30
3,3',4,4',5,5'-Hexachlorobiphenyl (PCB 169)	pg/g of lipid	43.0	<LD	23.20	36.15	196.0

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S1 Table, continued.

Persistent organic pollutant	Units of measurement	% ≥LOD	median	P75	P90	maximum
Dieldrin	ng/g of lipid	38.5	<LD	9.60	11.60	448.0
2,2',4,4',5-Pentabromodiphenyl ether (BDE 99)	ng/g of lipid	35.4	<LD	6.25	11.80	692.0
2,3,4,7,8-Pentachlorodibenzofuran (PeCDF)	pg/g of lipid	31.9	<LD	7.50	10.70	65.40
Heptachlor epoxide	ng/g of lipid	30.2	<LD	8.10	11.10	154.0
2,2',3,5,5',6-Hexachlorobiphenyl (PCB 151)	ng/g of lipid	29.0	<LD	0.40	0.70	9.30
p,p'-Dichlorodiphenyltrichloroethane (DDT)	ng/g of lipid	26.7	<LD	8.40	14.40	676.0
1,2,3,4,6,7,8-Heptachlorodibenzofuran (HpCDF)	pg/g of lipid	26.4	<LD	8.70	11.50	367.0
Perfluorodecanoic acid (PFDeA)	µg/L	20.9	<LD	<LD	0.40	3.70
2,2',4,4',5,6'-Hexabromodiphenyl ether (BDE 154)	ng/g of lipid	20.0	<LD	<LD	1.20	40.50
2,3,3',4,4',5,5'-Heptachlorobiphenyl (PCB 189)	ng/g of lipid	16.8	<LD	<LD	0.80	12.00
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)	pg/g of lipid	14.9	<LD	<LD	4.50	28.60
2-(N-Methyl-perfluorooctane sulfonamido) acetic acid (Me-PFOSA-AcOH)	µg/L	14.9	<LD	<LD	0.70	62.30
Perfluorooctane sulfonamide (PFOSA)	µg/L	12.1	<LD	<LD	0.20	3.10
Mirex	ng/g of lipid	7.8	<LD	<LD	<LD	166.0
1,2,3,4,7,8-Hexachlorodibenzofuran (HxCDF)	pg/g of lipid	7.4	<LD	<LD	<LD	32.10
Perfluoroundecanoic acid (PFUA)	µg/L	6.1	<LD	<LD	<LD	6.90
2,2',3,4,4'-Pentabromodiphenyl ether (BDE 85)	ng/g of lipid	5.4	<LD	<LD	<LD	66.90
2,2',3,3',4,4'-Hexachlorobiphenyl (PCB 128)	ng/g of lipid	5.4	<LD	<LD	<LD	9.20
1,2,3,6,7,8-Hexachlorodibenzofuran (HxCDF)	pg/g of lipid	5.3	<LD	<LD	<LD	35.90
2,3',4,4'-Tetrabromodiphenyl ether (BDE 66)	ng/g of lipid	4.7	<LD	<LD	<LD	17.40
1,2,3,4,7,8-Hexachlorodibenzo-*p*-dioxin (HxCDD)	pg/g of lipid	2.6	<LD	<LD	<LD	7.10
1,2,3,7,8,9-Hexachlorodibenzo-*p*-dioxin (HxCDD)	pg/g of lipid	2.5	<LD	<LD	<LD	7.60
3,4,4',5-Tetrachlorobiphenyl (PCB 81)	pg/g of lipid	2.3	<LD	<LD	<LD	7.70
2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid (Et-PFOSA-AcOH)	µg/L	2.1	<LD	<LD	<LD	4.10
Perfluoroheptanoic acid (PFHpA)	µg/L	1.9	<LD	<LD	<LD	3.80
2,2',3,4,4',5',6-Heptabromodiphenyl ether (BDE 183)	ng/g of lipid	1.9	<LD	<LD	<LD	21.10

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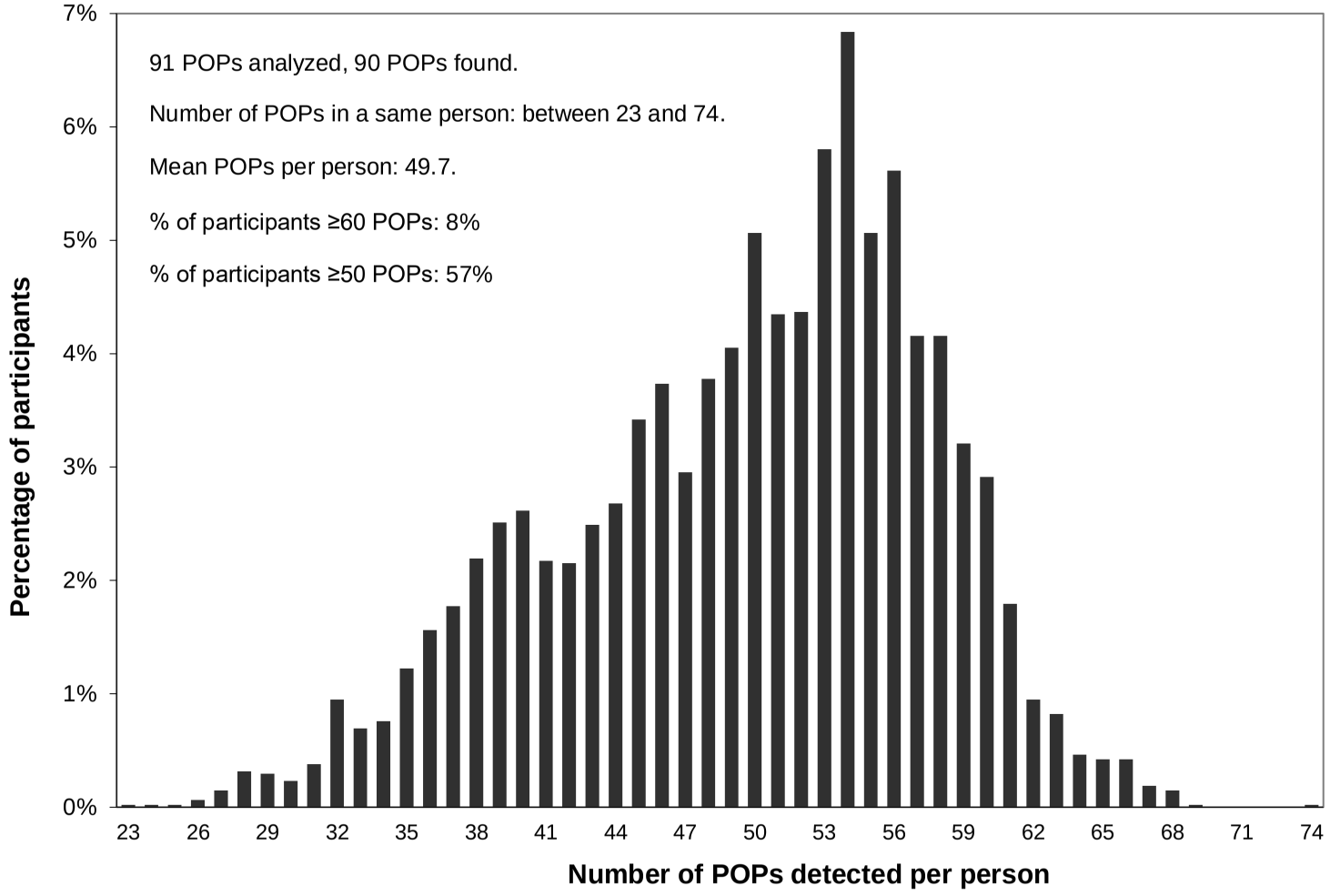
S1 Table, continued.

Persistent organic pollutant	Units of measurement	% ≥LOD	median	P75	P90	maximum
2,2',4-Tribromodiphenyl ether (BDE 17)	ng/g of lipid	1.2	<LD	<LD	<LD	20.60
1,2,3,4,6,7,8,9-Octachlorodibenzofuran (OCDF)	pg/g of lipid	1.0	<LD	<LD	<LD	434.0
o,p'-DDT	ng/g of lipid	0.5	<LD	<LD	<LD	223.0
Perfluorobutane sulfonic acid (PFBuS)	µg/L	0.4	<LD	<LD	<LD	0.60
2,3,7,8-Tetrachlorodibenzofuran (TCDF)	pg/g of lipid	0.3	<LD	<LD	<LD	12.30
gamma-Hexachlorocyclohexane (Lindane)	ng/g of lipid	0.2	<LD	<LD	<LD	304.0
1,2,3,7,8-Pentachlorodibenzofuran (PeCDF)	pg/g of lipid	0.1	<LD	<LD	<LD	19.60
1,2,3,4,7,8,9-Heptachlorodibenzofuran (HpCDF)	pg/g of lipid	0.1	<LD	<LD	<LD	53.70
1,2,3,7,8,9-Hexachlorodibenzofuran (HxCDF)	pg/g of lipid	0.0	<LD	<LD	<LD	26.90
2,3,4,6,7,8-Hexachlorodibenzofuran (HxCDF)	pg/g of lipid	0.0	<LD	<LD	<LD	11.60
Perfluorododecanoic acid (PFDoA)	µg/L	0.0	<LD	<LD	<LD	1.00
Aldrin	ng/g of lipid	0.0	<LD	<LD	<LD	58.10
Endrin	ng/g of lipid	0	<LD	<LD	<LD	<LD

S2 Table. Population characteristics by survey subsample.

Characteristics	Total (N = 4,739) N (%)	PFCs (N = 1,610) N (%)	OCs, PBDEs & PBB 153 compounds (N = 1,585) N (%)	PCBs & PCDD/Fs compounds (N = 1,544) N (%)	*p*-value
Gender					0.761
Women	2467 (52.1)	839 (52.1)	835 (52.7)	793 (51.4)	
Men	2272 (47.9)	771 (47.9)	750 (47.3)	751 (48.6)	
Age (years)					
mean (SD)	50.4 (19.5)	51.4 (19.8)	49.6 (19.4)	50.3 (19.4)	0.036[a]
median	49.0	50.5	48.0	49.0	0.041[b]
Race/ethnicity					0.233
Non-Hispanic white	2539 (53.6)	860 (53.4)	835 (52.7)	844 (54.7)	
Mexican American	951 (20.1)	323 (20.1)	325 (20.5)	303 (19.6)	
Non-Hispanic black	948 (20.0)	345 (21.4)	316 (19.9)	287 (18.6)	
Other Hispanic	140 (3.0)	38 (2.4)	49 (3.1)	53 (3.4)	
Other	161 (3.4)	44 (2.7)	60 (3.8)	57 (3.7)	
Educational level					0.361
College or above	2138 (45.1)	694 (43.2)	736 (46.5)	708 (45.9)	
High school	1193 (25.2)	427 (26.6)	387 (24.4)	379 (24.6)	
< High school	1399 (29.5)	485 (30.2)	460 (29.1)	454 (29.5)	
Poverty income ratio					0.915
>2	2394 (53.6)	810 (53.1)	797 (53.9)	787 (53.7)	
≤2	2075 (46.4)	714 (46.9)	682 (46.1)	679 (46.3)	
Body mass index (kg/m^2)					
mean (SD)	28.4 (6.3)	28.6 (6.4)	28.3 (6.0)	28.4 (6.4)	0.433[a]
median	27.4	27.6	27.4	27.3	0.593[b]
Pregnancy[c]					0.886
No	93 (3.8)	30 (3.6)	31 (3.7)	32 (4.0)	
Yes	1768 (71.7)	604 (72.0)	597 (71.5)	567 (71.5)	
No. of pregnancies resulting in live births[c]					
mean (SD)	2.8 (1.9)	2.9 (2.0)	2.7 (1.8)	2.8 (2.0)	0.157[a]
median	2.0	2.0	2.0	2.0	0.263[b]
Breastfeeding[d,e]					0.323
No	78 (4.4)	25 (4.1)	32 (5.4)	21 (3.7)	
Yes	975 (55.1)	333 (55.1)	322 (53.9)	320 (56.4)	
No. of children breastfed[d,e]					
mean (SD)	2.3 (2.0)	2.4 (2.0)	2.2 (1.9)	2.4 (2.0)	0.158[a]
median	2.0	2.0	2.0	2.0	0.074[b]

Unless otherwise specified, *p*-value derived from Pearson's Chi-Square test.
[a] ANOVA.
[b] Kruskal–Wallis test.
[c] Women only.
[d] Only women with ≥1 pregnancies resulting in live births.
[e] Breastfed ≥1 month.



S1 Figure. Percentage of participants according to number of POPs detected per person.
(91 POPs analyzed, n = 4,739)

S3 Table. Frequency of subjects with high concentrations of the most detected POPs according to different definitions of 'high concentration'.

		Number of the most prevalent POPs at 'high concentrations'					
		0	≥10	≥20	1 to 5	6 to 9	
Cutoff point of 'high concentration'	**N[a]**	N (%)	N (%)	N (%)	N (%)	N (%)	**GM**
Different cutoff point for each compound (No. of participants = 4,739)							
POPs detected ≥85% of participants	37						
≥Percentile 90 (top decile)		1,555 (32.8)	619 (13.1)	135 (2.8)	2,190 (46.2)	375 (7.9)	3.4
≥Percentile 80 (top quintile)		559 (11.8)	1,326 (28.0)	636 (13.4)	2,194 (46.3)	660 (13.9)	5.3
≥Percentile 75 (top quartile)		441 (9.3)	1,776 (37.5)	852 (18.0)	1,785 (37.7)	737 (15.6)	6.8
POPs detected ≥75% of participants	44						
≥Percentile 90 (top decile)		1,513 (31.9)	705 (14.9)	269 (5.7)	2,113 (44.6)	408 (8.6)	3.8
≥Percentile 80 (top quintile)		538 (11.4)	1,435 (30.3)	829 (17.5)	2,064 (43.6)	702 (14.8)	6.0
≥Percentile 75 (top quartile)		428 (9.0)	1,925 (40.6)	1,021 (21.5)	1,558 (32.9)	828 (17.5)	7.8
POPs detected ≥50% of participants	50						
≥Percentile 90 (top decile)		1,446 (30.5)	766 (16.2)	350 (7.4)	2,080 (43.9)	447 (9.4)	4.1
≥Percentile 80 (top quintile)		525 (11.1)	1,539 (32.5)	936 (19.8)	1,899 (40.1)	776 (16.4)	6.6
≥Percentile 75 (top quartile)		409 (8.6)	2,140 (45.2)	1,086 (22.9)	1,400 (29.5)	790 (16.7)	8.7
Participants ≥percentile 75 of [TEQ] and different cutoff point for compounds (No. of participants = 1,183)							
POPs detected ≥85% of participants	33						
≥Percentile 90 (top decile)		110 (9.3)	356 (30.1)	80 (6.8)	568 (48.0)	149 (12.6)	5.0
≥Percentile 80 (top quintile)		6 (0.5)	832 (70.3)	248 (21.0)	245 (20.7)	100 (8.5)	10.7
≥Percentile 75 (top quartile)		1 (0.1)	897 (75.8)	426 (36.0)	205 (17.3)	80 (6.8)	12.4
POPs detected ≥75% of participants	38						
≥Percentile 90 (top decile)		106 (9.0)	428 (36.2)	136 (11.5)	526 (44.5)	123 (10.4)	6.1
≥Percentile 80 (top quintile)		6 (0.5)	869 (73.5)	548 (46.3)	199 (16.8)	109 (9.2)	12.5
≥Percentile 75 (top quartile)		1 (0.1)	937 (79.2)	715 (60.4)	154 (13.0)	91 (7.7)	15.3
POPs detected ≥50% of participants	41						
≥Percentile 90 (top decile)		103 (8.7)	446 (37.7)	165 (13.9)	483 (40.8)	151 (12.8)	6.7
≥Percentile 80 (top quintile)		6 (0.5)	885 (74.8)	628 (53.1)	187 (15.8)	105 (8.9)	13.7
≥Percentile 75 (top quartile)		1 (0.1)	955 (80.7)	757 (64.0)	137 (11.6)	90 (7.6)	16.8

GM: geometric mean. Geometric means are calculated for subjects with ≥1 of respective most prevalent POPs at 'high concentrations' according to each cutoff point for 'high concentration'.

[a] Number of POPs included in the analyses.

S4A Table. Associations between sociodemographic characteristics and having one or more POPs with concentrations in the upper decile.

Characteristics	Model 1			Model 2		
	OR	(95% CI)	*p*-value	OR	(95% CI)	*p*-value
Gender						
Women	1.00			1.00		
Men	1.87	(1.64, 2.13)	<0.001	1.88	(1.64, 2.14)	<0.001
Age (years)	1.04	(1.04, 1.04)	<0.001	1.04	(1.04, 1.04)	<0.001
Race/ethnicity						
Non-Hispanic White	1.00		<0.001	--		
Mexican American	0.74	(0.63, 0.88)				
Non-Hispanic Black	1.10	(0.93, 1.31)				
Other Hispanic	0.73	(0.50, 1.05)				
Other	1.32	(0.90, 1.91)				
Educational level						
College or Above	1.00		0.616	1.00		0.460
High School	0.93	(0.79, 1.09)		0.95	(0.81, 1.12)	
< High School	0.95	(0.81, 1.11)		1.07	(0.90, 1.28)	
Poverty income ratio						
>2	1.00			1.00		
≤2	1.11	(0.97, 1.27)	0.137	1.17	(1.02, 1.35)	0.026
Body mass index (kg/m^2)						
Normal weight	1.00		<0.001 [a]	1.00		<0.001 [a]
Overweight	0.81	(0.68, 0.95)		0.83	(0.70, 0.98)	
Obesity	0.71	(0.61, 0.84)		0.73	(0.62, 0.86)	
Pregnancy [b]						
No	1.00			1.00		
Yes	0.77	(0.48, 1.23)	0.275	0.73	(0.45, 1.17)	0.189
No. pregnancies resulting in live births [b]	1.04	(0.98, 1.11)	0.224	1.00	(0.93, 1.07)	0.888
Breastfeeding [c,d]						
No	1.00			1.00		
Yes	0.64	(0.37, 1.11)	0.113	0.62	(0.36, 1.07)	0.087
No. children breastfed [c,d]	0.97	(0.85, 1.10)	0.597	0.96	(0.85, 1.10)	0.585

Model 1: adjusted by age, gender and body mass index.
Model 2: adjusted by age, gender, body mass index and race/ethnicity.
Number of POPs at high concentrations: number of POPs whose serum concentrations were ≥percentile 90.
Unless otherwise specified, *p*-value derived from Wald's test.
[a] Multivariate analogue of Mantel's extension test for linear trend.
[b] Women only.
[c] Only among women with ≥1 pregnancies resulting in live births and, in the two models, further adjusted by such number of pregnancies.
[d] Breastfed ≥1 month.

S4B Table. Associations between sociodemographic characteristics and having one or more OCs, PBDEs and PBB 153 with concentrations in the upper decile.

Characteristics	Model 1			Model 2		
	OR	(95% CI)	*p*-value	OR	(95% CI)	*p*-value
Gender						
Women	1.00			1.00		
Men	1.17	(1.04, 1.33)	0.013	1.17	(1.03, 1.33)	0.015
Age (years)	1.02	(1.02, 1.03)	<0.001	1.02	(1.02, 1.03)	<0.001
Race/ethnicity						
Non-Hispanic White	1.00		<0.001	--		
Mexican American	1.41	(1.20, 1.66)				
Non-Hispanic Black	0.76	(0.63, 0.90)				
Other Hispanic	0.85	(0.57, 1.27)				
Other	0.60	(0.41, 0.89)				
Educational level						
College or Above	1.00		0.002 [a]	1.00		0.069
High School	1.01	(0.86, 1.19)		0.99	(0.84, 1.16)	
< High School	1.28	(1.11, 1.49)		1.19	(1.01, 1.40)	
Poverty income ratio						
>2	1.00			1.00		
≤2	1.19	(1.04, 1.35)	0.011	1.15	(1.01, 1.32)	0.038
Body mass index (kg/m^2)						
Normal weight	1.00		0.013 [a]	1.00		0.006 [a]
Overweight	0.96	(0.83, 1.13)		0.93	(0.80, 1.09)	
Obesity	0.82	(0.70, 0.96)		0.80	(0.68, 0.94)	
Pregnancy [b]						
No	1.00			1.00		
Yes	1.34	(0.76, 2.14)	0.279	1.17	(0.67, 2.02)	0.588
No. pregnancies resulting in live births [b]	1.13	(1.07, 1.20)	<0.001	1.04	(0.98, 1.11)	0.168
Breastfeeding [c,d]						
No	1.00			1.00		
Yes	0.86	(0.51, 1.46)	0.571	0.71	(0.41, 1.22)	0.213
No. children breastfed [c,d]	1.02	(0.91, 1.13)	0.773	0.96	(0.86, 1.07)	0.438

Model 1: adjusted by age, gender and body mass index.
Model 2: adjusted by age, gender, body mass index and race/ethnicity.
Unless otherwise specified, *p*-value derived from Wald's test.
[a] Multivariate analogue of Mantel's extension test for linear trend.
[b] Women only.
[c] Only among women with ≥1 pregnancies resulting in live births and, in the two models, further adjusted by such number of pregnancies.
[d] Breastfed ≥1 month.

S5A Table. Serum pooled concentrations[a] of POPs most detected for the three most recent NHANES Surveys periods analyzed.

	2003-2004[b]		2005-2006		2007-2008	
Persistent organic pollutant	**mean**	**(SD)**	**mean**	**(SD)**	**mean**	**(SD)**
2,2',3,4,4',5' and 2,3,3',4,4',6-Hexachlorobiphenyl (PCB 138 & 158)	29.38	(24.6)	14.60	(17.5)	23.26	(22.1)
2,3',4,4',5-Pentachlorobiphenyl (PCB 118)	11.48	(10.4)	7.48	(9.6)	8.99	(9.6)
2,2',4,4',5,5'-Hexachlorobiphenyl (PCB 153)	39.47	(32.9)	25.11	(29.8)	30.69	(28.8)
2,2',3,4,4',5,5'-Heptachlorobiphenyl (PCB 180)	32.93	(26.9)	20.49	(24.7)	25.11	(26.9)
2,2',3,5'-Tetrachlorobiphenyl (PCB 44)	2.26	(0.7)	0.20	(0.1)	0.12	(0.1)
2,4,4',5-Tetrachlorobiphenyl (PCB 74)	8.73	(7.7)	5.83	(7.6)	6.01	(5.8)
p,p'-Dichlorodiphenyldichloroethene (DDE)	731.3	(766)	702.6	(1212)	585.6	(909)
2,2',4,4',5-Pentachlorobiphenyl (PCB 99)	6.83	(5.6)	4.21	(4.6)	4.76	(4.4)
2,2',3,3',4,4',5-Heptachlorobiphenyl (PCB 170)	11.49	(9.4)	7.38	(8.9)	9.93	(9.2)
2,2',3,4',5,5',6-Heptachlorobiphenyl (PCB 187)	9.66	(8.2)	6.47	(8.4)	8.44	(8.8)
2,4,4'-Trichlorobiphenyl (PCB 28)	5.48	(1.8)	1.95	(2.3)	1.36	(1.7)
2,2',4,5'-Tetrachlorobiphenyl (PCB 49)	1.46	(0.5)	0.15	(0.1)	0.11	(0.0)
2,2',3,4',5,5'-Hexachlorobiphenyl (PCB 146)	4.77	(4.3)	3.18	(4.3)	4.02	(4.2)
Hexachlorobenzene	16.76	(4.3)	8.78	(4.1)	11.23	(4.7)
2,2',5,5'-Tetrachlorobiphenyl (PCB 52)	3.05	(1.0)	0.27	(0.2)	0.17	(0.2)
2,2',3,3',4,4',5,6' and 2,2',3,4,4',5,5',6-Octachlorobiphenyl (PCB 196 & 203)	6.01	(4.8)	5.02	(6.1)	6.31	(6.1)
2,3,3',4,4'-Pentachlorobiphenyl (PCB 105)	2.24	(2.1)	1.41	(1.8)	1.85	(2.1)
2,2',4,4'-Tetrabromodiphenyl ether (BDE 47)	34.46	(30.2)	47.05	(41.2)	34.19	(25.1)
2,3,3',4,4',5-Hexachlorobiphenyl (PCB 156)	6.06	(6.5)	3.45	(4.2)	4.90	(4.8)
2,2',3,3',4,5,5',6-Octachlorobiphenyl (PCB 199)	7.71	(6.8)	5.72	(7.6)	7.14	(7.4)
2,2',3,4,4',5',6-Heptachlorobiphenyl (PCB 183)	3.11	(2.4)	1.97	(2.2)	2.59	(2.5)
2,2',4,5,5'-Pentachlorobiphenyl (PCB 101)	2.05	(0.8)	0.38	(0.3)	0.29	(0.5)
2,2',3,3',4,4',5,5'-Octachlorobiphenyl (PCB 194)	7.33	(5.9)	4.67	(5.9)	6.29	(6.1)
2,3',4,4'-Tetrachlorobiphenyl (PCB 66)	1.78	(1.1)	0.86	(1.0)	0.87	(0.8)
2,2',3,3',4,5',6'-Heptachlorobiphenyl (PCB 177)	2.89	(2.5)	1.29	(1.6)	1.67	(1.7)
1,2,3,4,6,7,8-Heptachlorodibenzo-*p*-dioxin (HpCDD)	36.71	(17.6)	28.11	(16.7)	25.46	(14.5)
2,2',4,4',6-Pentabromodiphenyl ether (BDE 100)	6.80	(6.4)	9.29	(8.7)	7.14	(5.5)
2,2',3,4,5'-Pentachlorobiphenyl (PCB 87)	1.04	(0.4)	0.21	(0.2)	0.19	(0.3)
2,2',3,4',5',6-Hexachlorobiphenyl (PCB 149)	0.75	(0.3)	0.18	(0.1)	0.15	(0.2)
2,2',4,4',5,5'-Hexabromodiphenyl ether (BDE 153)	10.06	(11.3)	11.63	(9.1)	12.06	(9.2)
2,2',4,4',5,5'-Hexabromobiphenyl (BB 153)	4.60	(4.7)	5.05	(11.0)	5.01	(9.9)
2,3,3',4',6-Pentachlorobiphenyl (PCB 110)	1.48	(0.6)	0.19	(0.1)	0.16	(0.3)
2,2',3,3',4,4',5,5',6-Nonachlorobiphenyl (PCB 206)	5.08	(4.6)	3.58	(5.4)	4.04	(4.4)

Values for participants ≥20 years old.
SD: standard deviation of arithmetic mean.
[a] All compounds measured in ng/g of lipid, except HpCDD (in pg/g of lipid). [b] Values for all 4,739 participants.

S5B Table. Serum concentrations of four perfluorinated compounds (µg/L) most detected for the most recent NHANES Surveys periods analyzed.

	2003-2004[a]		2005-2006		2007-2008		2009-2010		2011-2012	
Persistent organic pollutant	**GM**	**(SD)**	**GM**	**(SD)**	**GM**	**(SD)**	**GM**	**(SD)**	**GM**	**(SD)**
Perfluorooctane sulfonic acid (PFOS)	20.11	(1.7)	16.68	(2.2)	13.79	(2.3)	9.26	(2.3)	6.86	(2.5)
Perfluorooctanoic acid (PFOA)	3.64	(1.7)	3.53	(2.2)	4.03	(1.9)	2.89	(1.9)	2.04	(2.0)
Perfluorononanoic acid (PFNA)	0.94	(1.8)	1.06	(2.1)	1.22	(1.9)	1.25	(1.9)	0.94	(2.0)
Perfluorohexane sulfonic acid (PFHxS)	1.75	(1.9)	1.47	(3.0)	1.90	(2.6)	1.49	(2.5)	1.20	(2.6)

Values for participants ≥20 years old.
GM: geometric mean.
SD: standard deviation of geometric mean.
[a] Values for all 4,739 participants.

Publicacions relacionades: articles addicionals, inclosos en l'Annex A

Les referències dels sis articles inclosos en l'*Annex A* són:

– Porta M, Gasull M, Puigdomènech E, Garí M, Bosch de Basea M, Guillén M, López T, Bigas E, Pumarega J, Llebaria X, Grimalt JO, Tresserras R. Distribution of blood concentrations of persistent organic pollutants in a representative sample of the population of Catalonia. Environ Int. 2010; 36: 655-664.

– Porta M, López T, Gasull M, Rodríguez-Sanz M, Garí M, Pumarega J, Borrell C, Grimalt JO. Distribution of blood concentrations of persistent organic pollutants in a representative sample of the population of Barcelona in 2006, and comparison with levels in 2002. Sci Total Environ. 2012; 423:151-161.

– Porta M, Gasull M, Puigdomènech E, Rodríguez-Sanz M, Pumarega J, Rebato C, Borrell C. Sociodemographic factors influencing participation in the Barcelona Health Survey study on serum concentrations of persistent organic pollutants. Chemosphere. 2009; 76: 216-225.

– Gasull M, Pumarega JA, Rovira G, López T, Alguacil J, Porta M. Relative effects of educational level and occupational social class on body concentrations of persistent organic pollutants in a representative sample of the general population of Catalonia, Spain. Environ Int. 2013; 60: 190-201.

– Porta M, Pumarega J, Gasull M. Number of persistent organic pollutants detected at high concentrations in a general population. Environ Int. 2012; 44: 106-111.

– Gasull M, Pumarega J, Téllez-Plaza M, Castell C, Tresserras R, Lee DH, Porta M. Blood Concentrations of Persistent Organic Pollutants and Prediabetes and Diabetes in the General Population of Catalonia. Environ Sci Technol. 2012; 46: 7799-7810.

5. DISCUSSIÓ

Aquest capítol és complementari a les discussions de cada un dels articles de la tesi, tant els inclosos en el capítol de *Resultats* com en l'*Annex A.* Per això, en aquest capítol s'hi presenta un resum de les principals troballes i una discussió conjunta dels articles.

5.1. Principals troballes

Els resultats de la recerca duta a terme donen suport a les hipòtesis principals de que existeix una contaminació freqüent i generalitzada de la població general per compostos tòxics persistents i que aquesta es relaciona amb certs efectes adversos en la salut, com la diabetis tipus 2 i altres alteracions del fenotip metabòlic.

5.1.1. Contaminació de la població general per CTPs

Els resultats obtinguts ens mostren que més del 80% de la població general de Catalunya i de la ciutat de Barcelona presentava concentracions detectables en sèrum de plaguicides organoclorats (DDT, DDE, HCB i β-HCH) i de policlorobifenils (PCB congèneres 118, 138, 153 i 180). El DDE inclús es va detectar i quantificar en el 100% de la població en ambdós estudis [67,68,75].

Les corbes de distribució poblacionals de les concentracions de cadascun d'aquests compostos mostren com una minoria de la població presentava concentracions molt més elevades que la majoria de la població. (Per tant, les distribucions no segueixen una forma "normal", una "campana" simètrica, sinó que presenten una llarga cua cap a la dreta, cap a les concentracions més elevades) (Figura 1). No obstant, en la població de la ciutat de Barcelona, les concentracions d'aquests plaguicides organoclorats i PCBs l'any 2006 eren més baixes que les detectades l'any 2002.

Existeixen diferències en les concentracions sèriques de CTPs en la població general de Catalunya i de la ciutat de Barcelona en funció de diversos factors sociodemogràfics [67,68,75]:

a) les dones presentaven concentracions de plaguicides organoclorats –però no de PCBs– significativament més altes que els homes i aquestes diferències eren majors en els grups de més edat;

b) en l'estudi de Catalunya, les dones amb una major paritat presentaven menors concentracions de CTPs que les dones amb un menor nombre de fills/filles (un cop ajustant per edat i IMC); en canvi, aquesta relació no es va observar en l'estudi de Barcelona;

c) les concentracions de plaguicides organoclorats i de PCBs eren més elevades en els grups de més edat (en les cohorts de naixement més velles), augmentant de forma gradual;

d) en general, un cop ajustant per edat, les concentracions de plaguicides organoclorats eren més elevades en els individus amb sobrepès i obesitat, mentre que les concentracions de PCBs eren més elevades en els individus amb pes normal, encara que no sempre de forma estadísticament significativa; i

e) no es van observar patrons clars en les relacions de les concentracions de CTPs amb variables de posició socioeconòmica: les concentracions eren més elevades en els grups amb menor nivell educatiu i, en les dones (però no en els homes), en les classes socials més desafavorides; no obstant, aquesta relació s'explicava bàsicament per l'efecte de l'edat/cohort de naixement i l'IMC, sobretot en les dones. En els homes, l'educació estava més relacionada que no pas la classe social amb les concentracions de CTPs, observant-se com, un cop ajustant per edat i IMC, eren els homes amb estudis universitaris els que presentaven majors concentracions [70].

Una part significativa [vegeu la nota 2 a peu de pàgina] de la població general de Catalunya i dels Estats Units presentava un cert nombre de compostos detectats a altes concentracions; és a dir, tenia concentracions sèriques elevades de diversos CTPs a la vegada. Un 34% dels participants en l'estudi de Catalunya tenia concentracions en el quartil superior de 3 o més compostos dels 8 més detectats en aquesta població d'estudi, mentre que un 20% dels participants tenia concentracions en el decil superior de 2 o més compostos [71]. En l'estudi dels Estats Units, un 38% dels participants tenia concentracions en el quartil superior de 10 o més compostos dels 37 més detectats en l'estudi, mentre que un 13% tenia concentracions en el decil superior de 10 o més compostos (vegeu la Taula S3 del Material suplementari de l'*Article 3* del capítol de *Resultats*) [91].

El fet que el número de compostos analitzats i el número de compostos més freqüentment detectats en ambdós estudis sigui força dispar (8 vs. 37 compostos) fa difícil valorar amb més detall els resultats obtinguts. Creiem que calen més estudis que apliquin una metodologia similar (i que també apliquin diferents punts de tall per determinar valors d'altes concentracions) per tal de poder avaluar amb una perspectiva més àmplia aquests resultats.

Tanmateix, el fet és que subgrups importants de la població tenen concentracions altes de diversos CTPs. Podem dir, gràficament o pedagògicament, que en el cos de subgrups importants de la població trobem "còctels" de contaminants en els que cada "ingredient" es troba a dosis altes. No és doncs cert

que les concentracions siguin baixes sempre o en tothom. Aquest fet té importants implicacions científiques, clíniques, sanitàries i socials [77,97-99,139].

5.1.2. Relació dels CTPs amb alguns efectes adversos en la salut

En la població general de Catalunya, aquelles persones amb majors concentracions sèriques de CTPs presentaven pitjor salut autopercebuda que les persones amb menors concentracions de CTPs. Aquesta relació, però, s'explicava bàsicament per l'efecte de l'edat i també per la prevalença de trastorns crònics, ja que els individus amb majors concentracions de CTPs presentaven un major número de trastorns crònics. Un cop ajustant els models per edat, la relació entre CTPs i la prevalença de trastorns crònics es mantenia estadísticament significativa en el cas de l'HCB i el PCB 118 [72].

En concordança amb el coneixement existent, en la població general de Catalunya, les persones amb majors concentracions sèriques de PCBs i d'HCB presentaven una major prevalença de diabetis tipus 2 i prediabetis que aquelles persones amb menors concentracions. Així mateix, les persones amb majors concentracions dels CTPs mencionats i també de β-HCH presentaven una major prevalença de síndrome metabòlica. Tenint en compte l'efecte de l'edat, el sexe i l'IMC aquestes relacions s'afeblien però es continuaven observant [73,74].

Tant en persones amb sobrepès/obesitat com, per primer cop, en persones amb normopès, s'observà que majors concentracions de PCBs, HCB i β-HCH es relacionaven amb un fenotip metabòlic alterat; és a dir, es relacionaven amb presentar 2 o més alteracions cardiometabòliques definides a partir de la glucèmia, la pressió arterial, les concentracions de colesterol, triglicèrids, proteïna C-reactiva i l'índex HOMA-IR (*homeostatic model assessment-insulin resistance*). Les relacions observades eren de major magnitud en els individus amb normopès que en els individus amb sobrepès o obesitat [74]. Aquest patró també s'havia observat en el cas de la prediabetis [73].

Addicionalment, en estudiar la participació en l'estudi de determinació de CTPs en la població de Barcelona vam observar com el fet de ser dona i el fet de disposar d'un nivell educatiu més elevat influenciava favorablement a la participació; els individus dels grups d'edats més joves (<35 anys) i més grans (>74 anys) presentaven una pitjor predisposició [69].

5.2. Aspectes metodològics: fortaleses i limitacions

5.2.1. Disseny dels estudis

Estudis tranversals

En diverses de les publicacions sobre els estudis que conformen aquesta tesi [67-74,91] comentem que una de les limitacions importants dels estudis és el seu disseny transversal [40,140]. Aquest tipus de disseny suposa una limitació especialment rellevant a l'hora d'abordar els objectius de la tesi relacionats amb els efectes causals dels CTPs sobre la salut (és a dir, principalment amb la salut autopercebuda i amb alteracions metabòliques). El fet que *a)* la mostra de sang en que es mesuren les concentracions de CTPs i *b)* les dades sobre salut autopercebuda, trastorns crònics i sobre alteracions metabòliques s'obtinguin en el mateix moment temporal impedeix establir amb prou fermesa quina és la seqüència temporal entre l'exposició i l'efecte. Per tant, aquest criteri de causalitat no pot ser establert amb suficient claredat. No obstant, el disseny transversal sí que és útil per explorar possibles relacions i que els resultats obtinguts serveixin de base per realitzar nous estudis. Per exemple, la relació entre CTPs i un fenotip metabòlic alterat observada en persones amb pes normal, o el fet d'incorporar les concentracions de proteïna C-reactiva en la definició del fenotip metabòlic, són troballes noves –i innovadores– obtingudes mitjançant metodologies robustes; val doncs la pena que siguin analitzades i incorporades en nous estudis.

Els resultats obtinguts també són útils per conèixer quines són les associacions que es produeixen en persones reals que viuen en condicions reals: tot i que puguin ser associacions degudes –en part o completament– a l'efecte de variables confusores, són associacions que presenten les persones en la realitat. Per exemple, a la pràctica, les persones de més edat tenen concentracions més elevades de CTPs; i també en el món real, les persones amb una pitjor salut autopercebuda tenen concentracions més elevades d'aquests i altres contaminants.

En analitzar en estudis amb un disseny transversal efectes adversos en la salut relacionats amb les concentracions de CTPs cal tenir present que es podria estar produint un procés de causalitat inversa. En el cas que, per exemple, el fet de patir diabetis, prediabetis o presentar un perfil metabòlic alterat estigués lligat a algun procés patofisiològic que també comportés una major acumulació corporal de CTPs, les relacions observades podrien ser degudes a causalitat inversa [40,140]. Les concentracions detectades en participants amb alteracions metabòliques serien més altes, precisament a causa d'aquestes alteracions, que en els participants metabòlicament sans. Pel que sabem aquests processos no han estat descrits i la possibilitat real de que les relacions observades fossin degudes a causalitat inversa és poc plausible. En canvi, els estudis experimentals i els estudis longitudinals (i per tant, que sí compleixen el criteri de temporalitat) que analitzen la relació dels CTPs amb alteracions com la

diabetis tipus 2, donen suport a la hipòtesi de que la major acumulació de CTPs són causa d'un major risc de patir aquestes alteracions metabòliques [104,110,125,128,131,141]. Malgrat tot, sí que és cert que les alteracions metabòliques mencionades estan relacionades amb alteracions en el perfil lipídic; l'alta lipofilicitat dels CTPs estudiats fa necessari tenir en compte com aquestes alteracions podrien alterar la mesura dels compostos (vegeu l'apartat *5.2.3. Mesura de l'exposició* d'aquest mateix capítol).

Per fer inferència causal cal tenir present, a més, que el coneixement expert / coneixement substantiu és imprescindible [140,142]. Tant en el cas de les alteracions metabòliques com de la salut autopercebuda a través de l'increment dels trastorns crònics, el coneixement existent en la literatura va a favor de descartar que en els resultats observats en la present tesi es pugui estar produint aquesta causalitat inversa; o dit d'una altra manera, el coneixement dona suport a la hipòtesi que l'exposició a CTPs pot estar contribuint a causar una part de la càrrega de malaltia de la societat [77,139].

El disseny transversal afecta també a les anàlisis referents a la influència de determinats factors –com per exemple l'IMC, la classe social i l'educació– en les concentracions detectades dels diferents compostos analitzats. En aquest cas el disseny també impedeix establir amb prou fermesa la seqüència temporal. Tot i que difícilment les concentracions de CTPs puguin influir en aspectes socioeconòmics dels individus, sí que els CTPs podrien tenir un paper com a obesògens [101,124,125,143]. El disseny transversal també impedeix distingir si la influència observada de l'edat en les concentracions es deu a l'edat biològica (al procés d'envelliment en sí) o a la cohort de naixement (les cohort més velles van viure, per exemple, en els períodes de màxim ús d'alguns dels compostos). Aquest aspecte es comenta en diversos dels articles; vegeu per exemple l'apartat de discussió de l'*Article A4* de l'*Annex A* [70].

5.2.2. Validesa externa

Estudis en mostres representatives de la població general i lligats a enquestes de salut
Els resultats presentats s'han obtingut a partir de tres estudis lligats a enquestes de salut; aquest és un fet especialment rellevant ja que significa que s'han obtingut en mostres que es poden considerar el màxim de representatives de la població general [40]. A nivell espanyol, això suposa una important millora respecte al coneixement de la contaminació per CTPs existent a nivell poblacional, ja que la majoria de recerca realitzada es basa en grups concrets de la població, ja sigui població especialment vulnerable als efectes adversos d'aquests contaminants –com embarassades i els seus fills/filles– o població que podria estar altament exposada –com habitants de zones properes a incineradores (vegeu el capítol d'*Introducció*) [41-49,56-64].

Els estudis de la present tesi han analitzat la contaminació per CTPs de la població general de Catalunya i de la ciutat de Barcelona que, juntament amb l'estudi previ a les Illes Canàries, representen els primers estudis a nivell espanyol que es basen en mostres representatives de la població general.

Aquesta representativitat [40] permet que els resultats obtinguts siguin especialment útils –entre d'altres propòsits– per plantejar possibles nivells de referència dels CTPs. També ajuda a avaluar l'efectivitat de les polítiques i mesures que s'apliquen per reduir la contaminació humana per CTPs. Aquest darrer propòsit el situem en el marc conceptual i pràctic d'una salut pública basada en coneixements científics (basada en proves, en 'evidències' científiques), i també pensant la salut com un objectiu necessari i un resultat real de nombroses polítiques, tant les que es desenvolupen des de dins com les que ho fan des de fora del sistema sanitari [4,6-8,144- 151].

Una de les limitacions dels estudis de biomonitorització de CTPs que hem realitzat a la ciutat de Barcelona i a Catalunya és, però, que no inclouen població menor de 18 anys, i per tant no s'obté informació representativa d'aquest subgrup de la població. En l'estudi que hem realitzat amb les dades de la NHANES (a nivell d'Estats Units) no s'ha inclòs la població de 12 a 19 anys, tot i que sí que es van analitzar les concentracions sèriques de CTPs en aquest subgrup [138]. En el cas de l'estudi de Catalunya tampoc hi ha participants majors de 74 anys. En cap dels tres estudis s'inclou població institucionalitzada i alguns dels resultats trobats podrien diferir en aquest subgrup.

Els tres estudis estan lligats a enquestes de salut realitzades per l'administració, en el cas dels estudis de Catalunya i de Barcelona concretament les enquestes van ser realitzades pel Departament de Salut de la Generalitat de Catalunya i per l'Agència de Salut Pública de Barcelona, respectivament. Aquest és un fet rellevant ja que suposa comptar amb el suport d'organismes governamentals en la biomonitorització de CTPs, de tal manera que permet analitzar poblacions més àmplies, mostres representatives, i obtenir una major validesa externa i una major rellevància, no només científica, sinó també social, sanitària i ambiental. Les implicacions dels resultats obtinguts poden ser utilitzades més fàcilment a l'hora de plantejar polítiques ambientals, sanitàries, industrials o econòmiques [77,139]. A més, el fet d'involucrar l'administració, també obre la porta a la possibilitat de realitzar estudis d'aquest tipus de forma periòdica i establir, com en altres països, un programa de biomonitorització sostingut en el temps i que permeti analitzar un major nombre de compostos [75].

Els criteris i mètodes de selecció dels participants que es van usar en les enquestes de salut són un punt especialment rellevant ja que, juntament amb la posterior ponderació de la mostra obtinguda, garanteixen la màxima representativitat de la població general. Va més enllà dels propòsits de la tesi entrar en els detalls del complex disseny mostral dut a terme en les diferents enquestes, no obstant, en

els corresponents documents es descriuen minuciosament els passos seguits pel Departament de Salut, per l'Agència de Salut Pública i pel CDC, en cada cas [75,134-138].

5.2.3. Mesura de l'exposició

Biomarcadors

Sens dubte l'ús de biomarcadors –la mesura directa en sang de les concentracions dels diferents CTPs analitzats– és un dels punts forts de la recerca realitzada. A diferència dels estudis en que es pugui fer una estimació de l'exposició, l'ús de biomarcadors permet considerar simultàniament en un únic valor quantitatiu totes les diverses fonts i vies d'exposició que es puguin produir [152]. Per tant, l'anàlisi de la contaminació de la població general per CTPs duta a terme en la tesi no només és d'alt valor pel fet de provenir de mostres representatives de la població general, sinó que la mesura de l'exposició utilitzada també és el més acurada possible i especialment valuosa.

Cal assenyalar a més l'excel·lent qualitat de les anàlisis de laboratori realitzades, en el cas dels estudis de Catalunya i de Barcelona, pel laboratori del Departament de Química Ambiental de l'Institut de Diagnòstic Ambiental i Estudis de l'Aigua – Consell Superior d'Investigacions Científiques (IDÆA-CSIC) dirigit pel Dr. Joan O. Grimalt. Els límits de detecció i quantificació que es van obtenir són realment baixos i comparables als dels millors laboratoris a nivell internacional (vegeu la Taula 1 del Material suplementari de l'*Article A2* i la Taula A1 de l'informe publicat sobre l'estudi de Catalunya) [68,75].

En tractar-se de substàncies altament persistents, lipofíliques i que s'acumulen en l'organisme, la mesura de les concentracions de CTPs en un moment puntal pot ser considerada representativa de l'exposició al llarg de la vida [10]. Cal tenir en compte, però, que diferències en característiques com l'IMC, el canvi de pes al llarg de la vida i factors relacionats amb l'estil de vida (paritat, lactància, etc.) poden afectar a les concentracions acumulades finalment per cada persona. De fet, un dels objectius de la recerca ha estat l'anàlisi de la influència d'aquestes variables en les concentracions detectades (vegeu els *Articles A1, A2 i A4* de l'*Annex A*) [67,68,70].

Un punt rellevant en la mesura de les concentracions de CTPs –degut a la seva alta lipofilicitat– és la correcció per lípids totals, és a dir, tenir en compte les variacions de les concentracions en sang en funció dels lípids totals presents en aquesta [153,154]. La correcció s'acostuma a fer dividint la concentració de cada compost analitzat per la concentració de lípids totals. El principal motiu per dur-la a terme és els canvis que es produeixen en les concentracions de lípids en sang durant al dia en funció de l'estat de dejú. No obstant, en algunes de les anàlisis realitzades en la recerca de la tesi

[73,74], la correcció per lípids podria suposar un sobreajust, ja que tant la diabetis tipus 2 com els fenotips metabòlics alterats s'associen a canvis en les concentracions de lípids en sang. A més, cal tenir present que alguns estudis indiquen com alguns CTPs també podrien alterar el perfil lipídic i que, per tant, aquesta alteració podria formar part del mecanisme d'actuació dels CTPs a l'hora de causar diabetis i altres alteracions metabòliques [98,155,156]. Tot i que el coneixement existent encara no permet determinar amb certesa quina és la millor opció, en els casos mencionats –tenint en compte que tots els participants estaven en dejú– vam optar per realitzar les anàlisis utilitzant les concentracions de CTPs sense corregir per lípids [73,74].

Nou indicador d'exposició a múltiples compostos

El 'nombre de compostos detectats a altes concentracions' –aplicat en el nostre cas majoritàriament com el percentatge de participants que presenten concentracions en el quartil o en el decil superior d'un cert número de compostos– depèn tant del número de compostos analitzats com del grau de correlació que hi hagi entre aquests compostos. Aquest indicador ens permet conèixer com es plasma l'efecte d'aquestes correlacions, és a dir, ens permet conèixer de forma senzilla si els individus amb les concentracions més elevades d'algun compost també tenen les concentracions més elevades d'altres compostos. Es podria dir que permet plasmar fins a quin punt coincideixen (són les mateixes) les persones amb les concentracions més elevades dels diferents compostos. El fet que aquelles persones que tenen concentracions altes de certs compostos també tinguin concentracions elevades d'altres compostos suposa un motiu addicional de preocupació.

Una qüestió relacionada amb l'exposició a múltiples compostos, però que queda fora de l'abast de la present tesi, és la que aborda l'anomenat exposoma [40,157,158]. Tal com indiquen Dennis i col·laboradors existeixen raons per les que els mètodes de biomonitorització més tradicionals i els més innovadors han d'integrar-se i complementar-se entorn els objectius científics que persegueix l'estudi de l'exposoma [159]. També va més enllà dels propòsits de la tesi l'estudi dels efectes de l'exposició a les diferents barreges de compostos a les que es troba exposada la població. No obstant, sí que en la població de Catalunya, hem trobat com aquells participants amb un número més gran de compostos en el quartil superior tenien major risc de patir diabetis tipus 2 (vegeu la Taula 2 de l'*Article A6* de l'*Annex A*) [73].

Cal assenyalar la vigència de l'interès en desenvolupar nous mètodes per conèixer i caracteritzar en detall les combinacions de compostos a les que es troba exposada la població. Kapraun i col·laboradors han aplicat un nou mètode que els ha permès identificar 90 combinacions formades per relativament pocs compostos en almenys un 30% dels participants en la NHANES del període 2009-2010 [86].

5.2.4. Biaixos i variables confusores

Cal tenir present que la recerca sintetitzada en aquesta tesi sobre els efectes en la població de l'exposició a CTPs es realitza sempre en el marc d'estudis observacionals, ja que òbviament no fóra ètic ni factible fer estudis experimentals. Aquest marc ètic i metodològic implica, inevitablement, la limitació de no poder controlar tots els factors confusors que poden operar en aquest tipus d'estudis (observacionals); és una qüestió fonamental que sovint afecta també altres ciències de la salut, la vida i la societat [40].

En cadascun dels articles s'han tractat i discutit els possibles biaixos i variables confusores pel que, a banda dels aspectes comentats en apartats anteriors del present capítol, a continuació només s'apunten aquells més generals i que poden afectar de forma conjunta a la recerca de la tesi.

Dades autodeclarades

Convé tenir ben present el fet que part de la informació utilitzada és autodeclarada; és a dir, referida per la persona participant en l'estudi, provinent de les respostes dels participants al qüestionari de l'enquesta de salut, de l'examen de salut en el cas de l'estudi de Catalunya, o del qüestionari complementari en el cas de l'estudi de Barcelona (vegeu el capítol de *Metodologia*). Aquest fet comporta un possible biaix de memòria [40,140]. En l'estudi de Barcelona, per exemple, és autodeclarada la informació utilitzada sobre canvi de pes, recepció de lactància materna durant la infància o, en les dones, paritat i lactància dels fills/filles (vegeu l'*Article A2* de l'*Annex A*) [68]. Són dades rellevants que, per altra banda, normalment no formen part dels estudis de biomonitorització, com passa en el cas de l'estudi de Catalunya (excepte per la variable paritat, sí disponible en l'ESCA). La informació sobre classe social, educació i trastorns crònics utilitzada en l'estudi de Catalunya també és autodeclarada (*Article 1* capítol de *Resultats)* [72].

Manca de dades sobre dieta i altres fonts d'exposició

La manca d'informació sobre dieta dels participants és una de les limitacions de la recerca realitzada. Ni en l'Enquesta de Salut de Catalunya ni en l'Enquesta de Salut de Barcelona es recollia aquesta informació. En població no exposada laboralment la dieta és la principal font d'exposició als CTPs estudiats [160]. Tot i que les concentracions d'aquests contaminants en els aliments en el temps pot variar, es coneix com determinats aliments són fonts importants d'exposició; com per exemple és el cas del peix, que apart d'altres agents químics ambientals com el mercuri, també és una clara font d'exposició a PCBs [161- 165]. Vegeu els nivells detectats i l'estimació de la ingesta de PCBs i de pesticides organoclorats en els estudis de 'dieta total' que ha anat realitzant l'Agència de Salut Alimentària de Catalunya (ACSA) [166]. Cal comentar que malauradament en els darrers temps

l'ACSA pràcticament no publica cap nou estudi de l'evolució de CTPs i altres contaminants en la dieta de la població catalana.

De la mateixa manera que en els estudis de la present tesi no disposem d'informació sobre dieta, tampoc disposem d'informació sobre possibles exposicions ocupacionals. Tot i que l'anàlisi de les fonts d'exposició queda fora dels propòsits de la recerca realitzada, és cert que la manca d'informació sobre aquestes pot jugar un paper confusor, especialment a l'hora d'estudiar la influència en les concentracions corporals d'altres variables com la classe social i l'educació, ja que els patrons de dieta poden variar en funció d'aquestes característiques (vegeu l'apartat de discussió de l'*Article A4* de l'*Annex A*) [70].

Altres aspectes a considerar inclouen, per exemple: el fet que especialment en els estudis de Barcelona i Catalunya, el número de compostos analitzats (19 compostos, 8 detectats en més del 80% de la població) es pot considerar baix. La incorporació d'un nombre més elevat de compostos i incloure altres tipus de contaminants (com els retardants de flama, els compostos perfluorats etc.) podria aportar informació rellevant. Sense oblidar, però, que l'alt nombre de comparacions dut a terme en les anàlisis pot donar lloc en algun cas a falsos positius.

5.3. Implicacions per la salut pública

Les possibles implicacions per la salut pública, sanitàries i socials dels nostres resultats les hem analitzat en profunditat en nombrosos treballs, ja citats en aquesta tesi (vegeu, també l'*Annex B*). El coneixement obtingut posa de manifest com la contaminació per CTPs és una problemàtica sistèmica [40] que demana una visió poblacional i no pot ser valorada només des d'un punt de vista individual. De fet, cada persona per si sola té poques opcions per disminuir la seva exposició i les concentracions dels plaguicides organoclorats i dels PCBs que hem detectat en la immensa majoria de la població de Catalunya i de la ciutat de Barcelona. El manteniment i desenvolupament de polítiques enfocades a la disminució de l'exposició poblacional són factors clau [167]. Com també hem comentat a bastament, les visions sistèmiques i poblacionals no menystenen les dimensions individuals, també necessàries.

La contaminació generalitzada emfatitza la necessitat que –de la mateixa manera que es realitza a Estats Units o Alemanya– a Catalunya, la resta d'Espanya i el conjunt d'Europa es desenvolupin programes de biomonitorització que permetin dur a terme un seguiment periòdic, no només de les concentracions poblacionals dels compostos analitzats en els estudis de Catalunya i Barcelona, sinó també dels molts altres compostos als que estem exposats (des dels retardants de la flama com els PBDEs, fins a plastificants com els ftalats); molts d'aquests, a diferència dels inclosos en la present

tesi, són compostos no persistents però als quals hi estem exposats diàriament. En el plantejament de programes o iniciatives de vigilància de la contaminació per CTPs i altres agents químics ambientals és important que es consideri com diferents variables sociodemogràfiques, com l'edat, el sexe i també per exemple el nivell educatiu, poden influenciar tant en la participació en els estudis com en les concentracions corporals dels contaminants estudiats. A més, també cal que es plantegi i s'abordi com es realitza la comunicació dels resultats individuals als participants i la comunicació dels resultats generals a la societat [139,168,169].

Els programes de biomonitorització són essencials per entendre els patrons, les tendències i els determinants de la contaminació poblacional per CTPs i altres agents químics ambientals. A més, aquest tipus d'iniciatives també representen una peça clau a l'hora d'incrementar el coneixement i la conscienciació de la població, així com el suport a polítiques i estratègies poblacionals que impliquin diferents actors, des del govern a institucions, empreses i altres agents socials rellevants. De fet, la clara disminució de les concentracions observades dels CTPs estudiats en la població de Barcelona entre els anys 2002 i 2006 mostra com les polítiques aplicades fins al moment –principalment per l'adopció del Conveni d'Estocolm a nivell internacional– estan tenint una repercussió beneficiosa a nivell poblacional.

El coneixement sobre les implicacions de l'exposició a determinats CTPs –com la contribució a l'aparició d'alteracions metabòliques, incloent la diabetis tipus 2– posa de manifest com part de la càrrega de malaltia de la societat pot ser deguda a la contaminació general de la població per aquest tipus de compostos [119]. Per tant, el coneixement generat contribueix a reforçar la necessitat tant de caracteritzar la contaminació poblacional com d'aplicar polítiques de disminució d'aquesta. A més, el fet que estiguem exposats simultàniament a múltiples compostos i els efectes que se'n poden derivar també emfatitza la necessitat de protegir-nos com a societat d'aquestes exposicions [77,139,170].

En resum, el coneixement generat és útil tant a l'hora d'avaluar l'impacte i els efectes de la contaminació de la població per CTPs, com a l'hora d'avaluar l'impacte de les polítiques públiques i privades que es puguin realitzar per reduir-la [4,7,8,167].

5.4. Continuïtat i futures línies de recerca

La recerca realitzada en la present tesi té una clara continuïtat en l'estudi que s'està duent a terme en el marc d'un projecte finançat pel *Fondo de Investigación en Salud* (FIS) del *Instituto de Salud Carlos III*. Els objectius d'aquest projecte inclouen entre d'altres:

- l'estudi de l'evolució temporal en la població de la ciutat de Barcelona de les concentracions dels CTPs analitzats en els estudis inicials del 2002 i 2006 (plaguicides organoclorats i PCBs) en una nova mostra de participants representativa de la població general de Barcelona de l'any 2016. Concretament, en el marc de l'Enquesta de Salut de Barcelona realitzada per l'Agència de Salut Pública de Barcelona corresponent als anys 2016-2017, es van obtenir mostres de sang i orina d'una nova mostra representativa de la població general, constituïda aquest cop per 240 participants;

- l'anàlisi de nous tipus de compostos, tant en les mostres dels participants dels estudis inicials de Catalunya (2002) i Barcelona (2006), com en l'estudi en població general de Barcelona de l'any 2016. Els nous compostos a analitzar inclouen PBDEs, metalls, dioxines, hidrocarburs aromàtics policíclics (PAHs), ftalats i fenols;

- l'estudi prospectiu de la influència de les concentracions de CTPs en la mortalitat, trastorns crònics i hospitalitzacions transcorreguts més de 15 anys (període 2002-2018) en la mostra de participants representativa de la població general de Catalunya. Aquest objectiu es realitza a partir del creuament de les dades de l'estudi inicial del 2002 amb el Registre de Mortalitat i el Conjunt Mínim Bàsic de Dades. Encara que pocs estudis han analitzat aquesta relació en població general, hi ha raons per pensar que els CTPs poden tenir un cert impacte sobre la mortalitat [163,171].

La realització d'un nou examen de salut a nivell de Catalunya que inclogués l'estudi de les concentracions de CTPs, o de forma més formal, la instauració per part de l'administració d'un programa de biomonitorització de les concentracions de CTPs i altres agents químics ambiental a nivell de Catalunya, permetria fer el seguiment de la contaminació al llarg del temps. Si es plantegés un projecte similar a nivell d'Espanya les dades obtingudes en la recerca realitzada en aquesta tesi, també servirien com a un bon punt de referència, juntament amb l'estudi de Canàries, per valorar l'evolució de les concentracions d'aquests contaminants en població general.

Finalment, remarcar la necessitat de dur a terme estudis amb dissenys longitudinals prospectius que permetin refutar o confirmar els resultats obtinguts referents a alguns efectes adversos en la salut, especialment pel que fa a les relacions de determinats CTPs amb l'alteració del fenotip metabòlic, tenint en compte tant el paper de l'IMC com el d'altres factors ambientals i individuals. Aquest tipus d'estudis, que a més integressin aspectes de les ciències socials, també serien d'interès per determinar el paper que juguen factors socioeconòmics i culturals, entre d'altres possibles determinants, en l'exposició a contaminants al llarg de la vida i en períodes que puguin ser especialment crítics.

6. CONCLUSIONS

Les principals conclusions, exposades en relació a les hipòtesis específiques plantejades en l'apartat 2.1., són les següents:

1.- L'anàlisi de la distribució de les concentracions de CTPs mostra com més del 80% de la població general de Catalunya i de la ciutat de Barcelona tenia concentracions sèriques detectables de diversos plaguicides organoclorats i de PCBs. El DDE es va detectar en el 100% de la població general de Catalunya i de la ciutat de Barcelona.

   És probable que la contaminació de la població general per aquests compostos hagi disminuït considerablement amb el temps, ja que les concentracions de la població de Barcelona l'any 2006 eren notablement inferiors a les de l'any 2002.

2.- En la població de Catalunya i de Barcelona, diversos factors sociodemogràfics com el sexe, l'edat/cohort de naixement i l'IMC influïen en les concentracions sèriques de CTPs:
   a) les dones presentaven concentracions de plaguicides organoclorats més elevades que els homes;
   b) les concentracions tant dels plaguicides com de PCBs eren majors en els grups de més edat; i
   c) les concentracions de PCBs eren majors en el grup de població amb pes normal que en el grup amb sobrepès/obesitat.

   Malgrat l'absència de patrons clars en les relacions amb indicadors de posició socioeconòmica, en homes, el nivell educatiu es va relacionar amb les concentracions de CTPs, detectant-se majors concentracions en els universitaris un cop ajustant per edat i IMC.

3.- L'anàlisi de la distribució de cada compost en la població general de Catalunya i en la de Barcelona mostra com una petita part de la població tenia concentracions molt més altes que la gran majoria de la resta de la població.

   Hi ha una certa part tant de la població de Catalunya com de la dels Estats Units que presentava concentracions sèriques elevades de diversos CTPs a la vegada; és a dir, presentava un considerable 'nombre de compostos detectats a altes concentracions'. Aquest indicador

depèn tant del número de compostos analitzats com del grau de correlació que hi hagi entre aquests compostos.

4.- En la població de Catalunya s'observà que unes majors concentracions sèriques de CTPs estaven relacionades amb una pitjor salut autopercebuda i una major prevalença de trastorns crònics; tot i que la relació amb el nombre de trastorns crònics es mantenia per alguns compostos un cop es considerava l'efecte de l'edat, la relació amb la salut autopercebuda venia explicada bàsicament per la relació positiva entre l'edat/cohort de naixement i els trastorns crònics.

5.- En la població de Catalunya s'observà com majors concentracions sèriques d'alguns CTPs (com PCBs i HCB) es relacionaven amb una major prevalença de diabetis tipus 2 i de prediabetis i (en el cas de compostos com PCBs, HCB i β-HCH) de síndrome metabòlica. Aquestes relacions s'afeblien però es mantenien quan es considerava l'efecte de l'edat, el sexe i l'IMC.

Finalment, majors concentracions d'alguns CTPs (com PCBs, HCB i β-HCH) es relacionaren amb un fenotip metabòlic alterat (definit a partir dels nivells de glucèmia, pressió arterial, colesterol, triglicèrids, proteïna C-reactiva i l'índex HOMA-IR). Aquesta relació s'observà en persones amb sobrepès/obesitat i també en persones amb pes normal. En les persones amb normopès, la magnitud de les relacions observades era superior que en el grup amb sobrepès o obesitat.

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ANNEXOS

Annex A. Publicacions relacionades

Article A1

Títol: Distribution of blood concentrations of persistent organic pollutants in a representative sample of the population of Catalonia.

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Distribution of blood concentrations of persistent organic pollutants in a representative sample of the population of Catalonia

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ABSTRACT

Background: Although virtually all populations worldwide are commonly exposed to numerous persistent organic pollutants (POPs) and human concentrations vary widely, only a few countries conduct nationwide surveillance programs of POP concentrations in representative samples of the general population.
Objective: To evaluate the distribution of serum concentrations of nineteen POPs and their main predictors in a representative sample of the general population of Catalonia.
Methods: Participants in the Catalan Health Interview Survey aged 18–74 years were interviewed face-to-face, gave blood, and underwent a physical exam. Graphs (including "POP Geoffrey Rose curves") were used to represent the full population distribution of each POP in the 919 participants. Through multivariate statistical models we analyzed the influence on POP concentrations of sex, age, body mass index (BMI), socioeconomic status and, in women, parity.
Results: We detected dichlorodiphenyltrichloroethane (p,p′-DDT), dichlorodiphenyldichloroethane (p,p′-DDE), polychlorinated biphenyls (PCBs) congeners 118, 138, 153 and 180, hexachlorobenzene (HCB) and β-hexachlorocyclohexane (β-HCH) in more than 85% of the subjects. p,p′-DDE, HCB and β-HCH showed the highest concentrations (median = 399, 159 and 92 ng/g lipid, respectively). Distributions were highly skewed and interindividual differences were up to 7700-fold. POP levels differed significantly by gender, age, BMI, educational level, and parity.
Conclusions: In Catalonia, an advanced European society, exposure to POPs remains common, a vast majority of the population has much lower blood concentrations than a relative minority, and the population distributions of POP are hence highly skewed to the right. Shifting distributions towards lower concentrations requires more energetic policies and population strategies.

1. Introduction

Worldwide, systems monitoring human contamination by environmental chemical agents in a representative sample of the general population are surprisingly scarce (Porta et al., 2008; National Research Council, 2006; Thornton et al., 2002). Persistent organic pollutants (POPs) as dioxins, dichlorodiphenyltrichloroethane (DDT), hexachlorobenzene (HCB), hexachlorocyclohexanes (HCHs), and polychlorinated biphenyls (PCBs) are highly lipophilic and resistant to degradation; they thus bioaccumulate in the environment, food chains and living organisms, and are known or reasonably suspected to harm human health (Porta et al., 2008; National Research Council, 2006; Thornton et al., 2002; United Nations Environment Programme, 2003, 2009; World Health Organization, 2003; Department of Health

Abbreviations: β, regression coefficient; CI, confidence interval; DDD, dichlorodiphenyldichloroethane; DDE, dichlorodiphenyldichloroethene; DDT, dichlorodiphenyltrichloroethane; GLM, General Linear Model; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; OCs, organochlorine compounds; PCBs, polychlorinated biphenyls; PeCB, pentachlorobenzene; POPs, persistent organic pollutants; CHIS, Catalan Health Interview Survey; IMIM, Institut Municipal d'Investigació Mèdica; WHO, World Health Organization; BMI, body mass index.

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and Human Services, 2009; Patterson et al., 2009). Their potential adverse effects include neurotoxicity (World Health Organization, 2003; Grandjean & Landrigan, 2006), endocrine disruption and reproductive disorders (Diamanti-Kandarakis et al., 2009; Porta, 2006; Lee et al., 2007), cardiovascular effects (United Nations Environment Programme, 2003; World Health Organization, 2003; Institute of Medicine, 2003), and carcinogenicity (e.g., as tumor promoters or through other indirect, non-genotoxic mechanisms) (Engel et al., 2007; McGlynn et al., 2006; Luch, 2005; Irigaray & Belpomme, 2010; Hernández et al., 2009; Lee et al., 2009). As a consequence, many of these global and local ('glocal') contaminants have been targeted for elimination or reduction by governments, and treaties as the Stockholm convention encourage countries to integrate population-based surveillance of POP levels in humans within their health monitoring systems (Porta et al., 2008; Thornton et al., 2002; Patterson et al., 2009; Porta & Zumeta, 2002).

Since the end of World War II, vast changes have occurred in human exposure to POPs in most populations worldwide: while the body burden of many compounds (e.g., some organochlorines) first increased and then decreased, levels of other POPs seem stagnant, and new synthetic chemicals as flame retardants have in recent years contaminated humans widely (Porta et al., 2008; National Research Council, 2006; Thornton et al., 2002; United Nations Environment Programme, 2003, 2009; World Health Organization, 2003; Department of Health Human Services, 2009). Surveillance of such patterns has seldom been undertaken on a nationwide, continued basis, and the generalizability of many studies is limited (Porta et al., 2008; United Nations Environment Programme, 2003; Angerer et al., 2007; Needham et al., 2007; Glynn et al., 2003). Certainly, concentrations have been assessed in etiological studies and in some programs based on volunteers and convenience samples; since the 1970s the number of studies and reports that analyzed POP concentrations in human populations increased (Porta et al., 2008). Surprisingly, however, only the USA and Germany regularly monitor POP concentrations in representative samples of the general population (Porta et al., 2008; United Nations Environment Programme, 2003; Department of Health and Human Services, 2009; Becker et al., 2002; Link et al., 2005; Umweltbundesamt, 1985–2006; Ueda et al., 1999; Buckland et al., 2001; Harden et al., 2004; Cerná et al., 2007, 2008).

Monitoring programs are useful to quantify trends and patterns of human exposure to POPs and other environmental chemical agents, to identify highly exposed minorities in the often skewed distributions (Patterson et al., 2009; Angerer et al., 2007; Needham et al., 2007; Viso et al., 2009), and as a framework to evaluate health impacts and the effectiveness of public and private policies aimed at decreasing exposure to POPs (Department of Health and Human Services, 2009; Viso et al., 2009). Unfortunately, the population health impacts of POPs have seldom been assessed as comprehensively as those of a few other environmental pollutants. An outstanding example is US blood concentrations of lead, which have decreased since the mid-1970s following reductions in aerosolized lead emitted from combustion engines that used leaded gasoline; the corresponding increases in child health and intelligence have yielded enormous social gains, and economic benefits from just increased productivity are estimated over $110 billion per birth cohort (Department of Health and Human Services, 2009; Grosse et al., 2002).

In the general population, lifelong accumulation of POPs is largely the result of low-dose contamination of fatty foods (United Nations Environment Programme, 2003, 2009; World Health Organization, 2003; Department of Health and Human Services, 2009; Institute of Medicine, 2003; Darnerud et al., 2006; Baars et al., 2004; Kiviranta et al., 2001; Wang & Needham, 2007). There is little each individual can do to decrease personal exposure over the long term, and prevention of human POP contamination cannot be treated simply as an individual problem; rather, population strategies and policies are required (Porta et al., 2008; Rose, 1992; Porta, 2004). Therefore, it is also surprising that few efforts have been devoted to the analysis of the full population distribution of POP concentrations in humans. It is also remarkable how little is known on the statistical and epidemiological properties of such distributions.

In 2002, the Department of Health of the Catalan government undertook a new Health Interview Survey, which included a physical examination and blood drawing in a sample of participants. Later, the government decided to support the academic initiative to analyze the distribution of blood concentrations of POPs in the population. Serum concentrations of 19 POPs were thus determined in 919 subjects.

The aim of this report was to analyze the distribution of serum concentrations of such POPs in the non-institutionalized adult population of Catalonia, and its main sociodemographic predictors.

2. Materials and methods

2.1. Study population and health interview survey

Catalonia, an economically-advanced autonomous region in the North-east of Spain, had a population of 6,506,440 inhabitants in 2002. As part of its mission to monitor health status and use of health services, that year the Department of Health of the Catalan government conducted a new health interview survey (Juncà et al., 2003). The main objective of the Catalan Health Interview Survey (CHIS) was to obtain information on perceived health, health-related behaviors, and use of health services (Departament de Salut de la Generalitat de Catalunya, 2002). The selection of a representative sample of the non-institutionalized population followed a complex design, including a multiple-stage random sampling strategy. In the first sampling stage municipalities (for the city of Barcelona, districts) were selected from the eight health areas of Catalonia, according to their population size (eight strata). Based on the size of the municipality (or district), at the second sampling stage a random sample from the Census was used to select individuals using proportional probabilities. In order to guarantee that the demographic structure of the population is preserved with respect to the area of residence, age and gender, sampling weights were used in the statistical analyses of the present study (Juncà et al., 2003; Departament de Salut de la Generalitat de Catalunya, 2002). The target population of CHIS was all non-institutionalized residents in Catalonia in 2001. Face to face interviews were conducted at home by trained staff from October 2001 to April 2002.

At the end of the CHIS interview, participants 18–74 year old were offered to take part in a health examination, which included a physical exam, a supplementary interview, and the collection of urine and blood samples. Among those who explicitly consented to participate, a sample was randomly selected, contacted by phone and given an appointment at the primary health centre nearest to their home. Participation was voluntary and no economic compensation was offered. A total of 1374 individuals participated during 2002 in the health examination. Trained nurses recorded the weight and height, and the corresponding body mass index (BMI) was computed (measured weight [kg] divided by measured height squared [m^2]). Participants were asked to fast for 12 h before blood extraction. The blood sample was drawn by venipuncture, kept refrigerated, and centrifuged within 4 h; the separated serum was first stored frozen at −20 °C to determine immunologic, biochemical and nutritional parameters. Once these initial analyses were completed, the remaining serum was kept frozen at −80 °C until 2006, when POP concentrations began to be analyzed. Information on blood concentrations of lipids and at least 1 mL of serum (for organochlorine analyses) was available from 919 participants [Table 1 of supplementary material] (Departament de Salut de la Generalitat de Catalunya). There were no significant differences between them and the remaining participants in the health examination with respect to age, sex, BMI, educational level and social class.

2.2. Socioeconomic variables

We analyzed the influence upon POP concentrations of sex, age, educational level, occupational social class, and BMI. Age was grouped in the same categories previously used for calculating sample weights in the health examination (Juncà et al., 2003). The lower educational category of subjects without formal studies included the illiterate. To assign occupational social class we used the Spanish classification, which is based on Goldthorpe's scheme (Porta et al., 2009a); class was hence assigned through the current or last occupation of the head of the household, whom in 46.3% of cases was the participant himself.

The average age of participants was 45 years and 57% were women. About 20% were obese (BMI $\geq$ 30 kg/m^2), 72% were born in Catalonia, 85% had completed at least primary schooling (1st. stage) and 47% were from occupational social class IV [Table 1 of supplementary material]. There were no significant differences in the distribution of birth place, educational level and social class by sex. Men were 3 years older than women (median) and tended to have a higher BMI. These differences were accounted for in multivariate analyses.

2.3. Analytical chemical methods

We analyzed the following POPs in serum: o,p′-DDT, p,p′-DDT, o,p′-DDE, p,p′-DDE, o,p′-DDD, p,p′-DDD, PCBs 28, 52, 101, 118, 138, 153, and 180, PeCB, HCB, α-HCH, β-HCH, γ-HCH and δ-HCH (Porta et al., 2009b, 2009c). 10 mL screw-capped Pyrex centrifuge tubes capped with Teflon septa were used to keep and digest the samples. 25 mL of the surrogate solution (0.36 mg/L of tetrabromobenzene (TBB) and 0.52 mg/L of PCB 209), were added to 1 mL aliquots of serum in the same Pyrex centrifuge tubes where the samples were stored. Acid digestion of the mixture was performed by the addition of 3 mL of n-hexane and 2 mL of concentrated sulphuric acid. Gas chromatography (GC) analyses were performed with an Agilent Technologies model GC-6890N provided with an ECD and a 60 m, 0.25 mm i.d. DB-5 column (J & W Scientific, Folsom, CA, USA; film thickness 0.25 μm). A fused silica precolumn of 2 m × 0.32 mm i.d. was used and renewed every 30 samples. Selected samples were analyzed by NICI GC-MS with a Fisons MD 800. The linear range of the detector was determined from injection of standard mixtures. Calibration lines were performed for all compounds mentioned above. These compounds were then quantitated in the samples by the external standard method after replicate analysis. The concentrations of HCB and β-hexachlorocyclohexane (β-HCH) were corrected for volatility losses using TBB as internal standard. The recoveries of TBB and polychlorinated biphenyl 209 were 100.6% (±20.5) and 94.5% (±19.7), respectively. The main statistical analyses were limited to compounds that were detected (i.e., were above the limit of detection, LD) in 85% of participants. All analyses were carried out in the Department of Environmental Chemistry (IIQAB-CSIC) in Barcelona, Spain. Limits of quantification ranged from 0.0069 ng/mL for PCB 101 to 0.0706 ng/mL for γ-HCH. When a sample had a concentration of a compound below the detection threshold or LD, it was assigned the mid-value of this limit; when a POP was detected but under the quantification threshold, the mid-value between detection and quantification limits was used (Porta et al., 2009b, 2009c).

Total cholesterol and triglycerides levels were determined enzymatically (Txad-Pap and CIN-UV methods, respectively), using serum obtained in the health examination (Departament de Salut de la Generalitat de Catalunya, 2002). Total serum lipids (TL) were calculated by the standard formula 2 of Phillips et al., which is based on total cholesterol and triglycerides (Porta et al., 2009b; Phillips et al., 1989; Bernert et al., 2007). OC concentrations were individually corrected for TL by dividing the crude serum OC concentration by TL, and are expressed in nanograms per gram lipid (ng/g lipid). Among the 919 individuals, mean (standard deviation) serum concentrations of total cholesterol, triglycerides and total lipids were, respectively, 193.2 (40.4), 98.6 (61.0) and 599.5 (128.9) mg/dl.

2.4. Statistical analysis

Univariate statistics were computed as customary (Armitage et al., 2002; Kleinbaum et al., 1998). Kruskal–Wallis' and Mann–Whitney's *U* tests were used to assess differences in concentrations of POPs by sociodemographic characteristics of the participants. Spearman's rank correlation coefficients (ρ) were computed to evaluate correlations among pairs of POPs. The Kolmogorov–Smirnov test for normality was used to check the distributions of POPs; as none was normal, log-transformed values were used in regression analyses. Density plots were used to chart the distributions of POP serum concentrations in the different age and sex population groups; we named these graphs "POP Geoffrey Rose curves" to emphasize the analogy with Rose's 'population strategy' (Porta et al., 2008, 2009c; Rose, 1992; Porta, 2004; Porta, 2008). We analyzed three properties of the curves: kurtosis, skewness, and coefficient of variation. Kurtosis is a measure of the peakedness or sharpness of the peak of a distribution curve, i.e., of the extent to which the curve is flatter or more peaked than a distribution that has a kurtosis value of zero. Skewness is a measure of asymmetry in frequency distributions, i.e., the degree to which frequencies trail towards extreme scores in one direction away from the majority of cases. The normal distribution is symmetric and thus has zero skewness. The coefficient of variation is a measure of dispersion equal to the standard deviation of the sample divided by the mean (Armitage et al., 2002; Kleinbaum et al., 1998). Multivariate cluster analysis was used to identify similarities (s) and possible common sources and pathways of exposure for different OCs by an agglomerative hierarchical method (Armitage et al., 2002; Kleinbaum et al., 1998). In order to analyze variations in lipid-corrected, log-transformed concentrations of OCs, General Linear Regression Models (GLM) were used. The main effects of all predictors were independently explored in base models. Confounding variables were retained in the models when they materially altered the estimates. Due to the complex designs of the CHIS and health examination, and in order to compensate for differences in gender, age and place of residence, sample weights were used in the analysis. The level of statistical significance was set at 0.05 and all tests are two tailed. Analyses were conducted using SPSS version 12.0 (SPSS, Chicago, IL, USA, 2003), R version 2.7.1 (2008) and Minitab (version 15, 2007).

3. Results

Eight of the 19 POPs analyzed were each detected in >85% of the study subjects: p,p′-DDT, p,p′-DDE, PCB congeners 118, 138, 153 and 180, HCB and β-HCH. p,p′-DDE was detected and quantified in all samples, while PCB 180 was also detected in everybody and quantified in 99.7% of participants (Table 1 and Fig. 1). The percentage of detection for the rest of compounds ranged between 12% and 64%. Thus, all 19 POPs were detected, and no individual was free from POPs; the smallest number detected in one person was 3 compounds (Fig. 2). Ten or more compounds were detected in 73% of the population (in 67% of participants born in 1973–1984 and in 78% of subjects born in 1928–1942).

The median concentrations of the most frequently detected compounds were (in ng/g lipid): 29.33 for p,p′-DDT and 399.33 for p,p′-DDE; 22.83, 69.47, 100.12 and 77.28 for PCB congeners 118, 138, 153 and 180, respectively; 159.43 for HCB and 91.93 for β-HCH (Table 1). Among the less frequently detected compounds, median concentrations ranged from 0.21 ng/g (PCB 101) to 6.36 ng/g (o,p′-DDT) [Table 2 of supplementary material]. There were substantial interindividual differences: the highest individual concentration of p,p′-DDE (9036.01 ng/g) was over 7700 times higher than the lowest

Table 1
Serum concentrations of POPs detected in over 85% of the Catalan population, by sociodemographic characteristics.

Characteristics	p,p′-DDT	p,p′-DDE	PCB 118	PCB 138	PCB 153	PCB 180	HCB	β-HCH
All participants	29.3 (12.3–56.4)	399.3 (210.5–833.1)	22.8 (10.4–38.0)	69.5 (41.7–112.9)	100.1 (61.9–152.6)	77.3 (49.3–115.7)	159.4 (67.1–357.6)	91.9 (39.1–200.6)
GM and 95th. perc.	23.4 (130.6)	424.0 (2480.8)	17.4 (82.4)	63.5 (209.3)	91.2 (294.1)	75.1 (196.7)	140.1 (894.0)	83.0 (519.1)
Range	0.8, 1252.6	1.2, 9036.0	0.7, 465.0	0.7, 1829.7	0.7, 1912.1	2.6, 2047.2	0.8, 4798.6	1.4, 2716.2
Detected (%)	88.2	100.0	88.6	98.2	99.2	100.0	97.9	96.9
Quantified (%)	81.8	100.0	81.8	96.9	98.5	99.7	97.9	95.5
Non-quantified (%)	6.4	0.0	6.8	1.3	0.7	0.3	0.0	1.4
Non-detected (%)	11.8	0.0	11.4	1.8	0.8	0.0	2.1	3.1
Gender								
Male	27.6 (11.0–50.9)*	336.8 (194.4–752.7)*	21.2 (9.6–37.9)	68.6 (40.7–115.3)	100.6 (61.3–163.0)	82.7 (50.8–126.6)*	104.7 (44.3–239.8)*	70.5 (27.3–150.7)*
Female	33.0 (13.4–61.9)	468.4 (227.8–948.6)	24.2 (12.3–38.8)	70.3 (42.7–110.3)	98.9 (62.2–143.8)	75.0 (48.5–110.3)	247.3 (119.6–522.1)	118.1 (53.8–289.6)
Age (years)								
18–29	20.2 (7.1–43.8)*	190.5 (114.4–286.9)*	11.9 (4.7–21.8)*	35.7 (22.8–58.4)*	51.9 (32.9–77.3)*	43.2 (27.2–60.7)*	61.0 (32.6–122.3)*	29.3 (17.8–59.9)*
30–44	31.6 (12.4–50.9)	350.6 (222.1–656.3)	18.2 (10.4–30.6)	61.9 (43.1–83.8)	87.5 (65.9–114.5)	71.3 (53.0–101.1)	140.9 (57.0–244.6)	76.9 (34.9–119.1)
45–59	27.2 (13.1–57.4)	638.5 (332.7–1156.9)	27.8 (16.7–42.3)	90.7 (61.9–126.2)	125.0 (90.8–176.4)	96.8 (71.4–129.6)	297.7 (144.7–470.8)	164.2 (87.5–259.6)
60–74	45.1 (25.8–79.7)	945.6 (540.4–1507.0)	41.9 (25.0–61.9)	124.3 (85.3–174.0)	173.9 (120.1–252.9)	126.0 (89.1–169.0)	415.0 (214.3–777.9)	252.8 (140.1–440.7)
Body mass index (kg/m^2)								
Underweight	21.3 (13.8–44.1)*	292.2 (114.1–776.7)*	7.1 (1.5–14.1)*	65.9 (15.8–141.5)*	102.5 (20.5–225.1)*	93.1 (26.3–164.7)	38.1 (31.7–81.0)*	28.3 (18.8–67.7)*
Normal range	23.9 (9.5–49.6)	273.5 (182.0–619.0)	17.0 (6.6–28.5)	60.3 (35.7–91.3)	88.4 (51.9–133.5)	72.5 (46.9–111.1)	90.9 (45.9–198.4)	59.0 (25.3–110.4)
Overweight	32.7 (13.4–63.7)	478.0 (222.4–834.4)	26.6 (12.4–43.6)	75.7 (48.0–120.2)	106.8 (68.1–169.0)	83.8 (53.8–127.9)	189.5 (80.1–362.6)	114.7 (45.1–210.4)
Obese	37.2 (22.0–82.6)	678.7 (303.8–1248.9)	31.5 (18.7–52.2)	79.1 (52.1–133.4)	105.5 (73.2–176.0)	74.8 (52.6–119.1)	413.6 (222.2–713.7)	213.9 (109.3–375.3)
Parity[a]								
0	23.4 (8.8–51.2)*	252.5 (142.3–478.8)*	15.1 (7.0–28.6)*	48.5 (26.1–71.6)*	68.6 (38.2–97.8)*	49.5 (29.3–74.4)*	124.3 (59.0–199.4)*	60.5 (26.4–103.1)*
1	38.0 (19.5–63.2)	490.9 (253.9–819.8)	25.1 (14.6–39.6)	73.0 (43.7–133.6)	100.6 (66.1–156.1)	77.9 (51.5–116.7)	309.5 (116.8–425.7)	119.3 (51.2–305.1)
2	34.1 (15.7–63.7)	607.6 (284.4–1101.9)	25.5 (12.4–38.1)	77.2 (46.4–113.2)	109.8 (74.4–152.5)	82.8 (59.9–113.1)	316.6 (172.9–636.2)	164.6 (82.4–307.5)
≥3	41.5 (22.1–70.3)	930.6 (395.0–1515.5)	33.7 (20.1–53.3)	93.2 (68.9–139.4)	133.3 (99.2–186.6)	98.9 (71.8–130.1)	472.7 (292.3–829.2)	272.3 (146.1–446.3)
Occupational social class								
V (less affluent)	35.1 (15.9–78.6)*	667.5 (270.7–1182.8)*	19.4 (6.7–41.8)*	64.6 (48.1–129.0)*	91.7 (72.5–155.0)*	67.3 (47.3–130.0)	99.9 (34.0–480.3)	70.8 (24.7–254.4)
IV	28.3 (11.0–56.3)	377.3 (203.6–856.6)	22.5 (9.3–37.1)	67.8 (38.9–108.0)	97.5 (56.9–143.8)	77.7 (48.0–111.3)	165.2 (68.9–378.2)	95.7 (38.6–207.8)
III	32.7 (13.2–65.4)	423.7 (222.1–829.4)	23.2 (13.4–45.7)	72.5 (50.1–117.1)	105.2 (71.3–160.8)	82.6 (56.8–116.8)	170.6 (72.9–342.0)	88.1 (43.1–193.4)
II	25.9 (11.5–47.9)	377.3 (208.9–750.0)	28.1 (14.6–37.8)	82.9 (44.1–119.8)	108.6 (64.8–169.9)	86.7 (49.1–122.8)	154.0 (68.0–312.6)	107.4 (47.1–177.1)
I (most affluent)	27.2 (10.6–48.8)	277.4 (125.1–561.9)	16.1 (8.8–31.1)	51.7 (36.2–87.0)	80.0 (36.2–110.7)	65.7 (44.9–100.3)	144.7 (72.8–285.6)	77.1 (33.9–157.3)
Educational level								
WFE	48.2 (20.1–87.4)*	800.3 (390.3–1325.0)*	31.3 (18.7–54.8)*	101.6 (68.4–143.9)*	140.1 (98.9–206.5)*	97.9 (76.9–140.0)*	421.9 (227.4–792.5)*	245.1 (128.5–438.3)*
Primary (I)[b]	33.4 (14.8–59.1)	579.0 (249.9–1396.5)	25.4 (13.6–42.9)	86.8 (52.7–137.3)	119.9 (78.3–191.9)	97.0 (61.3–130.8)	190.1 (81.5–459.4)	131.3 (54.7–252.6)
Primary (II)[c]	23.8 (11.1–48.9)	296.5 (172.6–681.7)	17.1 (6.1–31.3)	57.6 (33.0–95.0)	82.1 (45.7–132.8)	65.7 (45.5–104.0)	142.8 (49.8–290.0)	65.9 (27.6–154.4)
Secondary	29.2 (11.7–52.2)	294.3 (193.4–609.1)	18.2 (9.9–34.0)	57.0 (34.5–80.2)	82.6 (49.0–113.4)	62.8 (43.2–100.0)	93.8 (45.5–222.2)	60.5 (29.3–118.1)
University	27.2 (6.7–56.4)	301.4 (178.0–693.6)	24.4 (11.7–38.1)	68.7 (44.6–108.1)	96.7 (66.9–145.1)	73.4 (53.8–117.0)	142.7 (60.6–250.3)	77.4 (41.2–130.7)

Results are weighted by gender, age and place of residence to account for the complex sample design.
Frequencies of population characteristics are detailed in Table 1 of supplementary material.
The concentrations are expressed in median (percentile 25–percentile 75) ng/g lipid. The second row for all participants presents the geometric mean (GM) and the 95th percentile. The third row for all participants presents the minimum and maximum concentrations. WFE: without formal education.
*$p<0.05$ (Kruskal–Wallis test).
[a] Women only.
[b] Primary schooling (1st stage).
[c] Primary schooling (2nd stage).

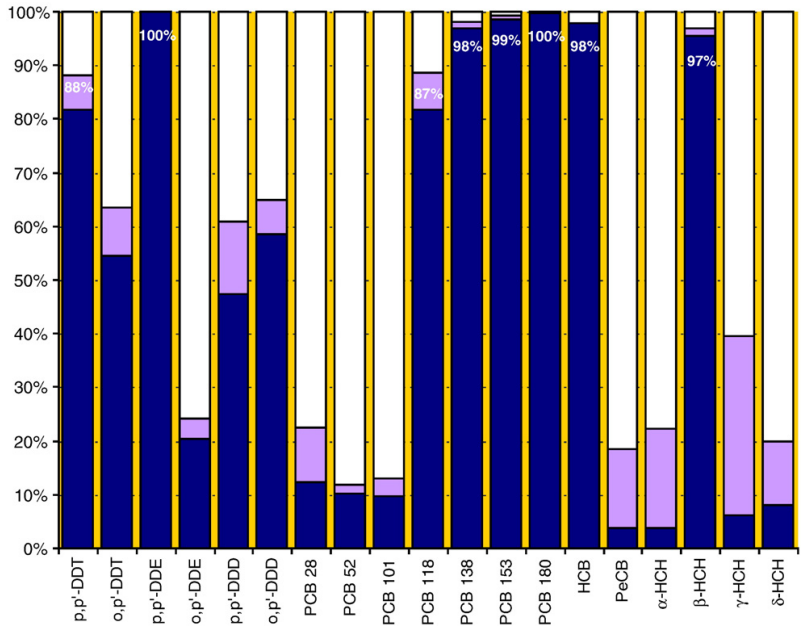

Fig. 1. Percentages of detection of organochlorine compounds in serum in a representative sample of the general population of Catalonia (samples collected in the year 2002). Blue (B): detected and quantified. Purple (P): detected, non-quantified. White: non-detected. The figures inside the bars refer to the percentage of detection (B + P) of the 8 most frequently detected POPs. DDT, dichlorodiphenyltrichloroethane; DDE, dichlorodiphenyldichloroethene; DDD, dichlorodiphenyldichloroethane; PCBs, polychlorinated biphenyls; HCB, hexachlorobenzene; PeCB, pentachlorobenzene; HCH, hexachlorocyclohexane.

(1.17 ng/g); for HCB the corresponding values were 4798.57 and 0.79 ng/g (a 6000-fold difference), and for β-HCH, 2716.16 and 1.35 ng/g (2000-fold). A majority of the population had much lower concentrations than a certain minority.

The two compounds whose serum levels showed maximum similarity were PCB congeners 153 and 180 (similarity [s] = 96.53) (Fig. 1 of supplementary material). The compound closest to them was congener 138 (s = 83.75). The next cluster formed between HCB and β-HCH (s = 90.50). These findings were consistent with results from correlation analyses. The highest Spearman's correlation coefficient was observed between PCBs 138 and 153 (ρ = 0.951), PCBs 153 and 180 (ρ = 0.919), HCB and β-HCH (ρ = 0.894), and PCBs

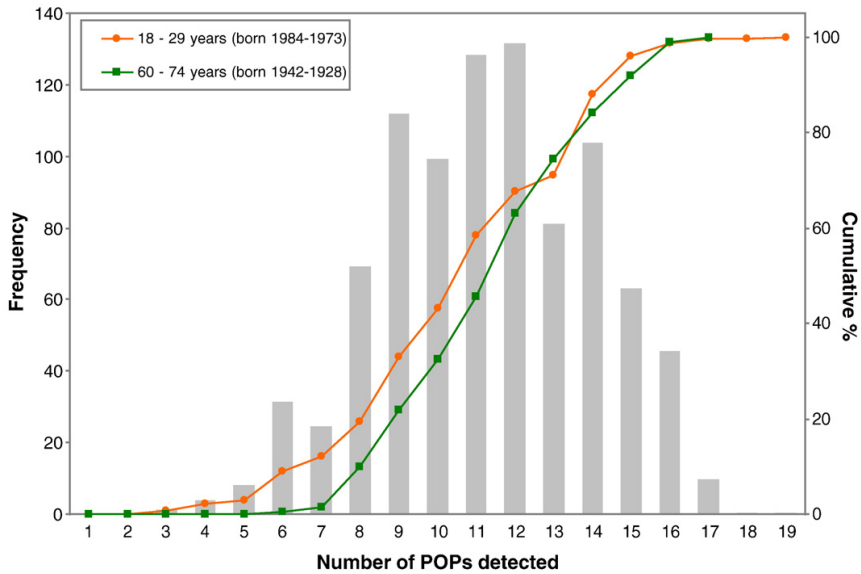

Fig. 2. Number of compounds detected in the study participants.

Table 2
Main sociodemographic predictors of serum concentrations of persistent organic pollutants in women.

Predictor	p,p′-DDT		p,p′-DDE		PCB 118		PCB 138		PCB 153		PCB 180		HCB		β-HCH	
	β	p	β	p	β	p	β	p	β	p	β	p	β	p	β	p
Age	0.026	<0.001	0.040	<0.001	0.032	<0.001	0.028	<0.001	0.029	<0.001	0.025	<0.001	0.057	<0.001	0.059	<0.001
Body mass index																
Continuous (kg/m^2)	0.043	0.002	0.007	0.419	0.015	0.155	−0.013	0.944	−0.016	0.026	−0.032	<0.001	0.043	<0.001	0.028	<0.001
Overweight vs. normal weight	0.171	0.237	−0.127	0.151	0.153	0.166	−0.092	0.267	−0.113	0.137	−0.257	<0.001	0.314	<0.001	0.206	0.012
Obesity vs. normal weight	0.412	0.016	−0.006	0.954	0.221	0.092	−0.182	0.066	−0.233	0.010	−0.445	<0.001	0.431	<0.001	0.245	0.012
Occupational social class																
Social class II vs. I	0.331	0.194	0.265	0.085	0.592	0.002	0.324	0.027	0.196	0.149	0.151	0.151	0.037	0.808	0.125	0.387
Social class III vs. I	0.864	<0.001	0.238	0.076	0.628	<0.001	0.276	0.031	0.118	0.317	0.101	0.274	0.226	0.093	0.163	0.198
Social class IVA vs. I	0.406	0.053	0.159	0.209	0.428	0.007	0.004	0.973	−0.006	0.958	−0.069	0.424	0.047	0.713	0.067	0.574
Social class IVB vs. I	0.370	0.189	0.054	0.749	0.317	0.138	−0.141	0.383	−0.109	0.468	−0.122	0.294	0.068	0.687	−0.058	0.717
Social class V vs. I	0.713	0.011	0.283	0.092	0.459	0.030	0.111	0.487	−0.037	0.803	−0.117	0.310	−0.044	0.793	−0.191	0.228
Manual vs. non manual workers[a]	−0.096	0.143	−0.031	0.671	−0.064	0.487	−0.028	0.001	−0.137	0.032	−0.175	<0.001	−0.092	0.201	−0.106	0.120
Educational level																
Primary schooling (1st stage) vs. WFE	0.084	0.667	0.100	0.404	−0.057	0.699	0.094	0.403	0.022	0.832	0.146	0.070	0.183	0.116	0.095	0.397
Primary schooling (2nd stage) vs. WFE	−0.314	0.144	−0.078	0.555	−0.287	0.079	0.004	0.975	0.004	0.975	0.096	0.280	0.241	0.061	0.021	0.865
Secondary schooling vs. WFE	−0.098	0.667	−0.031	0.824	0.052	0.764	0.035	0.791	0.088	0.467	0.060	0.525	0.022	0.873	−0.051	0.696
University vs. WFE	−0.264	0.267	0.046	0.751	0.060	0.742	0.362	0.008	0.275	0.029	0.297	0.003	0.134	0.346	0.125	0.357
Parity	−0.111	0.023	−0.066	0.029	−0.039	0.297	−0.055	0.050	−0.037	0.153	−0.017	0.401	−0.058	0.045	−0.057	0.040

Results are weighted by age and place of residence. Frequencies of population characteristics are detailed in Table 1 of supplementary material.
Each variable is adjusted by age; parity is further adjusted by BMI.
β: regression coefficient (all concentrations of organochlorine compounds were lipid-corrected and log-transformed).
p: p-value of each category of the variable when comparing with the reference group.
WFE: without formal education.
[a] Non-manual workers: classes I, II and III; manual workers: classes IV and V.

138 and 180 ($\rho = 0.865$). For p,p′-DDT and its main metabolite, p,p′-DDE, ρ was 0.404 (all $p < 0.001$).

The median of the DDT/DDE ratio was 0.06 (mean: 0.11). The ratio decreased with increasing age (median and mean both $p < 0.001$); the median ratio was 0.09, 0.07, 0.04 and 0.05 for age groups 18–29, 30–44, 45–59 and 60–74 years, respectively. Analyses stratifying by age confirmed that there were no differences in the DDT/DDE ratio between men and women in any age group. The ratio was greater

Table 3
Main sociodemographic predictors of serum concentrations of persistent organic pollutants in men.

Predictor	p,p′-DDT		p,p′-DDE		PCB 118		PCB 138		PCB 153		PCB 180		HCB		β-HCH	
	β	p	β	p	β	p	β	p	β	p	β	p	β	p	β	p
Age	0.023	<0.001	0.035	<0.001	0.034	<0.001	0.034	<0.001	0.030	<0.001	0.025	<0.001	0.044	<0.001	0.047	<0.001
Body mass index																
Continuous (kg/m^2)	−0.004	0.807	0.025	0.023	0.033	0.032	0.000	0.975	−0.011	0.181	−0.028	<0.001	0.096	<0.001	0.089	<0.001
Overweight vs. normal weight	−0.204	0.162	0.084	0.384	0.232	0.077	−0.124	0.165	−0.093	0.196	−0.202	0.001	0.240	0.055	0.540	<0.001
Obesity vs. normal weight	−0.129	0.510	0.164	0.205	0.267	0.130	−0.083	0.492	−0.137	0.156	−0.300	<0.001	0.948	<0.001	0.963	<0.001
Occupational social class																
Social class II vs. I	−0.111	0.701	0.378	0.045	0.576	0.022	0.447	0.011	0.390	0.006	0.220	0.055	0.079	0.747	−0.077	0.739
Social class III vs. I	−0.270	0.264	0.293	0.062	0.280	0.183	0.023	0.875	0.173	0.140	0.096	0.316	−0.223	0.276	−0.515	0.008
Social class IVA vs. I	−0.560	0.017	0.163	0.283	−0.248	0.222	0.053	0.710	0.037	0.743	−0.064	0.492	−0.649	0.001	−0.454	0.016
Social class IVB vs. I	−0.302	0.342	0.307	0.138	−0.121	0.660	0.116	0.549	0.103	0.503	0.003	0.982	−0.542	0.045	−0.451	0.079
Social class V vs. I	−0.184	0.530	0.692	<0.001	−0.380	0.136	−0.148	0.403	0.131	0.356	−0.072	0.534	−0.774	0.002	−0.926	<0.001
Manual vs. non manual workers[a]	−0.276	0.029	0.021	0.801	−0.544	<0.001	−0.084	0.276	−0.124	0.044	−0.161	0.001	−0.541	<0.001	−0.215	0.038
Educational level																
Primary schooling (1st stage) vs. WFE	0.087	0.737	0.324	0.061	0.391	0.094	0.257	0.111	0.231	0.070	0.259	0.012	−0.425	0.062	−0.174	0.412
Primary schooling (2nd stage) vs. WFE	0.398	0.157	0.338	0.072	0.464	0.068	0.202	0.247	0.247	0.074	0.277	0.013	0.081	0.742	−0.275	0.231
Secondary schooling vs. WFE	0.770	0.005	0.367	0.044	0.729	0.003	0.283	0.095	0.212	0.113	0.243	0.025	0.259	0.281	0.214	0.337
University vs. WFE	0.297	0.320	0.375	0.061	1.126	<0.001	0.197	0.288	0.442	0.003	0.456	<0.001	0.407	0.122	0.275	0.261

Results are weighted by age and place of residence. Frequencies of population characteristics are detailed in Table 1 of supplementary material.
Each variable is adjusted by age.
β: regression coefficient. All concentrations of organochlorine compounds were lipid-corrected and log-transformed.
p: p-value of each category of the variable when comparing with the reference group.
WFE: without formal education.
[a] Non-manual workers: classes I, II and III; manual workers: classes IV and V.

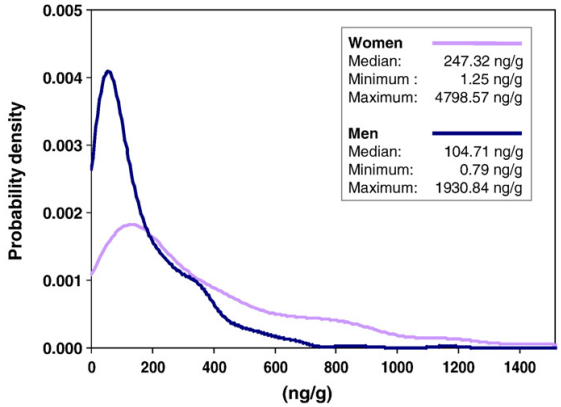

Fig. 3. Distribution of serum concentrations of hexachlorobenzene in Catalonia by sex. The figure includes 99% of the population with lower concentrations.

than 0.5 in 1.9% of the population, and greater than 1 in 0.4% of the population.

Concentrations were significantly different in women (Table 2) and men (Table 3). Women had statistically significantly higher concentrations of nine POPs, including p,p′-DDT, p,p′-DDE (median 39% higher than men's), HCB (more than two times higher) and β-HCH, as well as of o,p′-DDT, PCB 28, α-HCH, γ-HCH and δ-HCH. Fig. 3 shows the population distribution of HCB concentrations by sex. p,p′-DDT, p,p′-DDE, HCB and β-HCH were significantly higher in women than men even after adjusting by age and BMI, whereas men had higher concentrations than women of PCBs 153 and 180 after adjusting by age and BMI (data not shown). Age, sex and BMI were all statistically significant predictors of the concentrations of p,p′-DDT, p,p′-DDE, HCB, β-HCH and PCBs 153 and 180 when mutually adjusted for.

Serum levels of all the eight most frequently detected POPs increased with age; thus, for instance, among the oldest group median concentrations of p,p′-DDE and HCB were five and seven times higher than in the younger group (Table 1). Fig. 4 shows the distribution of p,p′-DDE by age group; with respect to older groups, the distribution of youngest individuals (born between 1984 and 1973) leans towards the left (lower DDE levels). There is a progressive flattening of the curves with increasing age, a pattern never reported before. The kurtosis of each of the two younger groups (27.56 and 30.98) is higher than that of the two older groups (7.95 and 3.27); i.e., in the younger groups DDE concentrations cluster more around a few values than in the older groups. Furthermore, the skewness of the distribution of the two younger groups (4.62 and 4.54) is about twice as large than that of the two older groups (2.44 and 1.77). In addition, the coefficient of variation of the distribution of DDE decreased from the younger to the older groups (111.5, 106.8, 105.0 and 86.7). This phenomenon — curve flattening, decreasing kurtosis, decreasing skewness, and decreasing coefficient of variation in increasingly older groups — was also seen in HCB and β-HCH, but not in PCBs and DDT; in the latter, kurtosis, skewness and coefficient of variation were highest in the oldest group.

The median, mean, geometric mean, standard deviation, maximum value, 25th percentile and 75th percentile of all commonly detected POPs increased with increasing age group (data not shown). The remarkable exception is the minimum value (i.e., the lower individual concentration), which was surprisingly similar in all four age groups in the eight POPs most frequently detected; i.e., among middle-aged and older subjects, a minority failed to accumulate the higher amounts of each POP that a majority accrued. This facet of the problem coexists with the fact that a vast majority of the population had much lower concentrations of all POPs than a certain minority (a fact that Figs. 5 and 6 also help visualize).

BMI was positively associated to serum concentrations of p,p′-DDT, PCB 118, HCB and β-HCH: in obese individuals medians were 1.6, 1.8, 4.5 and 3.6 times higher, respectively, than in individuals with normal weight (Table 1). After adjusting for age, men had monotonically increasing concentrations of p,p′-DDE, PCB 118, HCB and β-HCH with increasing BMI; this trend was also observed in women for p,p′-DDT, PCB 118, HCB and β-HCH. PCBs 153 and 180 showed decreasing concentrations with increasing BMI in men and women (Tables 2 and 3). Controlling by occupational social class, educational level or, in women, parity did not materially alter these patterns.

Crude analyses did not show decreasing OC concentrations in women with increasing number of children; in fact, parity was positively associated to concentrations of all the eight most prevalent compounds (Table 1); median concentrations in women who had at least 3 children were between 2 times higher (PCB 138, PCB 153, and PCB 180) and over 4 times higher (β-HCH) than in childless women. However, parity was — as expected — associated with age, and these

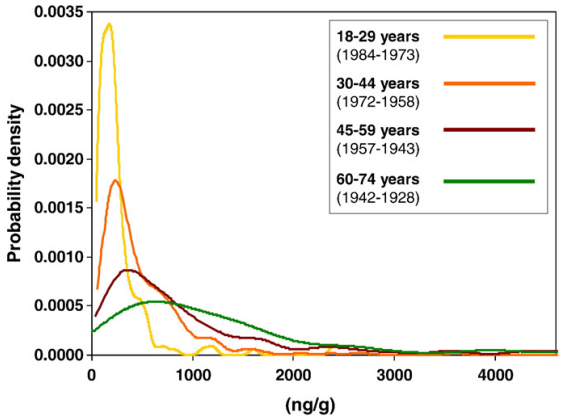

Fig. 4. Distribution of concentrations of dichlorodiphenyldichloroethene (p,p′-DDE) in Catalonia by age group. Figures in brackets are the corresponding birth years of each age group.

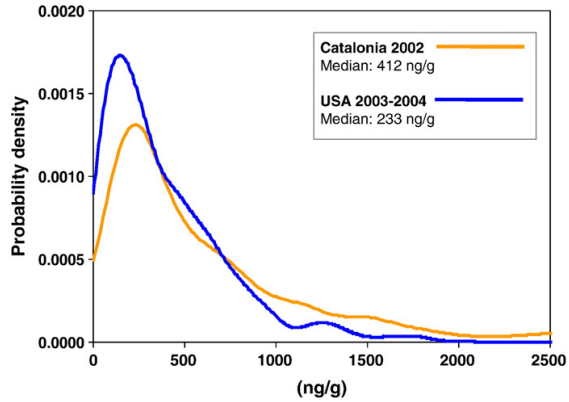

Fig. 5. Distribution of concentrations of dichlorodiphenyldichloroethene (p,p′-DDE) in the populations of USA and Catalonia. Catalonia: population from 20 to 74 years of age; USA: population ≥20 years.

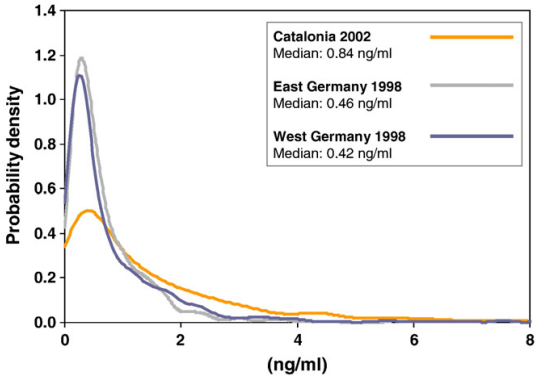

Fig. 6. Distribution of concentrations of hexachlorobenzene in the populations of Germany and Catalonia. All three curves refer to the population from 18 to 69 years of age.

two variables, to BMI. Thus, after adjusting by age and BMI, concentrations of the eight compounds decreased with increasing number of children ($p \leq 0.05$ for p,p′-DDT, p,p′-DDE, PCB 138, HCB and β-HCH) (Table 2).

Significant differences were observed in concentrations of p,p′-DDT, p,p′-DDE and some PCB congeners by occupational social class (Table 1). In women, all regression coefficients were positive for p,p′-DDT, p,p′-DDE and PCB 118; all classes had higher concentrations than class I, but not all were statistically significant and no compound showed a linear trend (Table 2). In men there were few clear patterns. Compared to class I, males of classes II to V had lower concentrations of p,p′-DDT and β-HCH, and higher of p,p′-DDE and PCB 153, but not all were statistically significant (Table 3).

Initially, in crude analyses, individuals with lower educational level showed higher median concentrations of the eight most prevalent compounds (Table 1). However, after adjusting by age, in men regression coefficients for education were in general of positive sign and few of them were statistically significant (i.e., higher POP concentrations with increasing education) (Table 3). In women there was no general association between education and serum POP levels. However, women with college education (i.e., university educational level) had higher concentrations of PCBs 138, 153 and 180 than women without formal studies (Table 2).

4. Discussion

We detected each of eight POPs (p,p′-DDT, p,p′-DDE, PCBs 118, 138, 153 and 180, HCB and β-HCH) in more than 85% of the participants. All citizens had traces of three or more POPs, and in 73% of the population ten or more compounds were detected. In Spain all 19 POPs analyzed have been prohibited or their use restricted for at least two decades (Porta et al., 2008, 2009c; United Nations Environment Programme, 2003). Yet, for instance, p,p′-DDT, prohibited in 1977, is still detected in 88% of the population 25 years later — a sobering illustration of what "persistent" means in population terms. The percentages of detection are consistent with other studies (Department of Health Human Services, 2009; Patterson et al., 2009; Glynn et al., 2003; Zumbado et al., 2005; Jakszyn et al., 2009; Moysich et al., 2002). We only analyzed 19 compounds; although the US Report now comprises over 200 chemical compounds, it began with 27 compounds (Porta et al., 2008; Department of Health and Human Services, 2009). Our sample size of 919 subjects is not small for a country of seven million inhabitants; furthermore, due to the rigorous sample design and sampling strategy, the study is representative of the 18–74 year old population of Catalonia.

While several population-based programs yielded relevant information (Porta et al., 2008; Glynn et al., 2003; Ueda et al., 1999; Buckland et al., 2001; Harden et al., 2004; Cerná et al., 2007, 2008; Zumbado et al., 2005; Jakszyn et al., 2009; Moysich et al., 2002; Luzardo et al., 2006; Agudo et al., 2009; Bates et al., 2004), this is one of very few reports worldwide based on a representative sample of the general population (Porta et al., 2008; National Research Council, 2006; Thornton et al., 2002; United Nations Environment Programme, 2003, 2009; World Health Organization, 2003; Department of Health and Human Services, 2009; Patterson et al., 2009). It has an innovative focus on the whole population distributions of POP concentrations and their properties. A distribution may seem a simple representation if viewed only from a narrow technical angle. However, as conceived, drawn and interpreted in this report, distributions of POP concentrations clearly stem from and belong to a population, they reflect the inherently population nature of the issues at stake, and thus convey pedagogically a core message: individual concentrations of POPs result from societal processes, there is little an individual alone can do to decrease personal exposure, and POP contamination cannot be viewed just as an individual problem. Our "POP Geoffrey Rose curves" emphasize the importance of shifting the whole population distribution of POP concentrations through public and private policies (e.g., policies to decrease contamination of animal feed and human food, industrial emissions and residues) (Rose, 1992; Porta, 2004, 2008; Porta et al., 2009c).

The median concentration of several POPs is slightly lower in the US than in Catalonia; e.g., the median of p,p′-DDE, PCBs 153 and 180, HCB and β-HCH for the US population ≥20 years were 233, 24.2, 21.5, 15.1 ng/g and <LOD (i.e., the median for β-HCH was less than the LOD of 7.8 ng/g), respectively. In the Catalan population (also of ≥20 years) these values were: 412, 102, 79, 170 and 97 ng/g, respectively. These differences might partly be explained by small differences in laboratory and epidemiologic methods, as well as by the sociodemographic and ethnic composition of each country (Porta et al., 2008; Department of Health and Human Services, 2009). Although the US reports and the Germany surveys do not present the full distribution of POP concentrations, they do offer selected percentiles; from such data the distribution in the US and German populations can be estimated. Fig. 5 shows the distributions of serum concentrations of p,p′-DDE in the USA and Catalonia. The shapes are remarkably similar, although the US curve trails further towards the left than the curve for Catalonia: there is a higher proportion of Americans in the zone of lower p,p′-DDE values and a higher proportion of Catalans with higher concentrations. As compared with the raw medians shown above, the curves convey better the exposure of the whole population.

Another outstanding POP surveillance program is the German biomonitoring program (Becker et al., 2002; Link et al., 2005; Umweltbundesamt, 1985–2006). It reported median levels of p,p′-DDE, PCBs 138, 153 and 180, HCB and HCHs of 1.52, 0.45, 0.72, 0.48, 0.43 and <0.1 ng/mL, respectively, in individuals 18–69 years old (Umweltbundesamt, 1985–2006). In the Catalan population of the same age range these figures are: 2.09, 0.39, 0.55, 0.44, 0.84 and 0.49 ng/mL, respectively. Levels of HCB and β-HCH in Catalonia are higher than in USA and Germany; while the exact reasons are unknown, differences are likely related to historical uses. Fig. 6 shows the distribution of serum concentrations of HCB in the Catalan and German (East and West) populations: the shape of the two German distributions is similar, and so is the long right tail of the three curves; yet, with respect to the German curves, the curve for Catalonia is shifted towards higher concentrations. Shifting the population distribution of a POP towards the left would decrease the percent of the population under the right end of the tail, lower the mean and median values, and substantially decrease the percent of the population under the area of intermediate concentrations. True, for many POPs the risk function is incompletely known. While the minority of the population with higher concentrations is of concern,

the long-term health effects of lifelong low concentrations are not negligible (Luch, 2005; Irigaray & Belpomme, 2010; Hernández et al., 2009; Lee et al., 2009).

Most lipid-corrected serum concentrations of POPs were associated with sex, age, BMI and, in women, parity. Higher concentrations of PCBs in men than women may result from differences in diet, occupational exposures or metabolism (Department of Health and Human Services, 2009; Needham et al., 2007; Glynn et al., 2003; Schaeffer et al., 2006; Verner et al., 2009; Wolff et al., 2007). For physiological, clinical and cultural reasons POP contamination deserves a more incisive gender approach than it has received so far (Porta et al., 2008, 2009c). Social class and educational level did not show clear monotonic patterns. Results of multivariate clustering and correlation analyses show that serum concentrations of hexa- and hepta-chlorinated PCBs are highly correlated, and so are HCB and β-HCH. High similarities and correlations among compounds may help to identify common sources and pathways of exposure for POPs (Porta et al., 2007). A detailed analysis of sources and predictors of exposure is beyond the scope of this article.

It seems well established that serum concentrations of many POPs increase with age, and it is commonly assumed that this is a result of continued exposure and absence of excretion (Porta et al., 2007, 2008; Department of Health and Human Services, 2009; Verner et al., 2009; Wolff et al., 2007; Laden et al., 1999; James et al., 2002). However, the association between POP concentrations and age may also be due to cohort and period effects (e.g., to differences in exposure 'in utero' and during childhood). While older participants have had more years to accumulate POPs, they also lived in periods when use of some POPs (e.g., DDT, PCBs) was more widespread (Porta et al., 2008; Patterson et al., 2009). However, age–cohort–period effects on POP concentrations have never been formally analyzed (Porta et al., 2008). Knowledge gaps are well illustrated by two examples. First, US authorities have convincingly argued that analyses of POP trends in their different surveys are unwarranted because of methodological differences, including changes in chemical analytical techniques (Patterson et al., 2009). And second, in Norway time trends in POP levels have been estimated with homogeneous laboratory techniques applied at one time to samples stored between 1973 and 1990; yet, the population were cases and controls of a study on breast cancer (Ward et al., 2000). Other types of controls from case–control studies, blood donors, and volunteers have been used to estimate POP properties (e.g., half-lives) and levels "in the general population" (Porta et al., 2008).

To improve knowledge on causes and mechanisms of disease, and for public health reasons, POP storage in lipid-rich organs and the relationships between POPs and BMI need further research (Glynn et al., 2003; Umweltbundesamt, 1985–2006; Verner et al., 2009; Wolff et al., 2007; Porta et al., 2007; Laden et al., 1999; James et al., 2002). In our study BMI was positively associated with p,p′-DDE in men, p,p′-DDT in women, and PCB 118, HCB and β-HCH in both sexes. PCBs 153 and 180 showed an inverse pattern: decreasing concentrations with increasing BMI both in women and men. This has also been observed by others (Glynn et al., 2003; Jakszyn et al., 2009; Agudo et al., 2009; Wolff et al., 2007; Vaclavik et al., 2006), but to study the dynamic relationships requires longitudinal studies (Wolff et al., 2007).

POP reports are not meant only for professionals but for concerned citizens and organizations as well (Porta et al., 2008; Department of Health and Human Services, 2009). Thus — even when analyses are relatively simple — results can be culturally sensitive. During pregnancy POPs are commonly incorporated into the fetus via the placenta (National Research Council, 2006; Thornton et al., 2002; United Nations Environment Programme, 2003; World Health Organization, 2003). Our analysis showed that after controlling by age and BMI, concentrations of the most prevalent POPs decreased with increasing number of children: the positive association between POPs and parity observed in descriptive analyses is reversed (it becomes inverse) when the confounding effect of age is taken into account. POP reports should carefully distinguish the practical and scientific implications of unadjusted and adjusted effects; e.g., the effect of parity on women's POP body burden may be small in the absence of extended breast-feeding (Needham et al., 2007; James et al., 2002), older women will, anyway, have higher parity and POPs, and the transient lowering effect of parity on POP levels may have more mechanistic than practical interest (Moysich et al., 2002; Verner et al., 2009; Wolff et al., 2007).

Virtually all populations worldwide bear a body burden of POPs — with large interindividual and inter-population differences (Porta et al., 2008; Thornton et al., 2002; United Nations Environment Programme, 2003, 2009; World Health Organization, 2003). Programs that monitor such distributions in a representative sample of the general population are essential to establish reference concentrations, to analyze predictors of exposure, to increase public awareness, to stimulate more energetic policies and population strategies and, hence, to diminish the burden of disease that these chemicals contribute to cause.

Conflicts of interest

The authors declare they have no competing financial interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.envint.2010.04.013.

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Supplemental Material, 1 : Table legends

[in the order in which tables appear in the text] **and Supplemental Tables**

Table 1 of Supplemental Material. Sociodemographic characteristics of study participants.

Table 1. Serum concentrations of POPs detected in over 85% of the Catalan population by sociodemographic characteristics.

Table 2 of Supplemental Material. Serum concentrations of persistent organic pollutants detected in less than 85% of the Catalan population.

Table 2. Main sociodemographic predictors of serum concentrations of persistent organic pollutants in women.

Table 3. Main sociodemographic predictors of serum concentrations of persistent organic pollutants in men.

Table 1 of Supplemental Material

Sociodemographic characteristics of study participants*

	Total N (%)	Men N (%)	Women N (%)	p value
All participants	919 (100)	399 (43.4)	520 (56.6)	
Age (years)				
Mean ± SD	45.2 ± 15.0	46.3 ± 15.0	44.4 ± 15.0	0.052 [a]
Median	45.0	47.0	44.0	0.045 [b]
18-29	175 (19.1)	66 (16.6)	109 (20.9)	0.239 [c]
30-44	272 (29.6)	117 (29.3)	155 (29.8)	
45-59	288 (31.3)	127 (31.8)	161 (31.0)	
60-74	184 (20.0)	89 (22.3)	95 (18.3)	
Body Mass Index (BMI) (Kg/m^2)				
Mean ± Standard deviation	26.4 ± 4.6	27.0 ± 4.1	25.9 ± 4.9	<0.001 [a]
Median	25.9	26.6	25.0	<0.001 [b]
Underweight (BMI<18.5)	10 (1.1)	4 (1.0)	6 (1.2)	<0.001 [c]
Normal weight (18.5-24.9)	381 (41.4)	127 (31.8)	254 (48.8)	
Overweight (25.0-29.9)	348 (37.9)	192 (48.1)	156 (30.0)	
Obese (BMI≥30)	180 (19.6)	76 (19.1)	104 (20.0)	
Birth place				0.687 [c]
Catalonia	656 (71.8)	288 (72.7)	368 (71.0)	
Rest of Spain	231 (25.3)	95 (24.0)	136 (26.3)	
Abroad	27 (2.9)	13 (3.3)	14 (2.7)	
Educational level				0.350 [c]
Without formal education	140 (15.3)	54 (13.7)	86 (16.6)	
Primary schooling (1st stage)	242 (26.5)	103 (26.1)	139 (26.8)	
Primary schooling (2nd stage)	227 (24.9)	98 (24.8)	129 (24.9)	
Secondary schooling	192 (21.0)	94 (23.7)	98 (18.9)	
University	111 (12.2)	45 (11.4)	66 (12.8)	
Others	1 (0.1)	1 (0.3)	0 (0.0)	
Occupational social class				0.626 [c]
V (less affluent)	75 (8.4)	31 (7.9)	44 (8.8)	
IV	420 (47.1)	177 (44.9)	243 (48.8)	
III	229 (25.7)	112 (28.4)	117 (23.5)	
II	94 (10.5)	41 (10.4)	53 (10.7)	
I (most affluent)	74 (8.3)	33 (8.4)	41 (8.2)	

* Unweighted results.
[a] Student's *t*-test (two-tail).
[b] Mann Whitney's *U* test (two-tail).
[c] Fisher's exact test (two-tail).
SD: standard deviation.

Table 2 of Supplemental Material

Serum concentrations of persistent organic pollutants detected in less than 85% of the Catalan population

Characteristics	o,p'-DDT	o,p'-DDE	o,p'-DDD	p,p'-DDD	PCB 28	PCB 52	PCB 101	PeCB
All participants	6.4 (1.0-17.5)	0.3 (0.3-0.5)	3.6 (0.4-7.8)	3.2 (0.7-7.2)	1.6 (1.3-2.1)	0.2 (0.2-0.3)	0.2 (0.2-0.2)	1.3 (1.1-1.6)
GM and 95th. perc.	5.0 (32.5)	0.6 (9.5)	2.3 (19.0)	2.7 (19.3)	2.2 (14.5)	0.3 (3.6)	0.3 (5.1)	1.6 (6.0)
Range	0.5, 846.4	0.1, 55.7	0.2, 140.1	0.4, 165.9	0.6, 58.2	0.1, 56.4	0.1, 108.2	0.6, 28.2
Detected (%)	63.5	24.3	65.0	61.0	22.5	11.7	13.0	18.4
Quantified (%)	54.5	20.4	58.6	47.3	12.4	10.1	9.8	3.8
Non-quantified (%)	9.0	3.9	6.4	13.7	10.1	1.6	3.2	14.6
Non-detected (%)	36.5	75.7	35.0	39.0	77.5	88.3	87.0	81.6
Gender								
Male	5.4 (1.0-17.7)*	0.3 (0.3-0.4)*	3.4 (0.4-7.8)	3.1 (0.7-7.0)	1.5 (1.3-1.9)*	0.2 (0.2-0.3)*	0.2 (0.2-0.3)*	1.3 (1.0-1.6)
Female	7.5 (1.1-17.5)	0.3 (0.3-0.5)	3.7 (0.4-7.9)	3.2 (0.8-7.6)	1.7 (1.4-2.2)	0.2 (0.2-0.3)	0.2 (0.2-0.3)	1.3 (1.1-1.6)
Age (years)								
18-29	4.0 (1.1-14.2)	0.4 (0.3-0.5)*	3.4 (0.5-8.2)	3.0 (0.8-8.1)	1.8 (1.6-2.2)*	0.3 (0.2-0.3)*	0.2 (0.2-0.3)*	1.4 (1.2-1.7)*
30-44	7.2 (1.0-19.1)	0.3 (0.3-0.4)	3.3 (0.4-7.5)	3.1 (0.8-7.3)	1.6 (1.3-1.8)	0.2 (0.2-0.3)	0.2 (0.2-0.2)	1.3 (1.1-1.6)
45-59	8.2 (1.0-17.0)	0.3 (0.3-0.4)	4.3 (0.4-8.6)	3.4 (0.7-7.1)	1.5 (1.3-2.0)	0.2 (0.2-0.3)	0.2 (0.2-0.2)	1.1 (1.0-1.3)
60-74	7.3 (1.0-21.4)	0.3 (0.3-1.1)	2.8 (0.4-7.2)	3.5 (0.7-6.6)	1.5 (1.2-4.0)	0.2 (0.2-0.2)	0.2 (0.2-0.2)	1.1 (1.0-1.5)

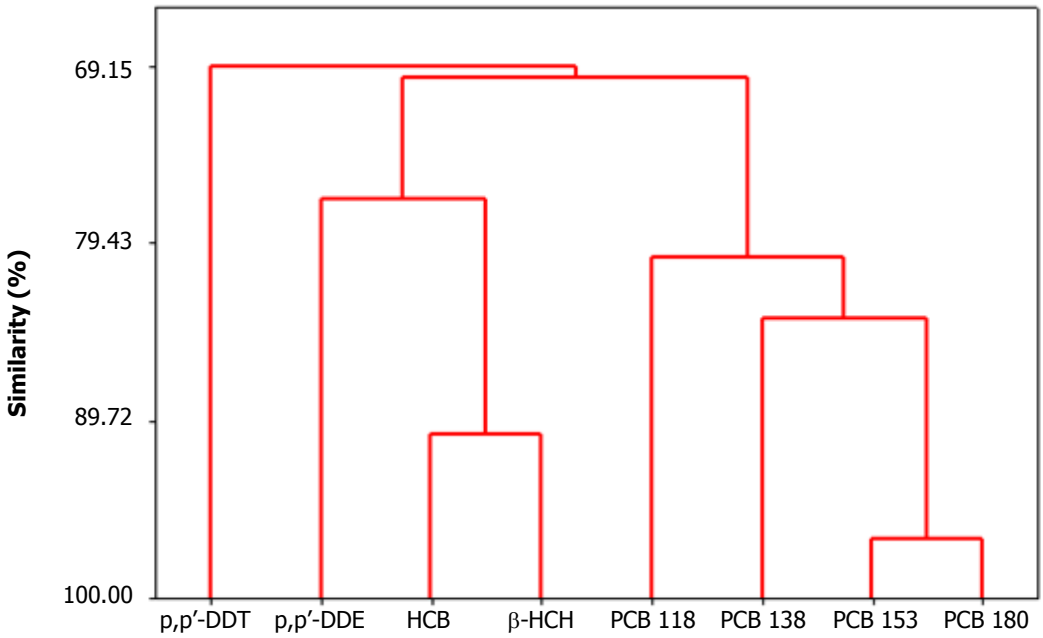
Characteristics	α-HCH	γ-HCH	δ-HCH
All participants	2.0 (1.7-2.7)	2.5 (1.9-7.7)	1.5 (1.3-1.9)
GM and 95th	2.6 (9.5)	3.7 (12.7)	2.0 (12.7)
Range	1.0, 164.6	0.9, 144.1	0.6, 67.4
Detected (%)	22.2	39.6	19.8
Quantified (%)	3.8	6.1	8.1
Non-quantified (%)	18.4	33.5	11.7
Non-detected (%)	77.8	60.4	80.2
Gender			
Male	2.0 (1.6-2.6)*	2.4 (1.9-7.4)*	1.5 (1.2-1.8)*
Female	2.1 (1.7-2.7)	2.6 (2.0-8.1)	1.6 (1.3-2.0)
Age (years)			
18-29	2.3 (2.0-2.8)*	2.9 (2.4-9.0)*	1.8 (1.5-2.2)*
30-44	2.0 (1.7-2.3)	2.4 (1.9-7.2)	1.5 (1.3-1.7)
45-59	1.9 (1.6-2.3)	2.2 (1.8-7.6)	1.4 (1.2-1.7)
60-74	1.9 (1.6-5.6)	2.2 (1.8-7.2)	1.4 (1.2-1.7)

Note:

Results are weighted by gender, age and place of residence to account for the complex sample design. Frequencies of population characteristics are detailed in Table 1 of Supplemental Material.
The concentrations are expressed in median (percentile 25 - percentile 75) ng/g lipid. The second row for all participants presents the geometric mean (GM) and the 95th percentile, and the third row (also, only for All participants) presents the minimum and maximum concentrations. For compounds that were undetected in ≥75% of subjects the values of the median and of the 25th. and 75th. percentiles correspond to imputed values (Limit of Detection / 2), after lipid-adjustment (see Methods); similarly, for compounds that were detected in <50% of subjects the values of the median and 25th. percentile correspond to imputed values. Thus, percentages of detection and quantification should be given proper attention.
*p<0.05 (Kruskal-Wallis test).

Supplemental Material, 2

Figure 1 of Supplemental Material. Dendrogram of the cluster analysis for the eight most frequently detected POPs.



p,p'-DDT, dichlorodiphenyltrichloroethane; p,p'-DDE, dichlorodiphenyldichloroethene; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; PCBs, polychlorinated biphenyls.

Article A2

Títol: Distribution of blood concentrations of persistent organic pollutants in a representative sample of the population of Barcelona in 2006, and comparison with levels in 2002.

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Distribution of blood concentrations of persistent organic pollutants in a representative sample of the population of Barcelona in 2006, and comparison with levels in 2002

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ABSTRACT

Introduction: POP biomonitoring programs are useful for exposure assessment, to analyze patterns, and to evaluate policies. However, population-representative surveys are scarce and heterogeneous. Reports on time trends in representative samples using the same methods are rare.
Objectives: To analyze the distribution of serum concentrations of 19 POPs in the general population of Barcelona city in 2006, and to compare it with the distribution in 2002.
Methods: 231 participants in the Barcelona Health Survey were interviewed face-to-face, gave blood, and underwent a physical exam. Density plots ("POP Geoffrey Rose curves") were used to represent the full population distribution of each compound.
Results: Eight POPs were each detected in >80% of the study subjects: *p,p′*-DDT, *p,p′*-DDE, PCB congeners 118, 138, 153 and 180, HCB and β-HCH. The minimum number of POPs detected in one person was 5, and 72% of the population accumulated ≥10 compounds. *p,p′*-DDE and HCB showed the highest concentrations (median = 219 and 109 ng/g lipid, respectively). Concentrations decreased by 34–56% from 2002 to 2006. The decrease was similar in women and men, and in all age groups/birth cohorts. It was larger with increasing BMI; for *p,p′*-DDT, HCB and β-HCH the decrease in obese individuals was 31–44 percentage points larger than in subjects with normal weight. The distribution of POP concentrations was always switched towards higher values in women than men. POP levels also differed significantly by age, body mass index, weight gain, birth place and social class, but not by parity and breastfeeding. The two younger cohorts had a higher DDT/DDE ratio than the oldest cohort.
Conclusion: Although human POP contamination remains common in the city of Barcelona, concentrations decreased significantly in 4 years. Our approach suggests innovative ways to conceive, analyze and present results for other monitoring programs.

1. Introduction

Persistent organic pollutants (POPs) comprise a large variety of toxic substances such as hexachlorobenzene (HCB), hexachlorocyclohexanes (HCHs), dioxins, dichlorodiphenyltrichloroethane (DDT) and its metabolites (notably, dichlorodiphenyldichloroethene, DDE), and polychlorinated biphenyls (PCBs). POPs are highly lipophilic and resistant to degradation; they thus accumulate in adipose tissue and in organs such as liver, brain, or pancreas (WHO, 2003). Many human populations are exposed to POP mixtures over the lifecourse, usually at low doses (Luzardo et al., 2009). A variety of studies have shown that POPs may adversely influence health and well-being: they contribute to cause infertility, birth defects, learning disabilities, endocrine disruption,

Abbreviations: BHS, Barcelona Health Survey; β, regression coefficient; BMI, body mass index; CHS, Catalan Health Survey; CI, confidence interval; DDD, dichlorodiphenyldichloroethane; DDE, dichlorodiphenyldichloroethene; DDT, dichlorodiphenyltrichloroethane; GLM, General Linear Model; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; LOD, limit of detection; LOQ, limit of quantification; PCBs, polychlorinated biphenyls; PeCB, pentachlorobenzene; POPs, persistent organic pollutants.

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diabetes, several cancers, Alzheimer's and Parkinson's disease, and other neurological, gynecological and immunological disorders (Alonso-Magdalena et al., 2011; Casals-Casas and Desvergne, 2011; Diamanti-Kandarakis et al., 2009; Kaiser, 2005; La Merrill and Birnbaum, 2011; Schug, 2011; Soto and Sonnenschein, 2011; UNEP, 2002). However, numerous uncertainties exist on the health effects of chronic exposure to POPs in the general population (Henkler and Luch, 2011; Hernández et al., 2009; Lee et al., 2009; Myers et al., 2009). To decrease such uncertainties and appropriately protect the health of citizens, better knowledge on the levels and trends of contamination of the population is essential.

Most POPs are presently targeted for elimination or reduction. Legal instruments as the Stockholm Convention encourage countries to integrate population-based surveillance of POP levels in humans within their health monitoring systems (Porta and Zumeta, 2002; UNEP, 2005). POP monitoring programs are useful for exposure assessment, to analyze trends and patterns of contamination, and to evaluate the effectiveness of policies aimed at decreasing exposure. However, worldwide, comprehensive monitoring of human contamination by POPs is scarce, fragmented and heterogeneous. Methodological characteristics of studies vary largely, including selection of participants, sociodemographic information, chemical and statistical methods, and frameworks for interpretation of results (Porta et al., 2008b, 2009a). For example, the full range of POP concentrations is often overlooked, and little attention is paid to the characteristics of the distribution of the concentrations (e.g., differences across subgroups in kurtosis, skewness, and coefficient of variation) (Porta et al., 2008b, 2010a). Also, national studies monitoring human exposure to POPs do not usually include data on parity and breastfeeding (Dewailly et al., 1996; Tajimi et al., 2004). Another example of a variable that is not usually collected in population biomonitoring studies is weight change, which may alter blood lipid levels and bias estimates of exposure to lipophilic compounds like POPs. As we shall see below, the influence of parity, breastfeeding and weight change was assessed in the present study.

As in other countries, in Spain most POPs were banned during the 1970s, and levels of some of them have decreased (Porta et al., 2008a). However, uncertainties abound, and the only two Spanish studies based on representative samples of a population detected a substantial number of compounds in over 85% of citizens (Zumbado et al., 2005; Porta et al., 2010b; Henríquez-Hernández et al., 2011; Porta et al., 2012). In 2006, the Public Health Agency of Barcelona conducted the fifth Barcelona Health Survey (BHS), which included a physical examination and, for the first time, blood drawing – explicitly conceived for POPs monitoring – in a sample of participants; serum concentrations of 19 POPs were thus determined in 231 subjects (Porta et al., 2009a). In 2002, POP concentrations were analyzed in the Catalan Health Survey (CHS); based on a representative sample of the population of Catalonia (Porta et al., 2010b), it included a subsample of individuals representative of the city of Barcelona. Therefore, for the first time in Spain, we could assess trends in POP levels in Barcelona measured in an identical way. Reports on POP time trends in representative samples using the same methods are also extremely rare worldwide.

The aim of the present study was, firstly, to analyze the distribution of serum concentrations of 19 POPs in the non-institutionalized adult population of Barcelona city, and its main socio-demographic predictors; and, secondly, to compare the concentrations of POPs analyzed in the BHS with the concentrations in individuals from Barcelona studied four years earlier in the CHS.

2. Methods

2.1. Study population and health interview survey

The study population of the Barcelona Health Survey of 2006 (BHS) has been described in detail elsewhere (Porta et al., 2009a; Rodríguez-Sanz et al., 2008). Briefly, at the end of the interview the study monitors offered BHS participants ≥15 years old to take part in the POP study (Porta et al., 2009a); the youngest person who actually participated in the POP study was 18 years old. Subsequently, a nurse personally interviewed each person who accepted to participate in the POP study, measured the weight, height, and the hip and waist circumference, and collected a blood sample. Participants had been asked to fast for at least 4 h before blood extraction. Blood was collected in a vacuum system tube and centrifuged for 15 min × 3000 rpm at 4 °C to obtain serum. Right after centrifugation, serum was divided in 1–3 mL aliquots and stored at −80 °C until 2008, when POP concentrations were analyzed. The additional interview for the POP study included structured questions about recent and past changes in body weight, and on whether the person had been breastfed. Women were also asked questions about parity, breastfeeding and abortion histories.

Body mass index was computed by measured weight [kg] divided by measured height squared [m^2]. The lower educational category of subjects without formal studies included the illiterate. To assign occupational social class we used the Spanish classification (Rodríguez-Sanz et al., 2008); class was hence assigned through the current or last occupation of the interviewee or, if the person had not worked, through the current or last occupation of the head of the household (Rodríguez-Sanz et al., 2008).

The average age of participants was 48 years and 59% of all participants were women. About 18% were obese (BMI ≥ 30 kg/m^2), 85% were breastfed in childhood, 67% were born in Catalonia, 96% had completed at least primary schooling (1st. stage), 31% were from occupational social class IV, and 61% were employed (Table 1). There were no significant differences in the distribution of age, BMI, educational level and social class by sex. However, a greater proportion of men than women had been breastfed, were born in Catalonia and were employed.

2.2. Analytical chemical methods

Analyses of BHS samples were carried out in the Department of Environmental Chemistry (IIQAB-CSIC) in Barcelona, Spain, during 2008. Analyses of POP concentrations in samples from the Catalan Health Survey (CHS) were also performed in the same Department, using the same methodology, in 2006–2008 (Porta et al., 2010b). The following POPs were analyzed in serum: *o,p′*-DDT, *p,p′*-DDT, *o,p′*-DDE, *p,p′*-DDE, *o,p′*-DDD, *p,p′*-DDD, PCB congeners 28, 52, 101, 118, 138, 153, and 180, PeCB, HCB, α-HCH, β-HCH, γ-HCH and δ-HCH (Porta et al., 2009b). 10 mL screw-capped Pyrex centrifuge tubes capped with Teflon septa were used to keep and digest the samples. 25 μL of the surrogate solution (0.36 mg/L of tetrabromobenzene (TBB) and 0.52 mg/L of PCB 209), was added to 1 mL aliquots of serum in the same Pyrex centrifuge tubes where the samples were stored. Acid digestion of the mixture was performed by addition of 3 mL of n-hexane and 2 mL of concentrated sulphuric acid. Gas chromatography (GC) analyses were performed with an Agilent Technologies model GC-6890N provided with an ECD and a 60 m, 0.25 mm i.d. DB-5 column (J & W Scientific, Folsom, CA, USA; film thickness 0.25 μm). A fused silica precolumn of 2 m × 0.32 mm i.d. was used and renewed every 30 samples. Selected samples were analyzed by NICI GC–MS with a Fisons MD 800. The linear range of the detector was determined from injection of standard mixtures. Calibration lines were performed for all POPs mentioned above. These analytes were then quantitated in the samples by the external standard method after replicate analysis. The concentrations of HCB and β-hexachlorocyclohexane (β-HCH) were corrected for volatility losses using TBB as internal standard. The recoveries of TBB and polychlorinated biphenyl 209 were 100.6% (SD 20.5) and 94.5% (SD 19.7), respectively. The calculation of the limits of detection (LOD) and quantification (LOQ) was based on the analysis of proficiency testing materials, an external quality assessment for selected pollutants, and the study of the signal/noise ratio of chromatograms obtained from GC-ECD injection (Garí and Grimalt, 2010).

Table 1
Sociodemographic characteristics of study participants (Barcelona Health Survey 2006 study on persistent organic pollutants).*.

	Total N (%)	Men N (%)	Women N (%)	P-value
All participants	231 (100)	94 (40.7)	137 (59.3)	
Age (years)				
Mean ± SD	48.4 ± 16.1	47.1 ± 16.0	49.3 ± 16.2	0.311[a]
Median	45.4	41.8	48.1	0.200[b]
18–44	112 (48.5)	53 (56.4)	59 (43.1)	0.098[c]
45–64	76 (32.9)	24 (25.5)	52 (38.0)	
≥65	43 (18.6)	17 (18.1)	26 (19.0)	
Body mass index (BMI) (kg/m^2)				
Mean ± SD	26.4 ± 4.6	26.7 ± 4.1	26.1 ± 4.9	0.311[a]
Median	25.7	26.3	25.3	0.081[b]
Underweight (BMI < 18.5)	2 (0.9)	1 (1.1)	1 (0.7)	0.431[c]
Normal (BMI 18.5–24.9)	100 (43.3)	35 (37.2)	65 (47.4)	
Overweight (BMI 25.0–29.9)	87 (37.7)	40 (42.6)	47 (34.3)	
Obese (BMI ≥ 30)	42 (18.2)	18 (19.1)	24 (17.5)	
Weight change in the last 6 months				0.407[c]
Lost 4–5 kg	22 (9.5)	6 (6.4)	16 (11.7)	
Little or no change (± 3 kg)	186 (80.5)	79 (84.0)	107 (78.1)	
Gained 4–5 kg	23 (10.0)	9 (9.6)	14 (10.2)	
Waist to hip ratio				
Mean ± SD	0.899 ± 0.086	0.954 ± 0.077	0.862 ± 0.071	<0.001[a]
Median	0.899	0.956	0.860	<0.001[b]
Was breastfed in childhood				0.002[c]
No	30 (14.4)	4 (5.0)	26 (20.3)	
Yes	178 (85.6)	76 (95.0)	102 (79.7)	
Birth place				0.036[c]
Catalonia	155 (67.1)	68 (72.3)	87 (63.5)	
Rest of Spain	48 (20.8)	12 (12.8)	36 (26.3)	
Other	28 (12.1)	14 (14.9)	14 (10.2)	
Occupational social class				0.334[c]
IV–V (less affluent)	92 (40.5)	37 (39.8)	55 (41.0)	
III	56 (24.7)	19 (20.4)	37 (27.6)	
I–II (most affluent)	79 (34.8)	37 (39.8)	42 (31.3)	
Educational level				0.346[c]
Without formal education	10 (4.3)	1 (1.1)	9 (6.6)	
Primary schooling (1st stage)	31 (13.5)	12 (12.9)	19 (13.9)	
Primary schooling (2nd stage)	45 (19.6)	20 (21.5)	25 (18.2)	
Secondary schooling	63 (27.4)	25 (26.9)	38 (27.7)	
University	81 (35.2)	35 (37.6)	46 (33.6)	
Employment status				<0.001
Employed	141 (61.0)	61 (64.9)	80 (58.4)	
Housewife	20 (8.7)	0 (0.0)	20 (14.6)	
Unemployed	15 (6.5)	11 (11.7)	4 (2.9)	
Retired	40 (17.3)	18 (19.1)	22 (16.1)	
Student	8 (3.5)	3 (3.2)	5 (3.6)	
Other	7 (3.0)	1 (1.1)	6 (4.4)	

*Unweighted results. SD: standard deviation.
[a] Student's *t*-test (two-tail).
[b] Mann–Whitney's *U* test (two-tail).
[c] Fisher's exact test (two-tail).

To be conservative, the main statistical analyses were limited to compounds that were detected above the detection limit in >80% of participants. LODs (all in ng/mL) ranged from 0.002 to 0.024, and LOQs from 0.007 to 0.071 for PCB 101 and γ-HCH, respectively. LODs for the eight compounds included in the main analyses ranged from 0.010 to 0.020 ng/mL, and LOQs from 0.029 to 0.060 ng/mL, for PCB 180 and β-HCH, respectively (all limits are shown in Supplementary Tables 1 and 2). LODs and LOQs were the same in BHS and CHS. When a sample had a concentration of an analyte below the detection threshold, it was assigned the mid-value of this limit; when a POP was detected but under the quantification threshold, the mid-value between detection and quantification limits was used (Porta et al., 2009b, 2010b).

Total cholesterol and triglyceride levels were determined with enzymatic methods, using serum specifically obtained in the BSH and CHS studies on POPs (Rodríguez-Sanz et al., 2008). Total serum lipids (TL) were calculated by the standard short formula (or Standard formula 2) of Phillips et al., which is based on total cholesterol and triglycerides (Bernert et al., 2007; Phillips et al., 1989; Porta et al., 2009b). POP concentrations were individually corrected for TL by dividing the crude serum POP concentration by TL, and are expressed in nanograms of analyte per gram lipid (ng/g lipid). Among the 231 individuals, mean (standard deviation) serum concentrations of total cholesterol, triglycerides and total lipids were, respectively, 207.9 (41.2), 102.1 (61.0) and 636.3 (131.2) mg/dL.

2.3. Statistical analysis

Univariate statistics were computed as customary (Armitage et al., 2002; Kleinbaum et al., 2007). Kruskal–Wallis' test and Mann–Whitney's *U* test were used to assess differences in concentrations of POPs by sociodemographic characteristics of the participants. Spearman's rank correlation coefficients (ρ) were computed to evaluate correlations among pairs of POPs. The Kolmogorov–Smirnov test for normality was used to check the distributions of POPs; as none was normal, log-transformed values were used in regression analyses. All new log-transformed variables, except log-PCB 118 in women, satisfied normality. The parametric tests and confidence intervals used in our regression analysis are robust to such departures from normality (Kleinbaum et al., 2007). Density plots were used to chart the distributions of POP serum concentrations in the different age and sex population groups; we named these graphs "POP Geoffrey Rose curves" to emphasize their relevance for Rose's "population approach" (Porta, 2004, 2008; Porta et al., 2008b, 2010a, 2010b; Rose, 1992).We analyzed three properties of the curves: kurtosis, skewness, and coefficient of variation (Armitage et al., 2002; Kleinbaum et al., 2007; Porta et al., 2010b). In order to analyze variations in lipid-corrected and log-transformed concentrations of POPs, General Linear regression Models (GLM) were used. The main effects of all predictors were independently explored in base models. Confounding variables were retained in the models when they materially altered the estimates. Due to the complex designs of the BHS and CHS, and in order to compensate for differences in gender and age, sample weights were used in the analysis. We compared the concentrations of POPs analyzed in the BHS with the concentrations analyzed in 147 individuals representative of the city of Barcelona from CHS through multivariate models. We used sample weights for both studies. The level of statistical significance was set at 0.05 and all tests were two tailed. Analyses were conducted using SPSS version 12.0 (SPSS, Chicago, IL, USA, 2003), R version 2.7.1 (2008), Minitab (version 15, 2007) and Stata 8.0.

3. Results

Eight of the 19 POPs analyzed were each detected in >80% of the study subjects: *p,p′*-DDT, *p,p′*-DDE, PCB congeners 118, 138, 153 and 180, HCB and β-HCH. *p,p′*-DDE was detected and quantified in all samples (Table 2, Fig. 1). The percentage of detection for the other 11 analytes ranged between 1% and 65% (Table 2 of Supplementary Material). Thus, all 19 POPs were detected. No individual was free from POPs: the smallest number detected in one person was 5 compounds, and the largest, 15 POPs. 72% of the population accumulated ≥10 compounds (45% of participants born in 1977–1988 and 76% of subjects born in 1914–1946). 59.7% of participants had 1 or more of the 8 most frequently detected POPs in the upper quartile, while 40.7% of participants had 2 or more POPs in the upper quartile and 33.3% had 3 or more POPs in the upper tertile.

Table 2
Comparison of serum concentrations of persistent organic pollutants in the Barcelona Health Survey of 2006 and in the Catalan Health Survey of 2002.

	Catalan Health Survey 2002 (subjects from Barcelona only) (N = 147)			Barcelona Health Survey 2006 (N = 231)			Change 2002–2006		
	%>LOD	Median (P25–P75)	aGM[a] (CI 95%)	%>LOD	Median (P25–P75)	aGM[a] (CI 95%)	%>LOD (P-value)[b]	Medians (%)[c]	aGM[a] (%)[d]
p,p′-DDT									
ng/g lipid		36.1 (19.7–76.1)	37.2 (31.9–43.5)		22.0 (13.0–34.9)	20.3 (17.9–22.9)	+0.3	−39	−45
ng/mL	96.3	0.22 (0.12–0.42)	0.22 (0.19–0.25)	96.9	0.14 (0.08–0.21)	0.12 (0.11–0.14)	(1.000)	−36	−45
p,p′-DDE									
ng/g lipid		470.5 (228.7–789.2)	491.2 (421.3–572.7)		219.1 (97.4–625.2)	233.6 (206.8–263.8)	0.0	−53	−52
ng/mL	100.0	2.53 (1.25–5.11)	2.85 (2.44–3.33)	100.0	1.36 (0.56–4.16)	1.44 (1.27–1.63)	(1.000)	−46	−49
PCB 118									
ng/g lipid		30.8 (17.7–48.5)	30.0 (25.3–35.5)		13.5 (5.2–22.7)	9.4 (8.2–10.8)	−12.7	−56	−69
ng/mL	95.2	0.17 (0.11–0.30)	0.17 (0.15–0.21)	82.5	0.09 (0.03–0.14)	0.06 (0.05–0.07)	(<0.001)	−47	−65
PCB 138									
ng/g lipid		91.9 (64.3-128.5)	88.0 (78.0 - 99.2)		48.3 (29.1-87.1)	44.0 (40.0 - 48.4)	−0.9	−47	−50
ng/mL	98.7	0.55 (0.32–0.77)	0.51 (0.45–0.58)	97.8	0.30 (0.17–0.58)	0.27 (0.25–0.30)	(0.411)	−45	−47
PCB 153									
ng/g lipid		121.9 (86.3-176.6)	122.6 (108.4 - 138.8)		68.6 (41.6-135.5)	63.4 (57.5 - 70.0)	−2.2	−44	−48
ng/mL	100.0	0.71 (0.45–1.01)	0.71 (0.63–0.81)	97.8	0.45 (0.25–0.86)	0.39 (0.35–0.43)	(0.161)	−34	−45
PCB 180									
ng/g lipid		95.6 (64.5–432.2)	92.4 (49.7–59.6)		63.4 (38.6–104.0)	54.4 (82.4–103.5)	−1.9	−34	−41
ng/mL	100.0	0.54 (0.37–0.77)	0.54 (0.48–0.60)	98.1	0.39 (0.22–0.68)	0.34 (0.31–0.37)	(0.159)	−28	−37
HCB									
ng/g lipid		233.4 (90.9–432.2)	226.9 (199.5–258.1)		109.0 (50.0–339.0)	106.8 (96.4–118.3)	−1.6	−53	−53
ng/mL	100.0	1.32 (0.52–2.61)	1.32 (1.16–1.50)	98.4	0.70 (0.29–2.32)	0.66 (0.59–0.73)	(0.159)	−47	−50
β-HCH									
ng/g lipid		128.9 (53.2–269.7)	119.4 (103.5–137.8)		64.2 (24.8–195.4)	59.3 (53.0–66.4)	+0.4	−50	−50
ng/mL	96.5	0.71 (0.29–1.55)	0.69 (0.60–0.80)	96.9	0.40 (0.14–1.26)	0.37 (0.33–0.41)	(0.774)	−44	−46

LOD: limit of detection. %>LOD: percent of subjects with concentrations above the LOD. Limits of detection and quantification are given in Tables 1 and 2 of Supplemental Material. P25, P75: 25th, and 75th percentiles, respectively.

[a] aGM: Geometric mean adjusted by age, sex and BMI.

[b] Difference in percentage points between the Catalan Health Survey 2002 and the Barcelona Health Survey 2006 in the percent of subjects with concentrations above the limit of detection (Fisher's exact test, two-tail test).

[c] Percent change in the median of the Catalan Health Survey 2002 and the median of the Barcelona Health Survey 2006; the differences between such pairs of medians were all statistically significant ($p \leq 0.001$, Mann–Whitney's *U* test, two-tail).

[d] Percent change in the aGM of the Catalan Health Survey 2002 and the aGM of the Barcelona Health Survey 2006; the differences between such pairs of aGM were all statistically significant ($p \leq 0.001$, Wald test).

The median concentrations of the most frequently detected compounds are shown in Table 2. Among the less frequently detected compounds, median concentrations ranged from 0.16 ng/g (PCB 101) to 5.46 ng/g (δ-HCH) (Table 2 of Supplementary Material). There were substantial interindividual differences: the highest individual concentration of *p,p′*-DDE (8227.20 ng/g) was over 1190 times higher than the lowest (6.89 ng/g); for HCB the corresponding values were 1210.47 and 1.41 ng/g (a 858-fold difference), and for β-HCH, 898.26 and 1.50 ng/g (600-fold). Thus, a majority of the population had much lower concentrations than a certain minority.

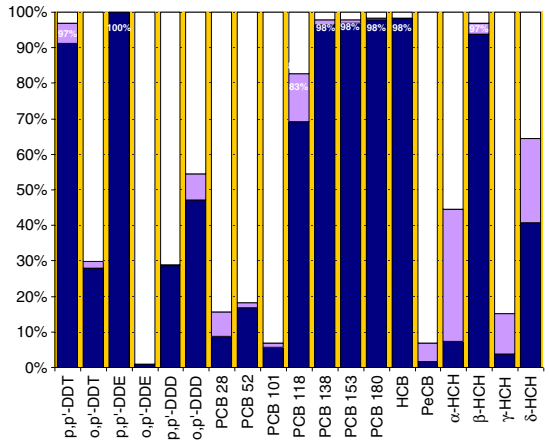

Fig. 1. Percentages of detection of organochlorine compounds in serum in a representative sample of the general population of Barcelona (samples collected in 2006). Blue (B): detected and quantified. Purple (P): detected, non-quantified. White: non-detected. The figures inside the bars refer to the percentage of detection (B + P) of the 8 most frequently detected POPs. DDT, dichlorodiphenyltrichloroethane; DDE, dichlorodiphenyldichloroethene; DDD, dichlorodiphenyldichloroethane; PCBs, polychlorinated biphenyls; HCB, hexachlorobenzene; PeCB, pentachlorobenzene; HCH, hexachlorocyclohexane.

The highest Spearman's correlation coefficient was observed between PCBs 138 and 153 ($\rho = 0.978$), PCBs 153 and 180 ($\rho = 0.958$), PCBs 138 and 180 ($\rho = 0.942$), and HCB and β-HCH ($\rho = 0.910$). For *p,p′*-DDT and *p,p′*-DDE, ρ was 0.542 (all $p < 0.001$).

The median value of the DDT/DDE ratio was 0.09; it was significantly higher in men than women ($p < 0.001$). The ratio decreased with increasing age ($p < 0.001$); the median values were 0.15, 0.06 and 0.05 for age groups 18–44, 45–64 and ≥65 years, respectively. Differences between men and women remained statistically significant for age group 18–44 years; in the two oldest groups' men still had a non-significant higher ratio than women.

POP levels in BHS were lower than those found four years earlier for the entire Catalonia in CHS (Porta et al., 2010b). When comparing only the subjects from Barcelona city in the two studies (BHS and CHS), the concentrations of the eight most prevalent POPs were significantly lower in BHS (Table 2). Specifically, the eight median POP concentrations corrected by lipids were 34–56% lower in BHS than in subjects from Barcelona in CHS (28–47% lower when uncorrected by lipids). When geometric means adjusted by age, sex and BMI were compared, concentrations in 2006 were 41–69% lower than in 2002 (37–65% lower when uncorrected by lipids) (Table 2). The decrease from 2002 to 2006 (in the adjusted geometric mean of the concentrations) was ≥7 percentage points higher in men than in women for *p,p′*-DDE and PCBs 153 and 180, and higher in women than in men for *p,p′*-DDT and

β-HCH; however, none of these differences was statistically significant (Table 3). The decrease in concentrations from 2002 to 2006 became smaller with increasing age for *p,p′*-DDE and PCBs 138, 153 and 180. Practically the same pattern was observed when individuals were grouped by birth cohort instead of age. The decrease in concentrations from 2002 to 2006 was larger with increasing BMI for seven of the eight POPs (all but *p,p′*-DDE); differences were statistically significant for *p,p′*-DDT, HCB and β-HCH; in these compounds, the decrease in obese individuals was 31–44 points larger than in subjects with normal weight.

The percentages of detection were similar in 2002 and 2006 (Table 2). For 9 of the 11 less frequently detected POPs, the percentage of detection was also statistically significantly lower in BHS. Fig. 2 shows the population distribution of concentrations of PCB 153 by sex and period. The four distributions lean towards the left (lower levels), but more so in 2006 than in 2002; levels are always higher in women. The population distribution of the concentrations of POPs was always switched towards higher values in women than men (Fig. 3); women had statistically significantly higher median concentrations than men of seven of the eight most prevalent POPs (the exception was *p,p′*-DDT). After adjusting by age and BMI, levels of *p,p′*-DDE, HCB and β-HCH remained significantly higher in women than men. The difference between women and men in median concentrations of HCB increased with age/cohort (Fig. 4); so did for concentrations of PCB 118 and β-HCH. This increase in the difference between women and men with age was not due to a higher weight with increasing age in women than men (results not shown).

The median, geometric mean, 25th percentile and 75th percentile of all 8 most commonly detected POPs increased with increasing age group; thus, for instance, among the eldest group median concentrations of *p,p′*-DDE, HCB and β-HCH were between four and nine times higher than in the younger group (Tables 4 and 5). Although differences were not statistically significant, the percentage of detection of the 11 POPs less frequently detected was always higher in the oldest than in the youngest age group (Table 2 of Supplementary Material); the possible exceptions were α-HCH, γ-HCH and δ-HCH, whose percentages of detection were slightly higher in the youngest than in the oldest group.

We observed a pattern of progressive flattening of the curves with increasing age. The kurtosis of each POP distribution in each younger group was between 2.2 and 33 times higher than that of the corresponding older group; i.e., in the younger groups POP concentrations clustered more around a few values than in the older groups. Simultaneously, the skewness of each POP distribution in the youngest group was between 1.6 and 9.4 times greater than that of the oldest group. In addition, the coefficient of variation of the distribution of each POP was between 1.2 and 2.0 times higher in the youngest than in the oldest group.

BMI was positively associated to concentrations of HCB and β-HCH in women and men, and of *p,p′*-DDE in men; obese individuals had medians of these POPs between 2.7 and 4.7 times higher than individuals with normal weight (Tables 4a and 5a). However, after adjusting for age, no positive association remained statistically significant between POP concentrations and BMI, while PCB 180 (in both women and men), and *p,p′*-DDT (in men), showed decreasing concentrations with increasing BMI (Tables 4a, 4b and 5b). Controlling by occupational social class, educational level (or parity, in women), did not materially alter these patterns.

Individuals who had gained 4–5 kg in the 6 months prior to BHS blood draw had lower median concentrations of all eight POPs – except PCB 118 in women – than those who had little or no weight change; although this pattern was common, none of the 15 differences was statistically significant (Tables 4 and 5). The general pattern remained apparent after adjusting for age, and the inverse association observed in men between *p,p′*-DDT and weight gain became statistically significant ($p = 0.029$). POP concentrations were similar between participants who had lost weight and those with little or no weight change; only significantly higher concentrations of PCB 118 were found in men who had lost weight, after adjusting for age ($p = 0.027$). Having been breastfed in infancy was virtually unrelated to POP levels (Tables 4 and 5).

Men who were born abroad of Spain had higher age-adjusted concentrations of *p,p′*-DDT and *p,p′*-DDE than men who were born in Catalonia (both $p < 0.03$). Women who were born abroad had higher concentrations of *p,p′*-DDT and *p,p′*-DDE, and lower concentrations of PCBs 138, 153 and 180, HCB and β-HCH (Tables 4 and 5).

Crude and multivariate analyses showed that concentrations of all 8 prevalent POPs were highest in women from the less affluent social classes (IV–V), although only differences for *p,p′*-DDE were statistically significant after adjusting for age (Table 4). Men in social classes IV–V had the highest concentrations of *p,p′*-DDT and *p,p′*-DDE ($p = 0.023$ and 0.181, respectively); they also had the lowest concentrations of HCB and PCB 118 (p-values ≤ 0.005) (Table 4). Men in class III had the lowest values of the other three PCB congeners (p-values ≤ 0.025).

Crude analyses did not show decreasing POP concentrations in women with increasing number of children or with increasing months of having breastfed their children; in fact, the highest (unadjusted) concentrations of almost all POPs were seen in women with ≥3 children, and in women who had breastfed > 6 months (Table 4). However, parity and breastfeeding were positively associated with age and, hence, after adjusting by age, there was no association between parity or breastfeeding and POP levels. Adjusting by BMI, social class or education did not change these results.

Table 3
Change in the concentrations of persistent organic pollutants in the population of the city of Barcelona from 2002 to 2006, by sex, age and body mass index.[a].

	Sex[b]		Age[c]			Body mass index[d]		
	Men	Women	18–44 years	45–64 years	≥65 years	Normal weight	Overweight	Obese
p,p′-DDT	−41	−49	−39	−54	−53	−25	−52	−69*
p,p′-DDE	−58	−45	−57	−44	−30	−52	−53	−51
PCB 118	−71	−66	−66	−74	−61	−59	−74	−79
PCB 138	−50	−49	−53	−48	−31	−42	−53	−65
PCB 153	−53	−43	−54	−43	−22	−44	−48	−63
PCB 180	−47	−35	−48	−38	−15	−36	−41	−58
HCB	−53	−52	−52	−53	−46	−38	−61	−64*
β-HCH	−46	−53	−48	−49	−48	−31	−61	−62*

*p ≤ 0.05, Wald test.
[a] Percent change in the adjusted geometric mean of the lipid-corrected serum concentrations of each compound (ng/g lipid) in the Catalan Health Survey of 2002 (subjects from Barcelona) and the Barcelona Health Survey of 2006.
[b] General linear regression models, adjusted by age.
[c] General linear regression models, adjusted by sex.
[d] General linear regression models, adjusted by age and sex.

4. Discussion

Eight POPs were each detected in > 80% of the study subjects, and no individual was free from POPs; the smallest number detected in one person was 5 compounds, while ten or more compounds were detected in 72% of the population. However, from 2002 to 2006 serum concentrations of POPs decreased 34–56% in Barcelona city (Porta et al., 2010b).

In the BHS a pattern of progressive "flattening" of the POP distributions with increasing age was also seen, as previously in the CHS (Porta et al., 2010b). Compared to older subjects, all POP distributions of younger participants had higher kurtosis, skewness and coefficient of variation. To our knowledge, these patterns have not been noticed in other populations, although they are likely to occur as well. In a cross-sectional study it is of course impossible to know whether the pattern is related to ageing or cohort effects. Either case, we hypothesize that the two main underlying processes may be: *a)* in the youngest age group/cohort there is both less and more inequality in the concentrations of each POP: less because most of the subjects have similar values,

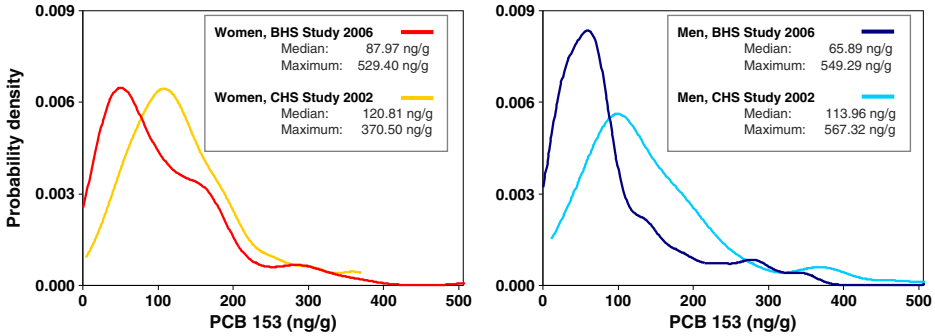

Fig. 2. Distribution of serum concentrations of PCB 153 in the city of Barcelona by sex (2006, BHS; 2002, subjects from Barcelona city in CHS).

and more because there is a large difference between their concentration and that of the minority of the subjects at the right end of the tail; and *b)* as age increases, inequalities increase in the subgroup with initially similarly low concentrations but, on average, such group gets closer to the minority with top concentrations. The processes of exposure and accumulation that underlie these phenomena deserve more attention than they have received so far (Porta, 2004; Porta et al., 2008b).

Our two younger age groups/cohorts had a higher DDT/DDE ratio than the oldest cohort. This observation results from the following two facts: in the younger cohorts concentrations of DDE were 7 times lower than in the oldest cohort, whereas concentrations of DDT were 2 times lower in the younger than in the oldest cohort. These relationships are in turn coherent with the fact that the DDT/DDE ratio increased from 2002 to 2006, given that concentrations of

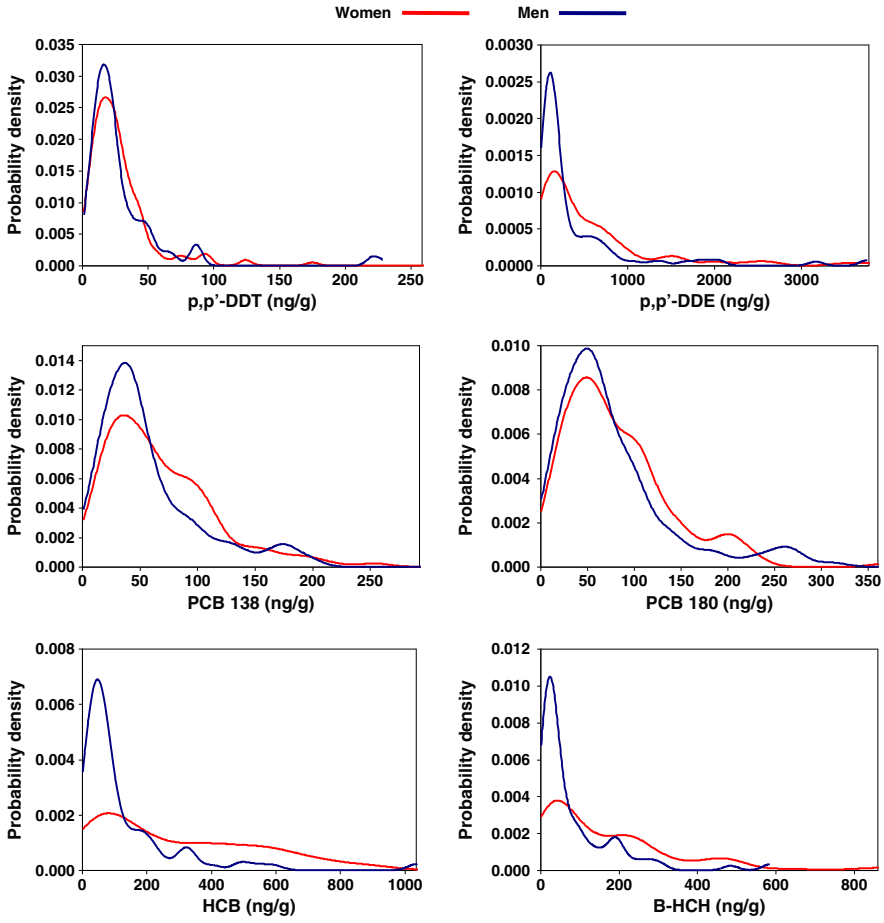

Fig. 3. Population distributions of six prevalent POPs by sex (Barcelona, 2006).

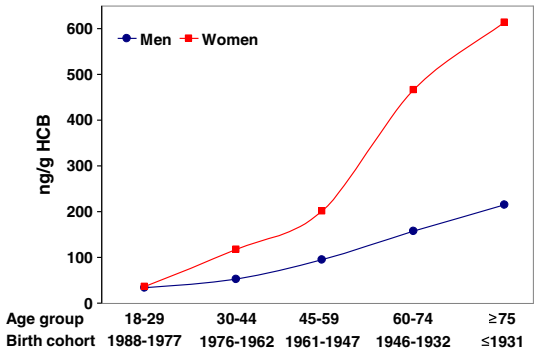

Fig. 4. Median concentration of HCB by age group/birth cohort and by sex (Barcelona, 2006).

DDE decreased more than concentrations of DDT (Table 2). As in individuals, the "population kinetics" of DDE and DDT is not linear, and levels decrease more slowly when they are lower (Porta, 2004; Porta et al., 2008b; Wolff et al., 2005, 2007).

Chemical analyses for BHS and CHS were performed in the same laboratory, using the same methodology. Nevertheless, two minor differences between the two studies could slightly affect the analysis of changes in concentrations from 2002 to 2006: *a)* while in BHS 2006 serum samples were stored frozen during two years before POP analyses, the corresponding time in CHS 2002 was four years, which might have caused a slightly underestimation of the decrease in concentrations seen in BHS relative to CHS; and *b)* the time of fasting requested before blood draw was ≥4 h in BHS and ≥12 h in CHS. However, almost all participants were fasting (98% in BHS an 99% in CHS); also, all POP concentrations were corrected for lipids, a common technique to account for inevitable differences in fasting in population-based studies (Bernert et al., 2007; Phillips et al., 1989; Porta et al., 2009b). In BHS, lipid concentrations were slightly higher than in CHS (Porta et al., 2010b); therefore, compared to crude values (uncorrected for lipids), lipid-corrected POP concentrations in BHS experienced a higher relative decrease than in CHS, which would tend to slightly overestimate the difference in concentrations between the two studies. Nevertheless, crude concentrations were also significantly lower in BHS than in CHS (Table 2). Furthermore, differences between 2006 and 2002 remained significant for all eight POPs when we adjusted by age, sex, lipids and BMI. The decrease in concentrations from 2002 to 2006 was similar in women and men, with no clear pattern. For *p,p′*-DDE and PCBs 138, 153 and 180 the decrease in concentrations was larger in the younger age groups; practically the same pattern was observed when individuals were grouped by birth cohort. The decrease in concentrations from 2002 to 2006 was larger in obese individuals (except for *p, p′*-DDE); this was so in spite of the positive association between most POPs and BMI in the two studies (BMI was inversely associated with PCBs in both BHS and CHS). Thus, POP contamination likely decreased in the citizens of Barcelona in the four years between studies, and reasons for the change deserve further research.

Papers reporting time trends in representative samples using similar methodologies are extremely rare (Hagmar et al., 2006; Axmon et al., 2008; Porta et al., 2008b; Hardell et al., 2010; Donaldson et al., 2010). Our findings are broadly in accordance with these studies. For instance, significant declines were observed for most contaminants in maternal blood from 1992–1996 to 2004–2006 within different Arctic regions (Donaldson et al., 2010). In a small convenience sample from Sweden, levels of PCB 153 also decreased more in obese than in lean individuals (Hagmar et al., 2006). In some 200 young Swedish males investigated in 2000 and 2004, the median serum concentration of PCB 153 decreased an average of 26% per year; this congener was detected in 100% of participants in 2000 and in 70% in 2004; the corresponding figures for *p,p′*-DDE were 94% and 35% (Axmon et al., 2008).

Women had significantly higher concentrations than men of seven POPs. Values of three compounds with high concentrations overall (*p,p′*-DDE, HCB and β-HCH) remained significantly higher in women after adjusting by age and BMI. Thus, the specific reasons for sex differences

Table 4a
Serum concentrations of POPs (ng/g lipid) detected in over 80% of the Barcelona population by sociodemographic characteristics (men).

	p,p′-DDT		*p,p′*-DDE		HCB		β-HCH	
	Median (P25–P75)	aGM[a] (CI 95%)	Median (P25–P75)	aGM[a] (CI 95%)	Median (P25–P75)	aGM[a] (CI 95%)	Median (P25–P75)	aGM[a] (CI 95%)
Men	21.1 (12.4–34.8)	20.9 (17.8–24.6)	147 (81.1–441)	194 (159–236)	69.4 (35.8–157)	71.0 (60.0–84.0)	39.6 (19.9–107)	42.9 (36.7–50.3)
Age (years)								
18–44	17.6 (10.4–28.1)*	17.0 (13.5–21.5)	97.0 (62.2–148)*	98.3 (74.9–129)	49.1 (27.2–62.7)*	37.2 (27.8–49.8)	22.8 (13.8–35.5)*	18.4 (14.0–24.2)
45–64	22.2 (12.9–26.1)	19.0 (13.7–26.3)	242 (131–542)	271 (185–397)**	103 (60.4–172)	90.3 (60.0–136)**	80.9 (40.9–113)	62.6 (42.8–91.5)**
≥65	40.6 (18.3–61.6)	36.6 (25.5–52.7)**	662 (255–1859)	566 (370–865)**	214 (122–351)	204 (130–322)**	193 (104–275)	165 (108–252)**
Body mass index								
Normal	21.7 (15.9–35.1)	27.8 (21.0–36.6)	114 (64.3–153)*	161 (116–224)	51.3 (28.2–70.6)*	64.3 (45.7–90.3)	23.9 (16.6–38.5)*	40.8 (29.8–55.9)
Overweight	20.2 (13.8–38.8)	17.5 (13.3–23.1)**	187 (122–552)	172 (124–239)	93.1 (57.5–197)	62.9 (44.8–88.2)	61.7 (24.0–164)	34.8 (25.5–47.6)
Obese	19.8 (9.2–29.6)	14.4 (9.9–20.8)**	313 (96.0–1675)	272 (175–424)	152 (47.3–331)	87.5 (55.4–138)	99.0 (40.6–191)	52.8 (34.6–80.7)
Weight change in last 6 months								
Lost 4–5 kg	33.8 (17.7–35.3)	24.4 (12.6–47.3)	113 (64.6–267)	124 (48.0–322)	77.5 (71.6–92.6)	73.7 (27.6–197)	51.0 (26.4–117)	53.6 (19.4–148)
Little or no change (± 3 kg)[b]	21.7 (12.6–39.7)	22.2 (18.5–26.8)	156 (91.9–464)	199 (152–260)	69.8 (35.8–177)	70.1 (53.2–92.4)	40.6 (19.9–113)	44.3 (33.3–58.9)
Gained 4–5 kg	14.6 (2.7–22.7)	8.8 (5.0–15.8)**	91.7 (54.7–488)	145 (63.1–331)	42.2 (9.1–350)	46.2 (19.7–109)	24.2 (1.6–105)	15.1 (6.2–36.6)
Was breastfed								
No	25.4 (15.2–60.0)	23.2 (9.3–58.2)	1433 (167–2047)	494 (176–1386)	106 (18.2–329)	45.1 (15.3–133)	77.7 (10.3–263)	27.2 (9.8–76.1)
Yes	18.7 (12.2–30.4)	19.7 (16.3–23.8)	140 (72.2–333)	175 (141–216)**	61.6 (35.2–134)	63.2 (50.6–79.0)	36.9 (19.2–99.9)	38.0 (30.7–47.0)
Birth place								
Catalonia	19.2 (11.2–30.2)	19.9 (16.3–24.2)	133 (67.7–267)*	162 (129–204)	59.7 (35.8–141)*	70.4 (55.4–89.5)	38.5 (19.7–87.4)*	39.9 (31.9–49.9)
Rest of Spain	24.1 (12.0–40.9)	15.8 (9.6–26.1)	346 (163–1498)	211 (119–376)	190 (89.0–311)	79.8 (43.8–146)	169 (69.8–239)	44.8 (25.5–78.8)
Abroad	22.5 (17.7–35.3)	29.9 (19.5–45.9)**	232 (130–609)	301 (184–493)**	53.8 (18.4–78.4)	46.1 (27.6–77.1)	27.4 (17.6–64.1)	37.8 (23.3–61.2)
Occupational social class								
I–II (more affluent)	18.8 (10.9–30.2)	19.2 (14.7–25.1)	129 (64.4–392)	160 (109–234)	70.1 (43.4–151)	85.6 (57.8–127)	33.7 (19.5–88.9)	43.1 (28.2–65.7)
III	16.5 (10.9–25.3)	13.5 (9.1–19.9)	139 (54.7–239)	156 (89.8–271)	66.2 (45.7–177)	65.2 (36.9–115)	41.6 (17.0–99.8)	32.7 (17.7–60.2)
IV–V (less affluent)	23.6 (16.0–51.6)	27.6 (21.0–36.3)**	187 (129–613)	242 (164–357)	70.9 (27.2–170)	54.3 (36.4–81.2)**	39.0 (22.9–149)	43.6 (28.3–67.1)

Results are weighted by age. [a]aGM: Geometric mean adjusted by age. *p-value<0.05 (median, Kruskal–Wallis test). **p-value<0.05 (aGM, Wald test; compared against the reference category). [b]Reference category (except where otherwise noted, the reference category is the first category mentioned above).

Table 4b
Serum concentrations of POPs (ng/g lipid) detected in over 80% of the Barcelona population by sociodemographic characteristics (men).

	PCB 118		PCB 138		PCB 153		PCB 180	
	Median (P25–P75)	aGM[a] (CI 95%)	Median (P25–P75)	aGM[a] (CI 95%)	Median (P25–P75)	aGM[a] (CI 95%)	Median (P25–P75)	aGM[a] (CI 95%)
Men	11.6 (4.6–18.0)	8.7 (7.0–10.5)	43.3 (25.6–72.0)	42.7 (37.1–49.3)	65.9 (36.3–114)	61.3 (52.2–72.1)	58.1 (36.8–96.7)	55.6 (47.8–64.7)
Age (years)								
18–44	7.9 (1.8–14.4)*	6.6 (4.8–9.2)	33.6 (21.5–43.9)*	26.0 (20.4–33.0)	48.4 (25.7–65.7)*	35.3 (26.8–46.5)	39.4 (24.2–66.6)*	34.4 (26.6–44.6)
45–64	11.7 (7.0–17.0)	8.8 (5.5–13.9)	52.3 (40.3–72.9)	52.3 (37.3–73.3)**	77.8 (64.1–128)	78.0 (53.1–115)**	65.9 (49.6–99.8)	66.8 (46.5–96.0)**
≥65	17.6 (10.5–27.2)	13.9 (8.3–23.1)**	107 (61.8–160)	97.3 (66.8–142)**	172 (92.6–255)	150 (97.8–230)**	129 (70.2–210)	124 (83.0–186)**
Body Mass Index								
Normal	8.7 (3.9–14.5)	8.8 (5.9–13.1)	38.5 (21.9–52.0)	48.5 (36.8–64.0)	56.8 (26.4–75.7)	70.0 (51.2–95.8)	51.8 (26.7–69.2)	69.6 (52.5–92.2)
Overweight	13.1 (7.3–19.2)	8.4 (5.6–12.4)	48.4 (35.6–92.6)	38.9 (29.6–51.3)	79.0 (48.5–140)	56.3 (41.2–77.0)	78.2 (48.9–107)	50.4 (38.1–66.7)
Obese	11.5 (1.2–24.2)	6.7 (3.9–11.5)	56.2 (37.5–87.3)	30.1 (20.7–43.7)	76.0 (50.0–136)	40.6 (26.6–61.9)	58.5 (36.7–99.8)	32.1 (22.0–46.9)**
Weight change in last 6 months								
Lost 4–5 kg	29.9 (13.3–62.9)	21.2 (8.5–52.9)**	42.5 (36.1–72.0)	46.6 (21.7–100)	72.5 (56.9–90.6)	71.2 (30.0–169)	63.5 (48.3–86.5)	63.5 (28.7–140)
Little or no change (±3 kg) [b]	10.3 (4.8–17.6)	8.4 (6.5–10.8)	43.7 (26.7–86.8)	45.5 (36.7–56.4)	66.5 (33.3–135)	65.4 (51.3–83.3)	59.9 (36.6–105)	59.4 (47.6–74.3)
Gained 4–5 kg	6.2 (1.1–14.5)	4.1 (1.9–9.1)	27.7 (3.3–56.3)	15.8 (8.1–30.7)	39.7 (3.8–90.3)	20.7 (9.7–43.8)	50.3 (4.2–66.1)	19.1 (9.6–38.1)
Was breastfed								
No	11.9 (1.1–13.1)	3.9 (1.2–12.7)	42.3 (16.9–57.8)	19.6 (8.1–47.7)	77.4 (25.8–83.4)	30.0 (10.9–82.3)	56.0 (28.2–78.0)	23.7 (9.2–60.8)
Yes	11.6 (4.7–17.2)	8.2 (6.4–10.5)	42.3 (23.2–69.0)	39.3 (32.7–47.2)	65.4 (31.7–101)	56.1 (45.5–69.2)	57.0 (31.5–94.0)	51.6 (42.4–62.7)
Birth place								
Catalonia	9.3 (4.5–17.1)	7.8 (5.9–10.2)	41.3 (23.2–68.7)*	41.0 (33.6–50.0)	65.0 (31.5–104)*	58.5 (46.6–73.4)	56.5 (28.9–94.0)*	55.2 (44.8–68.1)
Rest of Spain	14.2 (10.2–22.9)	7.6 (3.8–15.1)	60.9 (54.4–108)	38.5 (23.4–63.5)	105 (79.0–198)	57.0 (32.3–101)	106 (58.1–145)	51.0 (30.1–86.3)
Abroad	22.5 (17.7–35.3)	12.2 (6.7–22.2)	232 (130–609)	44.1 (28.8–67.7)	53.8 (18.4–78.4)	61.8 (38.0–101)	27.4 (17.6–64.1)	48.3 (30.7–75.8)
Occupational social class								
I–II (more affluent)	13.5 (5.8–28.1)*	11.5 (8.0–16.7)	42.2 (24.2–87.1)	46.7 (34.0–64.1)	76.2 (31.7–135)	67.9 (47.5–96.9)	58.9 (33.4–99.6)	58.5 (42.1–81.3)
III	11.5 (6.7–16.4)	8.1 (4.7–13.9)	40.6 (27.5–59.6)	29.0 (18.3–45.9)**	52.3 (37.3–81.8)	39.7 (23.7–66.5)**	51.6 (36.7–92.3)	37.7 (23.4–60.8)**
IV–V (less affluent)	23.0 (11.4–33.7)	6.1 (4.1–8.8)**	187 (82.6–620)	44.9 (32.5–62.0)	147 (53.4–355)	65.2 (45.3–93.8)	73.1 (20.6–205)	61.1 (43.7–85.6)

Results are weighted by age. [a]aGM: Geometric mean adjusted by age. *p-value<0.05 (median, Kruskal–Wallis test). **p-value<0.05 (aGM, Wald test; compared against the reference category). [b]Reference category (except where otherwise noted, the reference category is the first category mentioned above).

are unknown; gender differences in POP exposure and accumulation should be explored. Human POP contamination has important gender dimensions (Porta et al., 2008b). Furthermore – for reasons similarly unknown – the difference between women and men in concentrations of HCB, PCB 118 and β-HCH increased with age/cohort, a trend that was not due to a higher weight with increasing age in women than men.

The relationships of different socio-demographic variables with POP levels were similar in both studies, with few exceptions. Notably, while in the study of the entire Catalonia parity was inversely associated with POP concentrations (after adjustment by age, and by age and BMI) (Porta et al., 2010b), in BHS parity was unrelated to POP concentrations (again, after these adjustments).

Women excrete POPs through breastfeeding, which increases concentrations in the child (Aliyu et al., 2010; Thomsen et al., 2010). Yet, in the present study having breastfed was not associated with women's POP levels. Similarly, we did not find significant differences in POP levels between participants who were breastfed and non-breastfed as a child; the result may partly reflect bias in recalling breastfeeding, as well as the effect of POP exposure through other sources common during childhood and adulthood. Some studies found that individuals who had been breastfed had higher concentrations of PCBs, DDE and HCB (Barr et al., 2006; Den Hond et al., 2009; Gallo et al., 2011; Grimalt et al., 2010; Karmaus et al., 2001; Link et al., 2005; Nawrot et al., 2002; Schroijen et al., 2008). All these studies were carried out in children and adolescents, with few studies finding the association in adults. Glynn et al. (2007) reported that only concentrations of PCBs 156 and 180, and *p,p′*-DDE, increased significantly with the number of months women had been breast-fed during infancy. Breastfeeding is likely a relevant influence on POP levels in children, but not in adults (Verner et al., 2009).

Weight loss is common in clinically aggressive diseases as some cancers (Porta et al., 2008c, 2009c). Although no such diseases are prevalent in surveys of the general non-institutionalized population as ours, BHS participants were asked if they had experienced weight change in the last 6 months; since the information was self-reported, caution is needed. Individuals who reported weight gain had slightly and non-significantly lower POP concentrations than subjects without weight change. If weight gain entailed an extra storage of lipids in adipose tissue, blood concentrations of POPs would tend to be diluted with respect to subjects without weight gain (Kim et al., 2011; Porta et al., 2009b, 2009c). Indeed, Bachelet et al. (2011) observed an inverse association between PCB levels and gain in BMI during the last ten years. Glynn et al. (2003) also found negative associations between recent weight increase and serum concentrations of some PCBs, DDE and HCB. Wolff et al. (2005, 2007) also found DDE and PCBs inversely associated with BMI gain. Baris et al. (2000) found no association between weight change and concentrations of PCBs. In one study in healthy individuals (Schroijen et al., 2008) weight change explained about 2% of HCB levels. In any case, POP surveys should, if feasible, collect information on weight changes, and integrate this information in statistical analyses on POP distributions across population groups, and on health effects.

Almost all study subjects spent their childhood in their birth place, a variable that defines different types of culture and environment; exposure to POPs varies significantly among countries (UNEP, 2002; WHO, 2003). Industry, agriculture, food chains and nutritional patterns are slightly different in Catalonia and the rest of Spain, while they differ markedly from the native countries of immigrants to Spain; such factors likely explain the remarkably higher concentrations of DDT and DDE of individuals born abroad and in Spain, and underscore the problem of human contamination from DDT analogues in developing countries.

Population-based biomonitoring is developed or developing in regions as North America, the Arctic and Europe, with similar types of chemicals being measured. It is however difficult to compare studies, due to differences in laboratory techniques, detection limits, or methods of assigning values to non-detects, among other factors. Limits of detection of this study were between 0.01 and 0.02 ng/mL (Table 1 of Supplementary Material), similar to other studies (Van Oostdam et al., 2004; Koppen et al., 2002; Link et al., 2005). The limits of quantification were between 0.03 and 0.06 ng/mL, higher than the German study 2003–2006 (GerES IV, 2003–2006), but slightly lower than others studies

Table 5a
Serum concentrations of POPs (ng/g lipid) detected in over 80% of the Barcelona population by sociodemographic characteristics (women).

	p,p′-DDT		*p,p′*-DDE		HCB		β-HCH	
	Median (P25–P75)	aGM[a] (CI 95%)	Median (P25–P75)	aGM[a] (CI 95%)	Median (P25–P75)	aGM[a] (CI 95%)	Median (P25–P75)	aGM[a] (CI 95%)
Women	23.0 (13.7–35.5)	20.4 (17.5–23.8)	305 (122–728)	286 (237–344)	206 (71.7–484)	155 (133–182)	114 (33.2–241)	81.7 (70.3–94.9)
Age (years)								
18–44	22.2 (13.4–28.5)	17.5 (13.9–22.1)	130 (70.5–360)*	169 (127–225)	71.5 (36.1–170)*	72.0 (57.2–90.5)	30.3 (18.1–70.7)*	36.7 (29.5–45.7)
45–64	23.0 (13.8–35.4)	21.7 (16.4–28.8)	417 (255–802)	421 (299–593)**	207 (131–439)	222 (168–292)	134 (71.9–225)	118 (90.8–154)
≥65	33.1 (12.2–650.1)	27.5 (20.5–37.0)**	650 (265–989)	586 (409–839)**	568 (438–712)	551 (413–735)	289 (229–467)	316 (240–417)
Body Mass Index								
Normal	20.5 (14.9–30.0)	19.0 (15.2–23.8)	242 (89.1–642)	274 (208–362)	114 (52.8–348)*	143 (117–174)	65.7 (27.6–150)*	78.2 (64.6–94.7)
Overweight	23.5 (13.0–35.9)	21.6 (16.5–28.3)	368 (163–746)	310 (222–433)	321 (152–551)	169 (133–214)	173 (45.1–242)	86.3 (68.6–109)
Obese	30.8 (10.9–48.6)	23.6 (16.4–33.8)	459 (207–943)	340 (216–533)	538 (159–701)	212 (154–292)	244 (66.6–461)	113 (82.6–154)
Weight change in last 6 months								
Lost 4–5 kg	21.2 (14.2–29.7)	18.9 (11.6–30.9)	271 (98.0–619)	268 (140–513)	195 (74.1–315)	134 (69.8–256)	71.0 (28.8–234)	78.7 (40.9–151)
Little or no change (± 3 kg) [b]	23.6 (13.0–36.5)	21.2 (17.8–25.3)	321 (129–746)	336 (267–424)	233 (75.4–520)	185 (146–233)	133 (37.0–241)	98.4 (77.8–124)
Gained 4–5 kg	21.6 (14.9–35.2)	22.5 (13.8–36.7)	137 (71.6–635)	196 (103–374)	150 (55.8–370)	151 (78.8–288)	76.1 (29.3–248)	73.4 (38.2–141)
Was breastfed								
No	23.9 (13.9–30.9)	21.6 (15.2–30.6)	282 (95.0–693)	315 (202–489)	137 (48.8–520)	167 (122–229)	77.5 (20.7–241)	91.0 (67.1–124)
Yes	20.8 (13.2–34.0)	20.0 (16.7–24.0)	293 (125–733)	285 (227–358)	206 (73.2–466)	157 (134–185)	116 (33.7–241)	81.8 (69.9–95.8)
Birth place								
Catalonia	22.9 (12.4–33.2)	18.3 (15.2–22.1)	275 (104–654)	266 (211–336)	236 (77.8–468)*	185 (158–216)	104 (37.2–248)*	93.8 (79.8–110)
Rest of Spain	21.9 (13.4–44.1)	22.3 (16.5–30.2)	450 (207–819)	292 (200–425)	378 (134–599)	177 (138–227)	194 (71.6–257)	82.2 (63.3–107)
Abroad	24.5 (16.0–36.5)	36.2 (22.5–58.2)**	346 (84.0–2339)	590 (326–1066)**	65.7 (10.1–73.5)	57.3 (38.7–84.8)**	34.0 (11.4–67.8)	55.1 (36.5–83.2)**
Occupational social class								
I–II (more affluent)	23.0 (11.4–33.7)*	17.5 (13.2–23.3)	187 (82.6–620)*	212 (146–308)	147 (53.4–355)*	139 (95.0–203)	73.1 (20.6–205)*	66.4 (45.5–96.7)
III	18.0 (10.6–28.4)	17.5 (12.9–23.9)	225 (109–592.)	254 (169–382)	145 (70.4–351)	144 (94.7–218)	71.2 (29.3–174)	72.8 (48.2–110)
IV–V (less affluent)	26.0 (15.8–43.7)	26.4 (21.0–33.4)	464 (209–957)	442 (326–600)**	377 (87.8–591)	222 (162–302)	205 (43.2–332)	130 (95.8–178)
Breastfed her children								
Never	22.2 (10.7–38.0)	20.8 (16.6–26.1)	225 (89.7–695)	281 (213–371)	114 (49.8–415)	155 (127–190)	53.6 (22.1–206)*	78.3 (64.4–95.1)
≤6 months	21.1 (14.8–29.5)	18.5 (13.7–25.1)	355 (154–660)	252 (173–367)	347 (145–493)	175 (133–229)	138 (80.0–235)	95.4 (73.4–124)
>6 months	29.1 (16.4–41.6)	22.9 (16.9–31.1)	417 (215–1346)	387 (265–265)	309 (116–622)	159 (121–209)	197 (50.0–425)	91.4 (70.2–119)

Results are weighted by age. [a]aGM: Geometric mean adjusted by age. *p-value<0.05 (median, Kruskal–Wallis test). **p-value<0.05 (aGM, Wald test; compared against the reference category). [b]Reference category (except where otherwise noted, the reference category is the first category mentioned above).

(Becker et al., 2002; Jakszyn et al., 2009). The studies with higher limits of quantification were from years 1998 and 1992–96, respectively, which might explain the difference. Nevertheless, our laboratory techniques were state-of-the-art and are highly unlikely to have biased the results.

Almost all concentrations of POPs found in the U.S. population in 2003–2004 (Department of Health and Human Services, 2009) are lower than values found in the present study, except *p,p′*-DDE, whose levels were similar. Concentrations of *p,p′*-DDE, β-HCH and PCBs 138, 153 and 180 seen in the German population in 1998 (Becker et al., 2002) were higher than concentrations in the present study, probably because of the year of sampling. Values of *p,p′*-DDE in West Germany were similar to those we found in the age group 26–55 years, but lower in other age groups. Concentrations of HCB (in different age groups) were similar between the German study and the present study. Concentrations of *p,p′*-DDE and the sum of PCBs (138, 153 and 180) found in the adult Flemish population (50–65 years) in 2002–2006 (De Coster et al., 2008) were slightly higher than in the adult population of BHS, while HCB concentrations in Flemish adults were lower than HCB levels in the adult population of Barcelona. In a Czech study of adults conducted in 2006 (Cerná et al., 2008) concentrations of PCBs 18, 52, 118, 138, 153 and 180 were between 5 and 10 times higher than those in the population of Barcelona. Concentrations of PCBs 138 and 153 were very similar in a study of populations living near incinerators in Italy in 2005–2006 (De Felip et al., 2008), while levels of PCB 180 were higher in this Italian population. In a study in Slovakia in 2001 (Petrik et al., 2006), concentrations of *p p′*-DDT, *p,p′*-DDE, HCB and PCBs 118, 138, 153 and 180 were higher than concentrations in Barcelona; only β-HCH concentrations were lower in Slovakia. *p,p′*-DDE concentrations found in French women in 2005–2007 (Bachelet et al., 2011) were lower than values in BHS women, but values of PCB 153 were similar. In another Spanish study of 2006 (Zubero et al., 2009) concentrations of PCB 118 were similar to our study, while levels of PCBs 138, 153 and 180 were slightly higher.

Although our sample size was small in general terms, the size may be attractive to local and regional governments with limited resources. Furthermore, subjects were selected from a representative sample of the city, participation rates were carefully analyzed (Porta et al., 2009a), and sample weights were used to compensate for differences in age and sex (Porta et al., 2009a). Moreover, relevant indicators – that are not usually part of biomonitoring surveys – were prospectively collected, such as weight changes, lactation, and anthropometric data measured by nurses.

Sociodemographic variables as age, gender, occupational social class or place of birth are important determinants of POP levels or are associated with processes that influence POP exposure. Policies aimed at decreasing human POP contamination need to take into account such influences. Furthermore, these variables can decisively influence participation in a study where subjects provide biological samples (Porta et al., 2009a).

5. Conclusions

Although all POPs analyzed were banned decades ago, human contamination remains common in the city of Barcelona, as elsewhere. Eight of the 19 POPs analyzed were (each) detected in >80% of the study subjects, the minimum number of POPs detected in one person was 5, and there were large interindividual differences in concentrations. However, POP concentrations decreased 34–56% in 4 years.

While scarce and heterogeneous worldwide, population-based surveys on the distribution of POP concentrations in humans are essential to understand patterns, trends and determinants of POP contamination.

Table 5b
Serum concentrations of POPs (ng/g lipid) detected in over 80% of the Barcelona population by sociodemographic characteristics (women).

	PCB 118		PCB 138		PCB 153		PCB 180	
	Median (P25–P75)	aGM[a] (CI 95%)	Median (P25–P75)	aGM[a] (CI 95%)	Median (P25–P75)	aGM[a] (CI 95%)	Median (P25–P75)	aGM[a] (CI 95%)
Women	17.6 (5.6–25.8)	10.6 (8.8–12.9)	57.0 (32.2–92.7)	47.3 (41.4–54.1)	87.0 (45.3–150.1)	69.1 (59.3–80.4)	67.2 (41.6–109.2)	56.8 (49.2–65.5)
Age (years)								
18–44	8.6 (1.7–17.9)*	6.7 (5.1–8.7)	32.5 (20.4–50.7)*	30.9 (25.7–37.1)	47.5 (25.6–77.9)*	44.3 (35.9–54.5)	38.6 (23.1–66.5)*	38.3 (31.4–46.7)
45–64	17.5 (9.2–22.3)	11.6 (8.5–15.9)**	64.7 (45.5–88.5)	59.3 (47.5–74.0)**	103 (64.2–137)	88.3 (68.7–113)**	71.3 (58.6–106)	71.9 (56.6–91.3)**
≥65	31.1 (20.1–41.5)	25.5 (18.3–35.6)**	106 (60.2–142)	96.1 (76.2–121)**	167 (87.9–218)	144 (111–187)**	106 (75.0–163)	108 (83.8–138)**
Body Mass Index								
Normal	14.0 (5.6–22.0)	11.3 (8.8–14.6)	47.9 (28.2–89.2)	54.6 (46.1–64.8)	67.7 (47.5–148)	82.1 (67.7–99.6)	61.2 (37.1–112)	68.3 (56.9–82.0)
Overweight	17.7 (5.0–27.7)	9.6 (7.0–13.0)	61.3 (33.5–97.6)	43.7 (35.6–53.7)	91.6 (52.3–162)	63.1 (49.9–79.6)	72.7 (43.7–110)	50.3 (40.4–62.7)
Obese	22.9 (13.6–29.7)	11.8 (7.8–17.8)	63.6 (37.9–101)	43.0 (32.6–56.8)	104 (43.7–142)	60.1 (43.9–82.3)	69.1 (44.1–98.4)	49.9 (37.1–67.0)**
Weight change in last 6 months								
Lost 4–5 kg	11.6 (4.8–20.3)	8.8 (4.8–16.2)	55.4 (31.6–87.4)	47.5 (30.2–74.6)	85.7 (42.9–144)	68.9 (41.8–113)	70.4 (37.4–112)	58.7 (36.8–93.7)
Little or no change (± 3 kg) [b]	17.8 (5.6–27.6)	11.4 (9.2–14.2)	57.7 (33.5–97.0)	53.2 (45.3–62.6)	87.5 (49.6–158)	79.0 (66.1–94.5)	68.3 (44.2–110)	63.1 (53.4–74.6)
Gained 4–5 kg	19.1 (9.0–26.9)	13.7 (7.4–25.2)	33.8 (21.1–86.4)	39.6 (25.2–62.1)	46.2 (22.3–133)	53.8 (32.7–88.5)	44.8 (28.9–97.2)	49.8 (31.2–79.3)
Was breastfed								
No	9.7 (4.5–19.3)	9.6 (6.5–14.2)	52.5 (23.7–81.6)	55.0 (41.8–72.3)	83.9 (32.9–115)	79.6 (58.3–109)	56.5 (30.0–104)	62.2 (46.2–83.6)
Yes	17.9 (6.2–25.8)	10.8 (8.8–13.3)	54.7 (32.6–95.5)	46.3 (40.2–53.3)	80.6 (47.5–145)	67.4 (57.5–79.2)	68.0 (43.0–107)	56.5 (48.5–65.9)
Birth place								
Catalonia	15.9 (5.4–25.7)	10.6 (8.5–13.1)	57.7 (32.5–88.8)*	52.3 (45.3–60.3)	87.5 (48.4–154)*	78.7 (67.0–92.4)	68.7 (42.1–112)*	63.6 (54.6–74.2)
Rest of Spain	18.2 (8.8–29.7)	9.9 (7.0–14.0)	68.1 (42.9–103)	52.6 (41.7–66.2)	110 (62.6–163)	77.8 (60.0–101)	90.5 (51.4–110)	62.4 (48.7–80.0)
Abroad	19.1 (4.9–26.5)	15.0 (8.7–25.9)	21.0 (15.4–51.5)	27.6 (19.2–39.8)**	26.1 (15.0–62.7)	33.5 (22.3–50.4)**	35.7 (17.4–61.1)	31.3 (21.2–46.3)**
Occupational social class								
I–II (more affluent)	14.0 (4.6–20.9)*	9.5 (6.6–13.6)	41.3 (25.8–89.8)	43.6 (33.3–56.9)	63.0 (30.9–163)	66.7 (49.5–89.8)	57.3 (31.8–119)	58.1 (43.9–76.7)
III	12.6 (5.4–21.0)	9.5 (6.4–14.1)	56.8 (32.6–77.3)	49.8 (37.2–66.8)	87.5 (48.0–119)	75.6 (54.6–105)	65.6 (35.4–104)	57.4 (42.3–77.8)
IV–V (less affluent)	19.8 (6.7–30.6)	13.7 (10.2–18.3)	66.4 (37.8–107)	57.1 (45.8–71.1)	104 (46.9–163)	79.9 (62.6–102)	74.0 (44.1–110)	65.1 (51.8–81.8)
Breastfed her children								
Never	13.8 (5.5–21.8)	12.5 (9.7–16.1)	44.7 (21.3–85.4)*	45.2 (37.9–53.8)	62.9 (26.9–133)*	63.7 (52.3–77.7)	53.3 (26.9–97.2)*	52.0 (43.1–62.7)
≤6 months	18.8 (5.4–28.7)	9.1 (6.5–12.8)	63.6 (40.4–95.7)	51.7 (40.8–65.4)	93.2 (58.6–158)	78.9 (60.4–103.0)	80.6 (54.1–110)	67.5 (52.4–86.8)
>6 months	18.2 (8.6–30.0)	9.6 (6.8–13.6)	71.7 (46.3–104)	53.6 (42.3–67.9)	112 (63.6–164)	80.8 (61.8–106)	85.5 (55.7–113)	64.2 (49.8–82.7)

Results are weighted by age. [a]aGM: Geometric mean adjusted by age. *p-value<0.05 (median, Kruskal–Wallis test). **p-value<0.05 (aGM, Wald test; compared against the reference category). [b]Reference category (except where otherwise noted, the reference category is the first category mentioned above).

Improvements are necessary in their conception, methods, analysis, interpretation and, most importantly, subsequent use by governments, institutions, companies and relevant social agents. We believe our report suggests ways that may inspire others to make further progress towards such goals.

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Conflicts of interest

The authors declare they have no competing financial interests.

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Table 1 of Supplemental material. Serum concentrations of the 8 POPs detected in >80% of the population of Barcelona in 2006 (n = 231).

	LOD	LOQ	%>LOD	AM (SD)	GM (95% CI)	Median (P25-P75)	P95	Range
p,p'-DDT								
ng/g lipid				31.04 (38.72)	20.89 (18.61-23.45)	21.97 (13.04-34.92)	87.18	1.16-341.86
ng/ml	0.017	0.050	97	0.20 (0.25)	0.13 (0.12-0.15)	0.14 (0.08-0.21)	0.49	0.01-2.18
p,p'-DDE								
ng/g lipid				527.67 (848.19)	245.19 (208.99-287.67)	219.06 (97.37-625.24)	2047.16	6.89-8227.20
ng/ml	0.016	0.047	100	3.47 (5.80)	1.53 (1.29-1.80)	1.36 (0.56-4.16)	13.38	0.05-62.43
PCB 118								
ng/g lipid				16.30 (14.35)	9.82 (8.44-11.43)	13.50 (5.20-22.70)	42.29	0.82-83.40
ng/ml	0.014	0.042	83	0.11 (0.10)	0.06 (0.05-0.07)	0.09 (0.03-0.14)	0.30	0.01-0.59
PCB 138								
ng/g lipid				64.29 (51.51)	46.33 (41.09-52.24)	48.27 (29.05-87.07)	173.79	1.05-332.37
ng/ml	0.014	0.041	98	0.42 (0.36)	0.29 (0.25-0.33)	0.30 (0.17-0.58)	1.16	0.01-2.36
PCB 153								
ng/g lipid				99.73 (86.55)	67.20 (58.77-76.85)	68.63 (41.56-135.51)	281.26	1.05-549.29
ng/ml	0.014	0.041	98	0.65 (0.59)	0.42 (0.36-0.48)	0.45 (0.25-0.86)	1.95	0.01-3.76
PCB 180								
ng/g lipid				80.36 (64.00)	57.70 (50.97-65.32)	63.35 (38.57-103.95)	207.59	0.75-422.94
ng/ml	0.010	0.029	98	0.52 (0.42)	0.36 (0.32-0.41)	0.39 (0.22-0.68)	1.51	0.01-2.62
HCB								
ng/g lipid				217.64 (232.93)	112.17 (94.66-132.92)	109.00 (50.00-339.04)	716.63	1.41-1210.47
ng/ml	0.011	0.033	98	1.45 (1.62)	0.70 (0.58-0.84)	0.70 (0.29-2.32)	4.80	0.01-6.95
β-HCH								
ng/g lipid				130.05 (156.09)	63.31 (53.30-75.19)	64.21 (24.82-195.42)	473.94	1.50-898.26
ng/ml	0.020	0.060	97	0.88 (1.10)	0.39 (0.33-0.47)	0.40 (0.14-1.26)	3.59	0.01-5.88

LOD: limit of detection. LOQ: limit of quantification. AM: arithmetic mean. SD: standard deviation. GM: geometric mean.
P25, P75, P95: 25th, 75th and 95th percentile, respectively.

Table 2 of Supplemental material. Serum concentrations of the 11 POPs detected in less than 80% of the population of Barcelona.

Characteristic	o,p'-DDT	o,p'-DDE	o,p'-DDD	p,p'-DDD	PCB 28	PCB 52	PCB 101	PeCB
All participants	1.00 (0.82-7.60)	0.32 (0.28-0.37)	1.29 (0.33-6.64)	0.73 (0.60-9.60)	1.47 (1.23-1.76)	0.26 (0.22-0.33)	0.16 (0.14-0.19)	1.13 (0.99-1.34)
GM and 95th	1.97 (17.81)	0.33 (0.46)	1.52 (18.35)	1.61 (20.24)	1.88 (13.60)	0.47 (25.78)	0.19 (1.35)	1.27 (3.75)
Range	0.49, 699.33	0.18, 6.18	0.18, 52.50	0.36, 65.36	0.76, 61.17	0.13, 138.47	0.09, 4.50	0.63, 57.68
Detected (%)	29.57	0.81	54.61	29.06	15.38	18.38	6.73	6.88
Quantified (%)	27.99	0.81	47.29	28.73	8.52	16.95	5.47	1.81
Non-quantified (%)	1.58	0.0	7.32	0.33	6.86	1.43	1.26	5.07
Non-detected (%)	70.43	99.19	45.39	70.94	84.62	81.62	93.27	93.12
Gender								
Male	0.99 (0.82-6.66)	0.32 (0.28-0.37)	1.39 (0.35-7.63)	0.75 (0.59-9.19)	1.47 (1.25-1.87)	0.26 (0.22-0.34)	0.16 (0.14-0.20)	1.16 (1.01-1.41)
Female	1.0 (0.82-8.84)	0.32 (0.28-0.37)	1.23 (0.32-6.34)	0.73 (0.60-10.08)	1.47 (1.23-1.73)	0.26 (0.21-0.31)	0.16 (0.14-0.19)	1.12 (0.98-1.32)
Age – *Percent detected*								
18-29 years	16.0	0.0	48.0	20.0	4.0	12.0	4.0	0.0
30-44 years	29.9	0.0	49.4	31.0	21.8	23.0	9.2	8.0
45-59 years	30.2	0.0	60.3	30.2	12.7	12.7	4.8	7.9
60-74 years	40.0	0.0	62.5	30.0	20.0	10.0	7.5	7.5
≥75 years	31.3	6.3	56.3	31.3	18.8	37.5	6.3	6.3

Cont.

Characteristic	α-HCH	γ-HCH	δ-HCH
All participants	2.25 (1.67-7.34)	2.00 (1.72-2.48)	5.46 (1.49-10.55)
GM and 95th	3.39 (11.42)	2.46 (9.62)	4.53 (20.90)
Range	1.08, 22.15	1.07, 52.44	0.84, 30.46
Detected (%)	44.48	15.24	64.68
Quantified (%)	7.15	3.86	40.80
Non-quantified (%)	37.33	11.38	23.88
Non-detected (%)	55.52	84.76	35.32
Gender			
Male	2.51 (1.69-7.16)	2.03 (1.76-2.50)	4.92 (1.49-10.90)
Female	2.20 (1.64-7.52)	2.05 (1.71-2.44)	5.77 (1.48-10.38)
Age – *Percent detected*			
18-29 years	44.0	16.0	56.0
30-44 years	43.7	20.7	77.0
45-59 years	47.6	14.3	69.8
60-74 years	40.0	12.5	60.0
≥75 years	43.8	12.5	50.0

Results are weighted by gender and age to account for the complex sample design. Frequencies of population characteristics are detailed in Table 1 of Supplemental Material. The concentrations are expressed in median (percentile 25 - percentile 75) ng/g lipid. The second row for All participants presents the geometric mean (GM) and 95th percentile. The third row for All participants presents the minimum and maximum concentrations. *p-value for Kruskal-Wallis test <0.05.

The limits of detection and quantification (in ng/mL) were, respectively: 0.014 and 0.041 for PeCB; 0.022 and 0.065 for α-HCH; 0.016 and 0.049 for δ-HCH; 0.024 and 0.071 for γ-HCH; 0.011 and 0.032 for o,p'-DDT; 0.004 and 0.011 for o,p'-DDE; 0.004 and 0.012 for o,p'-DDD; 0.008 and 0.024 for p,p'-DDD; 0.017 and 0.051 for PCB 28; 0.003 and 0.008 for PCB 52; and 0.002 and 0.007 for PCB 101.

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Sociodemographic factors influencing participation in the Barcelona Health Survey study on serum concentrations of persistent organic pollutants

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ABSTRACT

Background: Little is known about factors affecting participation in population-based biomonitoring studies. We analyzed socioeconomic factors influencing participation in the Barcelona Health Survey (BHS) study on the distribution of serum concentrations of persistent organic pollutants (POPs).
Methods: After completing the BHS personal interview at home participants aged ⩾15 years were invited to donate blood. Conducted on a different date and location, the POPs study included additional questions, blood extraction, and a brief physical examination. Factors influencing participation were analyzed by logistic regression.
Results: Of 523 BHS participants that we contacted to participate in the study, 231 (44%) participated; they were broadly representative of the city population regarding sex, birth place, body mass index (BMI), employment status and occupational social class. Participants in the POPs study had higher educational level and family income. Controlling for confounders, participation was slightly higher among women than men (odds ratio [OR] = 1.38, $p = 0.02$), and lower among the youngest and oldest subjects ($p = 0.002$), with a strong and monotonic trend of increasing participation with increasing educational level ($p < 0.001$) (OR for university level *vs.* no studies = 4.58, 95% CI: 2.3–9.3).
Conclusions: Although participation was somewhat low, participants were similar to the city population regarding sex, BMI, birth place, employment, and occupational social class. Health surveys that integrate environmental biomarkers should invest specific resources to encourage participation of the youngest and oldest individuals, and of those with more disadvantaged socioeconomic position (particularly, citizens with lowest education).

1. Introduction

Health surveys are central components of health monitoring systems (De Bruin et al., 1996; Hupkens et al., 1999; Aromaa et al., 2003), but when they include a physical examination and blood extraction they usually have lower participation rates (Porta et al., 2008b); non-participation hampers the study representativeness and, hence, the validity of inferences to the general population. Biases will occur, for instance, when sociodemographic and economic variables as sex, age, educational level, family income or other measures of socioeconomic position are associated both with participation in the study and with the blood or tissue concentration of the biomarkers. While biomonitoring studies often report the response rate (Department of Health and Human Services, 2001; Becker et al., 2002; Link et al., 2005; Zumbado et al., 2005), little is known about factors influencing participation in such studies (Pullen et al., 1992; Sala et al., 1999; Merzenich et al., 2001; Boshuizen et al., 2006). Of course, the characteristics, causes and implications of non-response have long been analyzed in health interview surveys (HIS) and health examination surveys (HES) (De Bruin et al., 1996; Aromaa et al., 2003), but hardly ever

Abbreviations: BHS, Barcelona Health Survey; BMI, body mass index; CI, confidence interval; GerES, German Environmental Survey; HES, health examination surveys; HIS, health interview surveys; IMIM, *Institut Municipal d'Investigació Médica*; NRHEEC, National Reports of Human Exposure to Environmental Chemicals (USA); OR, odds ratio; ORa, adjusted odds ratio; POPs, persistent organic pollutants; WHO, World Health Organization.

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in the context of surveys in the general population that included blood, urine or tissue collection (Merzenich et al., 2001; Porta et al., 2008b).

The design of the most recent HIS in Barcelona included selecting survey participants with the explicit objective of analyzing the distribution of concentrations of persistent organic pollutants (POPs) in the city inhabitants. This prospective integration of POPs biomonitoring within a HIS occurred for the first time in Spain, and is surprisingly uncommon worldwide (De Bruin et al., 1996; Hupkens et al., 1999; Ueda et al., 1999; Buckland et al., 2001; Department of Health and Human Services, 2001; Becker et al., 2002; Aromaa et al., 2003; Bates et al., 2004; Harden et al., 2004; Link et al., 2005; Angerer et al., 2007; Needham et al., 2007; Porta et al., 2008b).

We therefore analyzed the recruitment process and factors influencing participation in the 2006 Barcelona Health Survey (BHS) study on the distribution of serum concentrations of POPs.

2. Methods

2.1. Recruitment process

The population of the city of Barcelona in 2006 was 1 605 602 inhabitants, with significant socioeconomic differences (Marí-Dell'Olmo et al., 2007; Rodríguez-Sanz et al., 2008). As part of its mission of evaluating the health needs of the general population, monitoring health determinants, developing policies for disease prevention and control, and contributing to the development of an environmental and social context that is sustainable for health, in 2006 the *Agència de Salut Pública de Barcelona* conducted the fifth Barcelona Health Survey (BHS). The main objective of the survey was to obtain information about subjective experiences related to health, morbidity, mental health, life styles, uses of health services and preventive practices. Detailed information on the survey is available elsewhere (Borrell and Rodríguez-Sanz, 2008; Rodríguez-Sanz et al., 2008). Briefly, a representative sample of the non-institutionalized population was selected by simple random sampling from the census; the sample comprised 3125 individuals, of whom 1644 were women. In order to obtain the sample 7933 individuals were contacted. On average, it was necessary to contact 2.5 persons to recruit one participant; this latter figure was higher for men (2.7) and for subjects between 30 and 39 years of age (3.4). The main factors that influenced non-participation were unwillingness to participate (33.5%), change of address (30.3%), and impossibility to get in touch with the potential participant (21.0%). Face to face interviews were conducted at home by trained monitors from May to November, 2006.

At the end of the BHS interview participants $\geqslant$15 years were informed and offered by the monitors to take part in a BHS study on POP levels in the city population. This study was conducted by our Unit at the *Institut Municipal d'Investigació Mèdica of Barcelona* (IMIM). Participants who consented in principle to participate were subsequently contacted by telephone; the call included a brief explanation of the aims, benefits and requirements of participation. No economic compensation in return of participation – except for travel expenses to IMIM – and no communication of individual POP results were offered. Participants were asked to fast for at least 4 h before blood extraction.

Upon arrival at IMIM, participants were offered a chance to ask further questions and then gave specific written informed consent to participate in the POPs study. There was no waiting time: the appointment was made for the time that suited each subject, and upon arrival the subject was immediately seen. A nurse interviewed each participant, measured the weight, height and the hip and waist circumference, and collected a blood sample. The interview included questions about recent and past changes in body weight, on whether the person had been breastfed, and on history of diabetes. Women were also asked about parity, breastfeeding and abortion histories. Thirty milliliters of blood were drawn by venipuncture to determine blood lipids and serum concentrations of POPs. Blood was collected in a vacuum system tube and centrifuged for 15 min $\times$ 3000 rpm at 4 °C to obtain serum. Right after centrifugation, serum was divided in 1–3 mL aliquots and stored at −80°. Written informed consent, blood sample, physical examination and questionnaire data were obtained for all the participants in the study. On average the visit took 19.3 min (median, 17).

The recruitment process and visits for the POPs study took place from July 2006 to January 2007, with a holiday break in August. Collection of information about phone calls evolved since the beginning of the study: complete information on when the phone call was placed, and on the number of calls made was registered from October 2006 to January 2007 (84.8% of total calls). Phone calls were performed at different times during the day (i.e., morning, afternoons, evenings) in order to increase the probability to contact possible participants. Information on sociodemographic factors was available for all subjects (participant and non-participant), during all months of study. A target of 230 participants was decided a priori based on scientific and budgetary factors. The scientific factors included: POP values expected on the basis of values observed in other studies (percentage of detection of each compound, mean concentration, variance), the desired precision of estimates (e.g., ±3% and ±4% were used), and the level of statistical confidence (90% and 95%). For common percentages of detection, the required number of subjects was 216 if the desired precision and confidence were 4% and 95%, and 271 if they were 3% and 90%, respectively.

For the remainder of this paper, the term "BHS participants" refers to all individuals who completed the BHS interview; those who at the end of the BHS interview agreed in principle to take part in the POPs study are referred to as "consenters", and subjects who declined, as "non-consenters". Finally, consenters are divided into subjects who underwent the physical examination and blood extraction (hereinafter, "study participants") and subjects who did not ("consenters who did not participate"). As we shall see in detail below, the term "non-participants" includes the latter and non-consenters.

To analyze the representativeness of study participants we compared them with a representative sample of the city population (n = 5399), which included all BHS participants aged $\geqslant$15 years (51%) and additional inhabitants of Barcelona aged $\geqslant$15 years interviewed for the 2006 Health Survey of Catalonia (49%). The two groups are similar because they were selected and interviewed using identical procedures; the final representative sample was obtained by weightening according to age, gender and city district (Rodríguez-Sanz et al., 2008; Borrell and Rodríguez-Sanz, 2008).

2.2. Socioeconomic variables affecting participation

For the purpose of this study, we analyzed the influence upon participation of the following socioeconomic variables collected in the BHS questionnaire: sex, age, place of birth, educational level, employment/occupational status, occupational social class, income, and body mass index (BMI) (self-reported weight [kg] divided by self-reported height squared [m^2]); individuals were grouped into four BMI categories as recommended by WHO (World Health Organization, 2008). The lower educational category of subjects without formal studies included the illiterate. To assign occupational social class we used the Spanish classification, which is based on Goldthorpe's scheme; class was hence assigned through

the current or last occupation of the interviewed or, if she/he had not worked, through the current or last occupation of the head of the household (Domingo-Salvany et al., 2000; Rodríguez-Sanz et al., 2008). The classification includes 5 well-established main social groups: I, Managers of companies with ⩾10 employees, senior technical staff, free professionals; II, Managers of companies with <10 employees, intermediate occupations; III, Administrative personnel and financial management supporting professionals, self employed professionals, supervisors of manual workers, other skilled non-manual workers; IV, Skilled and partly skilled manual workers; and V, Unskilled manual workers. The income variable refers to the family gross annual income according to the number of people living in the household (Rodríguez-Sanz et al., 2008).

2.3. Statistical analyses

Univariate statistics were computed as customary (Kleinbaum et al., 1998; Armitage et al., 2002). In contingency tables, Fisher's exact test for independence or homogeneity was applied to assess the relationship between two categorical variables; when this test could not be applied Pearson's Chi-square test was used. For comparisons between continuous variables, Student's *t*-test and Mann–Withney's *U* test were used (Kleinbaum et al., 1998). To analyze the socioeconomic factors influencing participation, multivariate-adjusted odds ratios (OR) and their corresponding 95% confidence intervals (CI) were calculated by unconditional logistic regression (Rothman et al., 2008). Age, sex and educational level were included in models as potential confounding factors. When a linear trend was apparent for a categorical ordinal variable it was assessed through the multivariate analogue of Mantel's extension test for linear trend. When such trend was not clearly apparent, Wald's test was used to assess statistical significance. The level of statistical significance was set at 0.05, and all tests are two-tailed. Statistical analyses were conducted using SPSS, version 12.0 (SPSS Inc., Chicago, IL).

3. Results

From the 2755 participants in the Barcelona's Health Survey who were ⩾15 years old, 634 (23%) initially declared interest in participating in the POPs study. Of them, we attempted to contact 595 subjects, and were able to do so for 523, of whom 323 made an appointment to attend the POPs study visit for the interview, physical exam and blood draw (Fig. 1). The visit was actually attended by 231 subjects, which yields a response rate of 44% of the 523 individuals contacted, and of 39% of the 595. In spite of the initial interest, eventually unwillingness to participate was the most common reason why people failed to attend the visit.

The specific flow of individuals who made an appointment for the study visit is illustrated in Fig. 1S in Supplementary material. Of the 323 individuals, 199 (62%) attended the visit. Of the

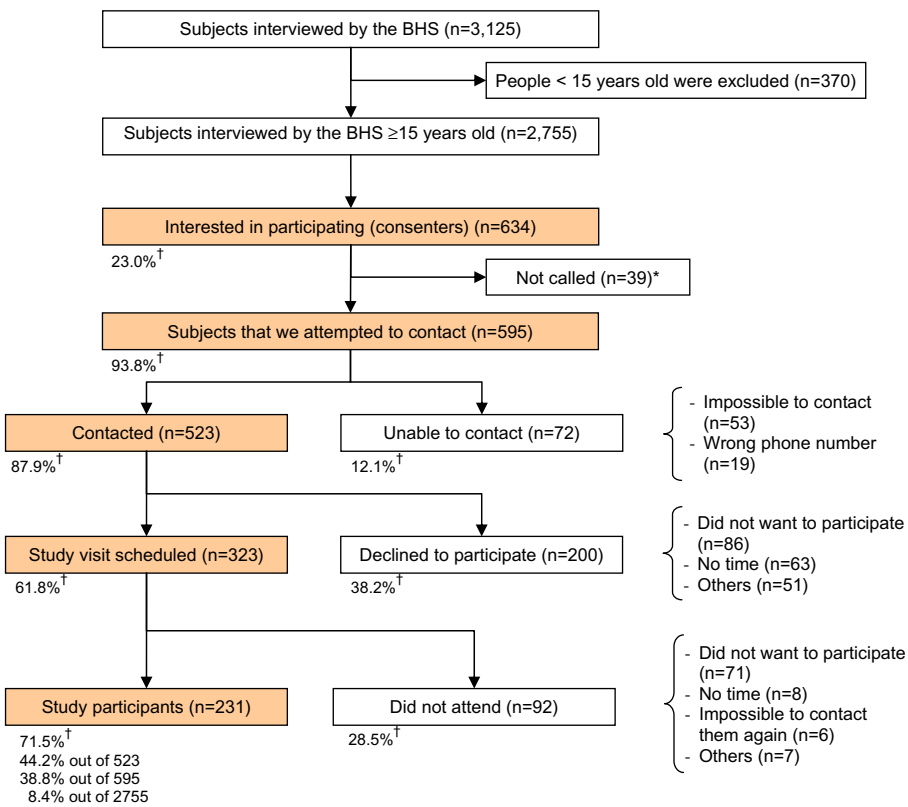

Fig. 1. Flow of participants through the recruitment process. †Percentage calculated with respect to the box immediately above (e.g., 23.0% = 634/2755 × 100). *These calls were not necessary because the target of 230 participants had been achieved. *Note:* Table 3 shows factors affecting participation in the POPs study by comparing participants in it (n = 231) and the other participants in the BHS (n = 2524 = 2755–231).

remaining 124, a new appointment could be scheduled for 50 individuals, of whom 27 (54%) showed up. Rescheduling was repeated up to four times, which yielded 5 additional participants.

The number of phone calls made to the 595 subjects to recruit the 231 participants was 2885 (includes non-answered calls). Thus, an average of 4.8 calls per subject was necessary to enroll a participant in the study (median: 3 calls). Only 5% of participants attended the visit after just one phone call; 3 calls were sufficient to recruit half of the 231 participants, and 5 calls to recruit 81% of them; the remaining 19% participants needed $\geqslant 6$ calls (Fig. 2). The maximum number of calls made to individuals that we attempted to contact was 17; to participants, the maximum number of calls made was 15.

Socioeconomic characteristics of the individuals who donated blood for the analysis of POPs (study participants) and from the representative sample of the population of the city of Barcelona are compared in Table 1. No statistically significant differences were found regarding sex and mean age, although among study participants there were more women and fewer individuals from the youngest and oldest age groups. No major differences were found either regarding autoreferred BMI, place of birth, and employment status. The distribution of social class was slightly more favorable among study participants, who also had a higher educational level ($p = 0.003$) and income ($p = 0.029$) (Table 1).

Characteristics of non-consenters, consenters who did not participate and participants are summarized in Table 2. There were no significant differences among the three groups in employment status, occupational social class and income. The percentage of women was higher in participants than in non-consenters ($p = 0.044$). More consenters who did not participate were born in Central and South America than non-consenters ($p = 0.005$). Non-consenters and consenters who did not participate had a lower educational level than participants (both $p < 0.005$).

Finally, we analyzed factors affecting participation in the POPs study by comparing participants in it ($n = 231$) and the other participants in the BHS ($n = 2{,}524$) (Table 3). Age and educational level were associated with a higher participation; thus, individuals with university education were 3.76 times more likely to participate than individuals without formal studies. Age remained significant when adjusted by sex and education, and so did education when adjusted by age and sex (ORa for university level = 4.58). Crude and adjusted ORs show a strong and monotonic trend of increasing participation with increasing educational level ($p < 0.001$). Adjusting for age and education showed that overall women were 38% more likely to participate than men (Table 3, last columns); the higher participation of women was evident in all educational subgroups, and the difference with men was particularly strong in the group without formal studies, among whom the age-adjusted OR of women *vs.* men was 12.25 (95% CI: 1.29–116.68, $p = 0.029$). Although unadjusted models showed higher participation with increasing social class and with increasing income (p for trend = 0.007 and 0.015, respectively), when controlling for sex, age and educational level, class and income were no longer statistically significant. As compared to participation by inhabitants of the city district where IMIM (the POPs study centre) is located, participation was significantly higher only by inhabitants of one of the other 9 districts (ORa = 1.81, 95% CI: 1.02–3.21); i.e., participation was similar in 9 of the 10 districts.

When participation was analyzed by gender, the influence of age and education was similar as among the two sexes combined; e.g., as compared to women in the two lowest categories of education (now combined as one reference category in Table 4), the ORa for women of university level was 2.49, while the corresponding OR for men was 2.68 (Table 4). There was little or no effect of BMI and place of birth. If unadjusted by age and education, employment, class and income did influence participation among women: students and the unemployed were half as likely to participate than employed women; women of social classes I and II were twice as likely to participate than women of class V (p for trend = 0.012); and women in the two upper income categories were 46–74% more likely to participate than women with lowest income (p for trend = 0.045) (data not shown). While unemployed men were more likely to participate than those employed (ORa = 3.51), a null or weakly inverse association was observed in women (OR = 0.49) (p for interaction = 0.002) (Table 4). Among men, both employment status and income were significant when included in the same model along with age ($p = 0.004$ and p for trend = 0.030, respectively).

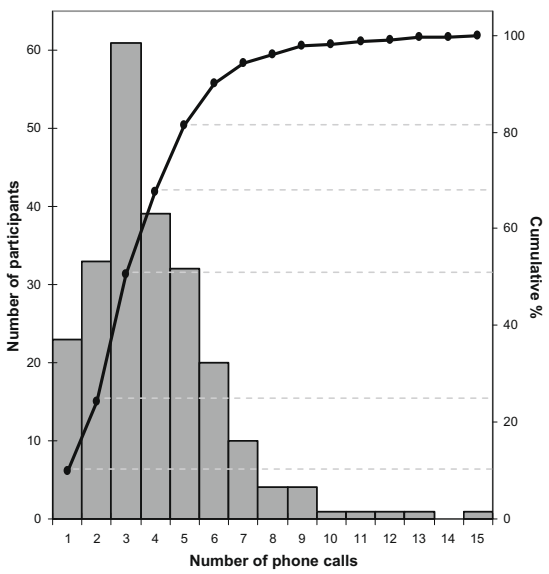

Fig. 2. Number of phone calls needed to achieve a visit among the 231 participants in the POPs study.

4. Discussion

Minimizing non-response in surveys is essential to make valid inferences to the target population. Common response rates for HIS range between 52% and 95%, whilst in HES they tend to be between 25% and 85% (Aromaa et al., 2003). The response rate achieved in the BHS POPs study among individuals with whom contact was attempted was 38.8% (231 of 595 individuals attempted to contact); the response among the 523 individuals actually contacted was 44.2%. There are several ways to report a study response rate (Sandler, 2002), especially when the recruitment process takes place within a relatively complex survey (Table 5) (Department of Health and Human Services, 2001, 2008a,b; Becker et al., 2002; Koppen et al., 2002; Bates et al., 2004; Link et al., 2005; Masuda et al., 2005; Zumbado et al., 2005; Schulz et al., 2007). Some authors prefer to detail the recruitment process instead of reporting a specific percentage (Glynn et al., 2000; Koppen et al., 2002; Bates et al., 2004). In the German Environmental Survey (GerES) of 1998, for instance, the response rate was 55% (4822 out of a subsample of 8,845 subjects interviewed in the National Health Survey who where asked to participate in the examinations of GerES III) (Becker et al., 2002). A 45% response was achieved in the biochemical part of

Table 1
Socioeconomic characteristics of individuals who donated blood for the analysis of POPs compared to a representative sample of the population of the city of Barcelona (all ⩾15 years old).

	Barcelona representative sample *N* (%)	Study participants *N* (%)	*p*-Value[a]
Total	5399	231	
Sex			
Men	2533 (46.9)	94 (40.7)	0.069
Women	2866 (53.1)	137 (59.3)	
Age (years)			
Mean ± SD	47.4 ± 19.4	47.7 ± 16.2	0.833[b]
Median	45.0	45.0	0.360[c]
15–24	625 (11.6)	12 (5.2)	<0.001[d]
25–34	1060 (19.6)	41 (17.8)	0.229[e]
35–44	1011 (18.7)	61 (26.4)	
45–54	791 (14.7)	43 (18.6)	
55–64	700 (13.0)	31 (13.4)	
65–74	594 (11.0)	27 (11.7)	
>74	618 (11.4)	16 (6.9)	
Body mass index (autoreferred)			
Mean ± SD	24.97 ± 4.24	25.30 ± 4.40	0.246[b]
Median	24.57	24.46	0.270[c]
Underweight (<18.5)	166 (3.1)	8 (3.5)	0.906
Normal (18.5–24.9)	2763 (51.6)	121 (52.8)	
Overweight (25.0–29.9)	1835 (34.3)	74 (32.3)	
Obese (⩾30.0)	592 (11.0)	26 (11.4)	
Place of birth			
Catalonia	3340 (62.3)	155 (67.1)	0.385
Rest of Spain	1158 (21.6)	48 (20.8)	
Central and South America	534 (10.0)	19 (8.2)	
Other	325 (6.1)	9 (3.9)	
Educational level			
Without formal studies	579 (10.7)	10 (4.3)	0.003
Elementary not completed	830 (15.4)	31 (13.4)	
Elementary completed	1166 (21.6)	45 (19.5)	
Secondary	1363 (25.3)	63 (27.3)	
University	1430 (26.5)	81 (35.1)	
Other	26 (0.5)	1 (0.4)	
Employment status			
Employed	3098 (57.5)	141 (61.0)	0.304
Housewife	571 (10.6)	20 (8.7)	
Unemployed	262 (4.9)	15 (6.5)	
Retired	897 (16.6)	40 (17.3)	
Student	343 (6.4)	8 (3.5)	
Other	215 (4.0)	7 (3.0)	
Occupational social class			
V	632 (12.0)	21 (9.2)	0.077
IV	1921 (36.6)	71 (31.3)	
III	1304 (24.8)	56 (24.7)	
II	579 (11.0)	34 (15.0)	
I	822 (15.6)	45 (19.8)	
Income[f]			
<6000 €/person	1309 (24.2)	53 (22.9)	0.029[g]
6000–11 999 €/person	1128 (20.9)	52 (22.5)	
12 000–18 000 €/person	911 (16.9)	54 (23.4)	
>18 000 €/person	485 (9.0)	36 (15.6)	
Not recorded	1566 (29.0)	36 (15.6)	

[a] Unless otherwise specified, *p*-value derived from Fisher's exact test (two-tail).
[b] Student's *t*-test (two-tail).
[c] Mann–Whitney's *U* test (two-tail).
[d] Pearson's chi-square test (two-tail).
[e] Chi-square test (two-tail), youngest and oldest age groups not considered.
[f] Family gross annual income according to number of people living in the household.
[g] Excluding "not recorded".

the Canary Islands Nutrition Survey (783 individuals out of 1747 participants in the entire survey) (Zumbado et al., 2005; Luzardo et al., 2006). In the US National Reports of Human Exposure to Environmental Chemicals (NRHEEC), the response rate ranged between 71% and 80% (e.g., in the NRHEEC I there were 3812 participants from 5325 individuals selected to participate in the National Health and Nutrition Examination Survey) (Department of Health and Human Services, 2001, 2008a,b). In studies that do not report response rates the design complexity makes it difficult to estimate participation; e.g., in the Flanders Environmental and Health Study of women 50–65 years old, we estimated a 78% response, although this figure corresponds to 200 out of 255 women selected from those who accepted to participate when they were contacted (Koppen et al., 2002).

Table 2
Comparison of socioeconomic characteristics of the individuals interviewed on the BHS according to their interest in participating in the analysis of POPs.

	Non-consenters	Consenters		*p*-Value[a,e]	*p*-Value[a,f]	*p*-Value[a,g]
	N (%)	Did not participate *N* (%)	Participants *N* (%)			
Total	2121	403	231			
Sex						
Men	1014 (47.8)	176 (43.7)	94 (40.7)	0.142	0.044	0.505
Women	1107 (52.2)	227 (56.3)	137 (59.3)			
Age (years)						
Mean ± SD	48.9 ± 20.0	46.57 ± 19.8	47.67 ± 16.2	0.029[c]	0.272[c]	0.447[c]
Median	47.0	44.0	45.0	0.029[d]	0.642[d]	0.211[d]
15–24	236 (11.1)	60 (14.9)	12 (5.2)	0.280[b]	<0.001[b]	<0.001[b]
25–34	393 (18.5)	77 (19.1)	41 (17.8)			
35–44	357 (16.8)	66 (16.4)	61 (26.4)			
45–54	305 (14.4)	63 (15.6)	43 (18.6)			
55–64	286 (13.5)	52 (12.9)	31 (13.4)			
65–74	244 (11.5)	38 (9.4)	27 (11.7)			
>74	300 (14.2)	47 (11.7)	16 (6.9)			
Body mass index (autoreferred)						
Mean ± SD	24.93 ± 4.04	25.16 ± 4.39	25.31 ± 4.40	0.310[c]	0.191[c]	0.692[c]
Median	24.66	24.61	24.46	0.961[d]	0.449[d]	0.514[d]
Underweight (<18.50)	64 (3.1)	8 (2.0)	8 (3.5)	0.051	0.623	0.544
Normal (18.5–24.9)	1066 (51.0)	204 (51.2)	121 (52.8)			
Overweight (25.0–29.9)	754 (36.1)	130 (32.7)	74 (32.3)			
Obese ($\geqslant$30.0)	205 (9.8)	56 (14.1)	26 (11.4)			
Place of birth						
Catalonia	1361 (64.6)	243 (60.6)	155 (67.1)	0.005	0.365	0.398
Rest of Spain	469 (22.2)	97 (24.2)	48 (20.8)			
Central and South America	143 (6.8)	45 (11.2)	19 (8.2)			
Other	135 (6.4)	16 (4.0)	9 (3.9)			
Educational level						
Without formal studies	261 (12.3)	43 (10.7)	10 (4.3)	0.483	<0.001	0.004
Elementary not completed	365 (17.3)	66 (16.4)	31 (13.4)			
Elementary completed	420 (19.8)	95 (23.6)	45 (19.5)			
Secondary	497 (23.5)	96 (23.8)	63 (27.3)			
University	557 (26.3)	98 (24.3)	81 (35.1)			
Other	18 (0.8)	5 (1.2)	1 (0.4)			
Employment status						
Employed	1160 (54.7)	244 (60.5)	141 (61.0)	0.324	0.153	0.446
Housewife	220 (10.4)	36 (8.9)	20 (8.7)			
Unemployed	93 (4.4)	16 (4.0)	15 (6.5)			
Retired	427 (20.1)	68 (16.9)	40 (17.3)			
Student	132 (6.2)	27 (6.7)	8 (3.5)			
Other	88 (4.2)	12 (3.0)	7 (3.0)			
Occupational social class						
V	238 (11.5)	57 (14.3)	21 (9.2)	0.223	0.070	0.073
IV	773 (37.4)	151 (37.9)	71 (31.3)			
III	507 (24.6)	81 (20.3)	56 (24.7)			
II	214 (10.4)	48 (12.0)	34 (15.0)			
I	332 (16.1)	62 (15.5)	45 (19.8)			
Income[h]						
<6000 €/person	512 (24.1)	120 (29.8)	53 (22.9)	0.290[i]	0.095[i]	0.065[i]
6000–11 999 €/person	522 (24.6)	96 (23.8)	52 (22.5)			
12 000–18 000 €/person	398 (18.8)	71 (17.6)	54 (23.4)			
>18 000 €/person	220 (10.4)	45 (11.2)	36 (15.6)			
Not recorded	469 (22.1)	71 (17.6)	36 (15.6)			

[a] Unless otherwise specified, *p*-value derived from Fisher's exact test (two-tail).
[b] Pearson's chi-square test (two-tail).
[c] Student's *t*-test (two-tail).
[d] Mann–Whitney's *U* test (two-tail).
[e] Non consenters vs. consenters who did not participate.
[f] Non consenters vs. participants.
[g] Consenters who did not participate vs. participants.
[h] Family gross annual income according to number of people living in the household.
[i] Excluding "not recorded".

Despite the fact that the participation achieved in the present study is not high, participants were similar to the population of Barcelona regarding sex, BMI, birth place, employment status, and occupational social class; their mean age was also similar to that of the city population, but there were less participants from the youngest and oldest age groups, and participants had a higher educational level and family income.

Variables positively influencing participation in the present study were female sex, age 35–74, and higher educational level; in the simpler analyses and in some multivariate analyses, social

Table 3
Factors affecting participation in the POPs study of the 2006 Barcelona Health Survey.[a]

	Participation			Unadjusted OR			Adjusted OR[b]		
	No *N* (%)	Yes *N* (%)	*p*-Value[c]	OR	(95% CI)	*p*-Value[e]	OR[b]	(95% CI)	*p*-Value[e]
Total	2524 (91.6)	231 (8.4)							
Sex									
Men	1190 (92.7)	94 (7.3)	0.063	1		0.06	1		0.023
Women	1334 (90.7)	137 (9.3)		1.3	(0.99–1.71)		1.38	(1.04–1.81)	
Age (years)									
15–24	296 (96.1)	12 (3.9)	<0.001[d]	1		<0.001	1		0.002
25–34	470 (92.0)	41 (8.0)		2.15	(1.11–4.16)		1.98	(1.01–3.87)	
35–44	423 (87.4)	61 (12.6)		3.56	(1.88–6.72)		3.35	(1.76–6.40)	
45–54	368 (89.5)	43 (10.5)		2.88	(1.49–5.57)		2.82	(1.46–5.49)	
55–64	338 (91.6)	31 (8.4)		2.26	(1.14–4.49)		2.47	(1.24–4.94)	
65–74	282 (91.3)	27 (8.7)		2.36	(1.74–4.75)		3.01	(1.46–6.19)	
⩾74	347 (95.6)	16 (4.4)		1.14	(0.53–2.44)		1.6	(0.72–3.54)	
Body Mass Index (autoreferred)									
Underweight or normal (<24.9)	1342 (91.2)	129 (8.8)	0.602	1		0.612	1		0.598
Overweight (25.0–29.9)	884 (92.3)	74 (7.7)		0.87	(0.65–1.17)	0.746[f]	1.01	(0.73–1.39)	0.439[f]
Obese (⩾30.0)	261 (90.9)	26 (9.1)		1.04	(0.67–1.61)		1.26	(0.80–1.99)	
Place of birth									
Catalonia	1604 (91.2)	155 (8.8)	0.508	1		0.497	1		0.771
Rest of Spain	566 (92.2)	48 (7.8)		0.88	(0.63–1.23)		1.06	(0.73–1.52)	
Central and South America	188 (90.8)	19 (9.2)		1.05	(0.63–1.72)		1.03	(0.62–1.71)	
Other	151 (94.4)	9 (5.6)		0.62	(0.31–1.23)		0.71	(0.35–1.42)	
Educational level									
Without formal studies	304 (96.8)	10 (3.2)	0.001	1		<0.001[g]	1		<0.001[g]
Elementary not completed	431 (93.3)	31 (6.7)		2.19	(1.06–4.53)	0.001	2.36	(1.14–4.91)	0.001
Elementary completed	515 (92.0)	45 (8.0)		2.66	(1.32–5.35)		3.16	(1.53–6.52)	
Secondary	593 (90.4)	63 (9.6)		3.23	(1.63–6.38)		3.98	(1.94–8.14)	
University	655 (89.0)	81 (11.0)		3.76	(1.92–7.35)		4.58	(2.27–9.27)	
Other	23 (95.8)	1 (4.2)		1.32	(0.16–10.78)		1.5	(0.18–12.27)	
Employment status									
Employed	1404 (90.9)	141 (9.1)	0.188	1		0.187	1		0.581
Housewife	256 (92.8)	20 (7.2)		0.78	(0.48–1.27)		0.91	(0.51–1.62)	
Unemployed	109 (87.9)	15 (12.1)		1.37	(0.78–2.42)		1.39	(0.78–2.46)	
Retired	495 (92.5)	40 (7.5)		0.81	(0.56–1.16)		1.04	(0.61–1.78)	
Student	159 (95.2)	8 (4.8)		0.5	(0.24–1.04)		0.57	(0.26–1.24)	
Other	100 (93.5)	7 (6.5)		0.7	(0.32–1.53)		0.97	(0.42–2.25)	
Occupational social class									
V	295 (93.4)	21 (6.6)	0.063	1		0.065	1		0.741
IV	924 (92.9)	71 (7.1)		1.08	(0.65–1.79)	0.007[f]	1.01	(0.60–1.68)	0.341[f]
III	588 (91.3)	56 (8.7)		1.34	(0.79–2.25)		1.01	(0.59–1.76)	
II	262 (88.5)	34 (11.5)		1.82	(1.03–3.22)		1.36	(0.73–2.53)	
I	394 (89.7)	45 (10.3)		1.6	(0.94–2.75)		1.2	(0.65–2.23)	
Income[h]									
<6000 €/person	632 (92.3)	53 (7.7)	0.022	1		0.015[g]	1		0.362[g]
6000–11 999 €/person	618 (92.2)	52 (7.8)		1	(0.67–1.49)	0.022	0.92	(0.61–1.37)	0.139
12 000–18 000 €/person	469 (89.7)	54 (10.3)		1.37	(0.92–2.04)		1.14	(0.76–1.73)	
>18 000 €/person	265 (88.0)	36 (12.0)		1.62	(1.04–2.53)		1.25	(0.77–2.03)	
Not recorded	540 (93.8)	36 (6.2)		0.79	(0.51–1.23)		0.69	(0.44–1.08)	

OR: odds ratio (OR = 1.00 denotes the reference category).
[a] Factors affecting participation in the POPs study are analyzed by comparing participants in it (n = 231) and the other participants in the BHS (n = 2524 = 2755 – 231, see Fig. 1).
[b] Odds ratio adjusted by sex, age and educational level.
[c] Fisher's exact test (two-tail).
[d] Pearson's chi-square test (two-tail).
[e] *p*-Value derived from Wald's test.
[f] *p*-Trend.
[g] *p*-Trend without "other" or "not recorded".
[h] Family gross annual income according to number of people living in the household.

class and income, two other measures of socioeconomic position, were influential as well. Importantly, these sociodemographic factors have been found associated with human concentrations of POPs (Davies et al., 1972; Department of Health and Human Services, 2001; Borrell et al., 2004; Porta et al., 2008a; Umweltbundesamt, 2008). The higher participation of women was observed in all educational subgroups, and the difference with men was particularly strong among those with no formal studies. Some analyses of participation in studies that included blood extraction found women to participate more than men (Department of Health and Human Services, 2008a), while others found the opposite (Merzenich et al., 2001; Boshuizen et al., 2006). In some studies (Pullen et al., 1992; Boshuizen et al., 2006) – but not all (Sala et al., 1999; Merzenich et al., 2001; Aragonés et al., 2008) – participants were more likely to be from the more affluent social classes or more educated. In our study occupational social class was not related to participation as strongly as education. The latter may have enabled individuals

Table 4
Main results of multivariate analyses, by gender.

	Women			Men		
	OR	(95% CI)	*p*-Value[a]	OR	(95% CI)	*p*-Value[a]
Educational level						
Without formal studies or elementary not completed	1		0.001[c]	1		0.008[c]
Elementary completed	1.5	(0.82–2.73)	0.017	2.24	(1.06–4.76)	0.082
Secondary	2.36	(1.31–4.23)		2.07	(1.01–4.22)	
University	2.49	(1.41–4.39)		2.68	(1.36–5.27)	
Other	–			2.63	(0.31–22.33)	
Employment status						
Employed	1		0.638	1		0.012
Housewife	0.96	(0.51–1.79)		n.a.	n.a.	
Unemployed	0.49	(0.17–1.40)		3.51	(1.70–7.24)	
Retired	1.25	(0.60–2.57)		0.92	(0.40–2.10)	
Student	0.59	(0.22–1.60)		0.54	(0.15–1.88)	
Other	1.29	(0.49–3.42)		0.44	(0.06–3.31)	
Occupational social class						
V	1		0.58	1		0.696
IV	1.37	(0.70–2.67)	0.265[b]	0.6	(0.27–1.32)	0.803[b]
III	1.38	(0.67–2.82)		0.61	(0.25–1.44)	
II	2.02	(0.88–4.68)		0.75	(0.29–1.93)	
I	1.58	(0.68–3.69)		0.77	(0.31–1.91)	
Income[d]						
<6000 €/person	1		0.396[c]	1		0.710[c]
6000–11 999 €/person	0.93	(0.55–1.56)	0.695	0.86	(0.45–1.64)	0.184
12 000–18 000 €/person	1.18	(0.68–2.04)		1.04	(0.55–1.96)	
>18 000 €/person	1.28	(0.65–2.53)		1.14	(0.56–2.33)	
Not recorded	0.85	(0.50–1.46)		0.41	(0.18–0.96)	

OR: odds ratio adjusted by age and educational level (OR = 1.00 denotes the reference category).
n.a.: not applicable.
[a] *p*-Value derived from Wald's test.
[b] *p*-Trend.
[c] *p*-Trend without "other" or "not recorded".
[d] Family gross annual income according to number of people living in the household.

to understand better what POPs are and the relevance of the POPs study when BHS interviewers informed BHS participants and asked whether they would donate blood. The finding does not rule out that social class might be related to concentrations of POPs among participants (Porta et al., 2008a). Participation was similar in 9 of the 10 city districts; the only district with a significantly higher participation is not particularly near or far away from the POPs study centre.

Additional factors that may have favored non-participation in our study include: apprehension to blood draw, the request to be fasting, lack of time, difficulties to travel to the POPs study centre and the nature of the institution (IMIM is a research centre, not a hospital), and our decisions to not communicate individual POP results to participants and to not provide payment other than for travel (Pullen et al., 1992; Becker et al., 2002; Boshuizen et al., 2006; Schulz et al., 2007; Reis et al., 2008). Due to budgetary constraints, it was not feasible to apply a structured questionnaire (e.g., to the 2121 non-consenters and to the 403 consenters who did not participate) to elicit why they were not participating; this is another limitation of the study.

Table 5
Response rates in studies on POP levels in the general population.

Country (region)	Reference	Year of study conduct	Study population	Age of study population (range, years)	Response rate (%)
West Germany (GerES I)	Schulz et al. (2007)	1985–1986	General population	25–69	73
West Germany (GerES IIa)	Schulz et al. (2007)	1990–1991	General population	25–69	63
East Germany (GerES IIb)	Schulz et al. (2007)	1991–1992	General population	18–79	69
Germany (Baden-Wuerttemberg)	Link et al. (2005)	1993–2003	Children from general population	10	68–89
New Zealand	Bates et al. (2004)	1996–1997	General population	>15	62[a]
Germany (GerES III)	Becker et al. (2002)	1997–1999	General population	18–69	55
Spain (Canary Islands)	Zumbado et al. (2005)	1997–1998	General population	6–75	45
Belgium (Flanders)	Koppen et al. (2002)	1999	Women from general population	50–65	78[a]
Japan	Masuda et al. (2005)	1999	General population	20–60	58
USA	CDC (2001)	1999	General population	>1	71
USA	CDC (1999–00)	1999–2000	General population	>1	76
USA	CDC (2001–02)	2001–2002	General population	>1	80
Germany (GerES IV)	Schulz et al. (2007)	2003–2006	Children from general population	3–14	77

GerES, German Environmental Survey; CDC, Centers for Disease Control and Prevention.
[a] Response rate calculated from the recruitment process reported by the authors.

Health interview surveys (HIS) and combinations of health interview and health examination surveys (HIS/HES) are central components of health surveillance systems (De Bruin et al., 1996; Aromaa et al., 2003). They are also an important framework for biomonitoring studies because of their representativeness (i.e., they enable to extrapolate results to the target population), their collection of information on self-perceived health status and health determinants (which can be linked to data on POPs and other environmental factors) (Lee et al., 2007), and their potential to inform health policies (De Bruin et al., 1996; Hupkens et al., 1999; Aromaa et al., 2003; Porta et al., 2008b; Rodríguez-Sanz et al., 2008). However, traditionally HES have rarely included biomarkers of environmental agents from inception (De Bruin et al., 1996; Aromaa et al., 2003). The relevance of studies on POPs embedded in HES is also supported by the Stockholm convention on POPs, whose Article 11 refers to the responsibility that countries signatories of the treaty have to conduct research and monitoring on the presence, levels and trends of POPs in humans, and on POP effects on human health (Porta and Zumeta, 2002).

Thus, the prospective integration of POPs biomonitoring within the most recent HIS in Barcelona is innovative and relevant. Results may also help plan other surveys with biomarkers; for instance, in the present study, more than five telephone calls did not significantly improve response, an issue that few other biomarker studies have reported (Becker et al., 2002; Angerer et al., 2007; Needham et al., 2007). Naturally, different results may be observed in other sociocultural settings and research designs.

Health surveys that integrate biomarkers should invest specific resources to encourage participation of youngest and oldest individuals, and of those with more disadvantaged socioeconomic position (particularly, citizens with lowest education). Since this paper is one of few comprehensively reporting participation rates and factors affecting participation in a population-based biomonitoring public health survey, further studies are needed to refute or replicate the findings.

Conflict of interest

None declared.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.chemosphere.2009.03.030.

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Article A4

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Relative effects of educational level and occupational social class on body concentrations of persistent organic pollutants in a representative sample of the general population of Catalonia, Spain

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ABSTRACT

Scant evidence is available worldwide on the relative influence of occupational social class and educational level on body concentrations of persistent organic pollutants (POPs) in the general population. The objective was to analyse such influence in a representative sample of the general population of Catalonia, Spain. Participants in the Catalan Health Interview Survey aged 18–74 were interviewed face-to-face, gave blood, and underwent a physical exam. The role of age, body mass index (BMI), and parity was analysed with General Linear Models, and adjusted geometric means (GMs) were obtained. Crude (unadjusted) concentrations were higher in women and men with lower education, and in women, but not men, in the less affluent social class. After adjusting for age, in women there were no associations between POP levels and social class or education. After adjusting for age and BMI, men in the less affluent class had higher *p,p′*-DDE concentrations than men in class I (p-value = 0.016), while men in class IV had lower HCB than men in the upper class (p-value < 0.03). Also in contrast with some expectations, positive associations between education and POP levels were observed after adjusting for age and BMI in men; e.g., men with university studies had higher HCB concentrations than men with first stage of primary schooling (adjusted GM 153.9 and 80.5 ng/g, respectively) (p-value < 0.001). When education and social class were co-adjusted for, some positive associations with education in men remained statistically significant, whereas class remained associated only with *p,p′*-DDE. Educational level influenced blood concentrations of POPs more than occupational social class, especially in men. In women, POP concentrations were mainly explained by age/birth cohort, parity and BMI. In men, while concentrations were also mainly explained by age/birth cohort and BMI, both social class and education showed positive associations. Important characteristics of socioeconomic groups as age and BMI may largely explain crude differences among such groups in internal contamination by POPs. The absence of clear patterns of relationships between blood concentrations of POPs and indicators of socioeconomic position may fundamentally be due to the widespread, lifelong, and generally invisible contamination of human food webs. Decreasing historical trends would also partly explain crude socioeconomic differences apparently due to birth cohort effects.

1. Introduction

POPs are highly lipophilic and degradation-resistant synthetic chemicals, which essentially originate from the production and use of organochlorine and other synthetic compounds. They bioaccumulate in the environment, food webs and living organisms, and contribute to cause severe health effects, even at concentrations traditionally deemed low (Alonso-Magdalena et al., 2011; Bergman et al., 2013; Department of Health and Human Services, 2009; Engel and Wolff, 2013; Henkler and Luch, 2011; NRC, National Research Council and Committee on Human Biomonitoring for Environmental Toxicants, 2006; Porta, 2012; Porta et al., 2008b, 2012b; Schug et al., 2013; Stein, 2012; Thayer and Kuzawa, 2011; Thornton et al., 2002; Vandenberg et al., 2012;

Abbreviations: DDT, dichlorodiphenyltrichloroethane; DDE, dichlorodiphenyldichloroethene; PCBs, polychlorinated biphenyls; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; PeCB, pentachlorobenzene; POPs, persistent organic pollutants; BMI, body mass index; GM, geometric mean; CI, confidence interval; WFE, without formal education; Primary (I), primary schooling (1st stage); Primary (II), primary schooling (2nd stage); CHIS, Catalan Health Interview Survey; IMIM, Hospital del Mar Research Institute.

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WHO, World Health Organization, 2003; Woodruff et al., 2010; Wu et al., 2012; Yang et al., 2012). Exposed to such agents throughout life, mostly from the ingestion of fatty parts of animal foods, virtually all humans store POP mixtures in fat tissues. Although some POPs were prohibited decades ago – and their concentrations thus decreased – human exposure, contamination and clinical effects remain relevant (Bergman et al., 2013; Department of Health and Human Services, 2009; Institute of Medicine, 2003; NRC, National Research Council and Committee on Human Biomonitoring for Environmental Toxicants, 2006; Porta et al., 2008b, 2012b; Quinn and Wania, 2012; Quinn et al., 2011). Body concentrations of POPs are known to often be associated with age, body mass index (BMI), and, in women, also with parity (Agudo et al., 2009; Porta et al., 2008b, 2010, 2012b; Quinn and Wania, 2012; Quinn et al., 2011; Wolff et al., 2005). Some relationships have also been observed between POP concentrations and socioeconomic variables (Chao et al., 2010; Freire et al., 2011; Morrens et al., 2012; Porta et al., 2008a, 2012a; Vrijheid et al., 2012).

Although some mixed evidence exists, reasons for differences in internal body concentrations of persistent organic pollutants (POPs) across socioeconomic groups are largely unknown worldwide. In spite of the involvement in health disorders of both environmental pollutants and social factors, there are wide gaps in knowledge of the influence of socioeconomic position on human contamination by POPs and other pollutants (Bergman et al., 2013; Borrell et al., 2004a; Davey Smith et al., 1998; Martikainen et al., 2007; Morrens et al., 2012; NRC, National Research Council and Committee on Human Biomonitoring for Environmental Toxicants, 2006; Porta et al., 2008b, 2012a; Subramanyam et al., 2013; Thayer and Kuzawa, 2011). Some evidence from studies based on non-representative samples indicates that such contamination does not affect all social and educational groups homogeneously; rather, some compounds seem to contaminate more intensely the more disadvantaged groups, generating a potentially unfair and perhaps avoidable gradient of inequalities in health (Brown, 1995; Freire et al., 2011; Hoffmann et al., 2009; Porta et al., 2008a). Even so, it has seldom been assessed to what extent structural differences among social groups in age and body weight explain their differences in POP contamination. Evidence on the relationships between social factors and human concentrations of environmental pollutants can also lead to a better understanding of health patterns by social class and educational level (Davies et al., 1972; Morrens et al., 2012).

Socioeconomic position is often related to environmental and occupational exposures, other living conditions, diet and lifestyle (Freire et al., 2011; Glynn et al., 2007; Ibarluzea et al., 2011; León-Muñoz et al., 2012; López-Azpiazu et al., 2003; Mesas et al., 2012; Rothman et al., 2011). Though commonly related, the nature and health effects of education and social class are different, sometimes outcome specific, and they cannot be used interchangeably: they measure different phenomena and act through different mechanisms (Martikainen et al., 2007; Schnittker, 2004; Thayer and Kuzawa, 2011). In addition to their potential to explain part of the population variation in human contamination by POPs, social class and education are also common possible confounders of associations between POPs and epidemiologic factors.

It is thus somewhat surprising that the evidence on the possible relation between indicators of socioeconomic position and human POP concentrations is so scant in studies based on representative samples of the general healthy population. To date, only reports from the United States (NRHEEC) (Department of Health and Human Services, 2009) and Germany (GerEs) (Becker et al., 2002) have assessed the relationship between body POP concentrations and ethnicity or socioeconomic status, respectively, in such samples.

Therefore, the present study aimed to investigate the separate and combined effects of occupational social class and educational level on body concentrations of several POPs in a representative sample of the general population of Catalonia, Spain. Special attention was paid to assess to what extent important characteristics of social groups, as age and body mass index, explain differences in internal contamination by POPs.

2. Materials and methods

2.1. Study population

The study population has been described in detail elsewhere (Porta et al., 2010). Briefly, participants in the Catalan Health Interview Survey (CHIS 2002) aged 18–74 years old (N = 6243) were offered to take part in a health examination, which included a physical exam, a supplementary interview, and the collection of urine and blood samples. A total of 1374 individuals participated in the health examination during 2002. Trained nurses recorded the weight and height, and the corresponding body mass index (BMI) was computed (measured weight [kg] divided by measured height squared [m^2]). Participants were asked to fast for 12 h before blood extraction. Blood was first stored frozen at −20 °C to determine immunologic, biochemical and nutritional parameters. Once these initial analyses were completed, the remaining serum was kept frozen at −80 °C until 2006, when POP concentrations were analysed. Information on blood concentrations of lipids and at least 1 mL of serum (for POP analyses) was available from 919 participants (Porta et al., 2010).

There were no significant differences between the 919 participants with data on POP concentrations and the remaining participants in the health examination (1374–919) with respect to age, sex, BMI, social class and educational level. The present study included 902 (of the 919) individuals with information on both POP concentrations and social class, and 912 individuals with information of POP concentrations and educational level. Information on educational level was also available for 896 of the 902 individuals. The proportion of women and the mean age were slightly higher in the 902 individuals included in the study than in the remaining participants of CHIS (6243–902).

2.2. Socioeconomic variables

Sociodemographic variables (sex, age, occupational social class, educational level and, in women, parity) were obtained from the CHIS. People were asked for the highest completed level of education, and the different educational levels were classified in five categories (without formal education (WFE), primary schooling (1st stage), primary schooling (2nd stage), secondary, and university studies). WFE included the illiterate.

Occupational social class was based on the "dominant approach" (Borrell et al., 2004b; Krieger et al., 1997), that is, it was assigned through the current or last occupation of the participant or, if he/she had a less privileged social class than the head of the household, through the current or last occupation of the latter. In 69.6% of participants social class was the same in both persons, and in 19.2% the social class of the head of the household was more affluent. Occupations were coded using the four-digit Spanish 'Clasificación Nacional de Ocupaciones' (CNO94), which is closely related to the international ISCO88 coding system (INE, Instituto Nacional de Estadística, 2010). Variables from the CHIS considered to code the occupation of each participant or head of the household based on CNO94 were: current or last job, company activity, and job status. Six social class categories were then created following the methodology proposed by the Spanish Epidemiological Society (Domingo-Salvany et al., 2000): social class I: managers of companies with 10 or more employees, senior technical staff, higher level professionals (associated to a complete degree); social class II: managers of companies with less than 10 employees, intermediate level professionals; social class III: administrative and financial management supporting personnel, other self-employed professionals, supervisors of manual workers, other skilled non-manual workers; social class IV: skilled (IVa) and partly skilled (IVb) manual workers; and social class V: unskilled manual workers.

Parity was defined as the number of children born per women. Place of birth was not analysed because only 2.7% of women and 3.3% of men were born outside Spain. Moreover, individuals born abroad were

similarly distributed across the different social classes and levels of education.

Of the 902 participants in the study, 56.2% were women. Mean age in women was lower than in men (44.0 and 46.2 years, respectively), and women had a lower mean BMI (1.1 kg/m^2 less); 72.8% of women had had one or more deliveries. Occupational social class and educational level did not show significant differences by sex: about one third of women and men belonged to social class IVa (Table 1), while about 26% of women and men received only up to first stage of primary schooling (see Supplemental material, Table 1). Age and BMI (and parity, in women) were inversely associated with educational level in both men and women; these three variables were associated with social class in women but not in men (Table 1 and Supplemental material, Table 1). Some associations with social class and educational level were also observed for physical activity, tobacco and alcohol consumption (see Supplemental material, p. 2).

2.3. Analytical chemical methods

Laboratory methods have also previously been described in detail (Porta et al., 2010). The following 19 POPs were analysed in serum: *o,p′*-DDT, *p,p′*-DDT, *o,p′*-DDE, *p,p′*-DDE, *o,p′*-DDD, and *p,p′*-DDD; PCB congeners 28, 52, 101, 118, 138, 153, and 180; PeCB; HCB; and α-HCH, β-HCH, γ-HCH and δ-HCH (Porta et al., 2009). Gas chromatography (GC) analyses were performed with an Agilent Technologies model GC-6890N provided with an ECD and a 60 m, 0.25 mm i.d. DB-5 column (J & W Scientific, Folsom, CA, USA; film thickness 0.25 μm). Main statistical analyses were limited to compounds that were detected above the detection limit in more than 85% of participants (*p,p′*-DDT, *p,p′*-DDE, PCB congeners 118, 138, 153, and 180, HCB and β-HCH). The percentage of detection for the rest of compounds ranged between 12% and 64%. *p,p′*-DDE, HCB and β-HCH showed the highest median concentrations (399, 159 and 92 ng/g, respectively) (Porta et al., 2010). Analyses were carried out in the Department of Environmental Chemistry (IIQAB-CSIC) in Barcelona, Spain. Limits of quantification ranged from 0.0069 ng/mL for PCB 101 to 0.0706 ng/mL for γ-HCH. When a sample had a concentration of a compound below the detection threshold, it was assigned the mid-value of this limit; when a POP was detected under the quantification threshold, the mid-value between detection and quantification limits was used (Porta et al., 2009, 2010).

Total cholesterol and triglyceride concentrations were determined enzymatically (Txad-Pap and CIN-UV methods, respectively), using serum obtained in the health examination (Porta et al., 2010). Total serum lipids (TL) were calculated by the standard formula 2, based on total cholesterol and triglycerides (Bernert et al., 2007; Phillips et al., 1989; Porta et al., 2009). POP concentrations were individually

Table 1
Main sociodemographic characteristics of participants by occupational social class, in women and men.

	Occupational social class							p-Value
	Total	Class V	Class IVb	Class IVa	Class III	Class II	Class I	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	
Women								
Total	507 (97.5)	34 (6.7)	36 (7.1)	173 (34.1)	138 (27.2)	72 (14.2)	54 (10.7)	
Age (years)								
Mean ± SD	44.0 ± 14.8	50.9 ± 16.1	45.9 ± 15.3	46.4 ± 15.1	42.4 ± 14.3	41.4 ± 13.2	38.2 ± 13.2	<0.001[a]
Median	44.0	52.0	46.0	46.0	40.0	41.5	38.5	<0.001[b]
Min–Max	18–74	21–74	18–71	18–74	18–74	18–65	18–69	
BMI[c] (kg/m^2)								
Mean ± SD	25.9 ± 4.9	28.1 ± 6.6	26.3 ± 5.2	26.6 ± 5.1	25.3 ± 4.4	25.2 ± 4.7	24.1 ± 3.8	0.001[a]
Median	25.0	27.5	25.7	25.7	24.9	23.4	23.3	0.001[b]
Education								
WFE[d]	80 (15.8)	12 (35.3)	7 (19.4)	40 (23.3)	19 (13.8)	2 (2.8)	0 (0.0)	<0.001[e]
Primary (I)[f]	135 (26.7)	14 (41.2)	8 (22.2)	68 (39.5)	34 (24.6)	7 (9.9)	4 (7.4)	
Primary (II)[g]	127 (25.1)	4 (11.8)	12 (33.3)	48 (27.9)	33 (23.9)	19 (26.8)	11 (20.4)	
Secondary	97 (19.2)	1 (2.9)	7 (19.4)	14 (8.1)	39 (28.3)	23 (32.4)	13 (24.1)	
University	66 (13.1)	3 (8.8)	2 (5.6)	2 (1.2)	13 (9.4)	20 (28.2)	26 (48.1)	
Parity								
Nulliparity	136 (27.2)	7 (20.6)	9 (25.7)	33 (19.3)	41 (30.1)	19 (26.8)	27 (50.9)	0.001[e]
≥1 deliveries	364 (72.8)	27 (79.4)	26 (74.3)	138 (80.7)	95 (69.9)	52 (73.2)	26 (49.1)	
GM[h]	5.0	3.3	4.9	5.9	4.5	5.6	4.5	
Men								
Total	395 (99.0)	26 (6.6)	41 (10.4)	132 (33.4)	116 (29.4)	47 (11.9)	33 (8.4)	
Age (years)								
Mean ± SD	46.2 ± 15.0	45.2 ± 16.5	45.0 ± 15.1	47.9 ± 15.4	47.5 ± 14.4	41.2 ± 13.6	44.6 ± 14.9	0.133[a]
Median	46.0	44.0	49.0	49.5	46.5	41.0	42.0	0.137[b]
Min–Max	18–74	18–73	18–73	18–74	18–74	19–64	18–71	
BMI[c] (kg/m^2)								
Mean ± SD	27.0 ± 4.1	25.8 ± 3.6	26.4 ± 3.9	27.2 ± 3.3	27.7 ± 4.8	26.4 ± 3.7	26.6 ± 4.8	0.147[a]
Median	26.6	25.7	25.8	27.1	26.8	25.6	26.8	0.135[b]
Education								
WFE[d]	54 (13.8)	5 (19.2)	8 (19.5)	25 (19.4)	15 (13.0)	1 (2.1)	0 (0.0)	<0.001[e]
Primary (I)[f]	102 (26.1)	9 (34.6)	11 (26.8)	49 (38.0)	24 (20.9)	6 (12.8)	3 (9.1)	
Primary (II)[g]	97 (24.8)	7 (26.9)	14 (34.1)	31 (24.0)	30 (26.1)	11 (23.4)	4 (12.1)	
Secondary	94 (24.0)	5 (19.2)	8 (19.5)	21 (16.3)	36 (31.3)	16 (34.0)	8 (24.2)	
University	44 (11.3)	0 (0.0)	0 (0.0)	3 (2.3)	10 (8.7)	13 (27.7)	18 (54.5)	

[a] ANOVA.
[b] Kruskal–Wallis' test.
[c] BMI: body mass index.
[d] Without formal education.
[e] Fisher's exact test (two-tail).
[f] Primary schooling (1st stage).
[g] Primary schooling (2nd stage).
[h] GM, geometric mean adjusted for age (only for women with ≥1 deliveries).

corrected for TL by dividing the crude serum POP concentration by TL, and are expressed in nanogrammes per gramme lipid (ng/g). Among the 902 individuals included in the present study, mean (standard deviation) body concentrations of total cholesterol, triglycerides and TL were, respectively, 196.2 (40.1), 97.0 (64.6) and 604.5 (130.6) mg/dl.

2.4. Statistical analysis

Univariate statistics were computed as customary (Armitage et al., 2002; Kleinbaum et al., 2007), and all analyses were stratified by sex. ANOVA or Kruskal-Wallis' tests were used to analyse normally or non-normally distributed quantitative variables, respectively. Chi–square test was only used when Fisher's exact test could not be computed to assess the relationship between two categorical variables. The Kolmogorov–Smirnov test for normality was used to check the distributions of POPs; as none was normal, logtransformed values were used in regression analyses. We computed the number of POPs detected per person with concentrations in the upper quartile as previously reported (Porta et al., 2012b). Multivariate analysis was used, through General Linear Regression Models, to study the relationship, and the individual and combined contributions of social class and level of education on concentrations of POPs, corrected (in ng/g) and uncorrected for TL (in ng/mL) (Armitage et al., 2002; Kleinbaum et al., 2007). Results are expressed as adjusted geometric means (GMs) with the corresponding 95% confidence intervals (CIs). Covariates evaluated were those associated with social class and educational level and those reported to influence concentrations of POPs in the literature: age, BMI and, in women, parity. The main effects of all predictors were independently explored in base models. Including physical activity, tobacco or alcohol consumption did not change the results; thus, these factors were not included in the final models (see Supplemental material, p. 2). Social class and education were included in the same model because no colinearity was observed. In order to assess the possible interaction between class and education, a variable considering at the same time social class and educational level was created combining social class, classified in 3 categories (I and II; III; IVa, IVb and V), with educational level, also classified in 3 categories (without formal studies and first stage of primary schooling; second stage of primary schooling and secondary; university), resulting in a new variable of 9 categories. We refer to this new variable as the joint variable of educational level and social class. Furthermore, in order to assess the combined effect of social class and education on body POP concentrations, we also created a variable assessing the affinity/discrepancy between social class and educational level: we calculated the difference between social class, classified in 5 categories (I; II; III; IVa and IVb; V), and educational level, also in 5 categories, producing a value ranging between −4 (when an individual was in social class V and had university studies) and 4 (when an individual was in social class I and WFE); however, the maximum value was 3, i.e., nobody was in social class I and WFE (see Supplemental material, p. 2). The level of statistical significance was set at 0.05 and all tests were two tailed. Analyses were conducted using SPSS version 12.0 (SPSS, Chicago, IL, USA, 2003).

3. Results

3.1. Results in women

In women, the number of POPs detected per person showed no significant differences by social class. However, the number of POPs detected per person with concentrations in the upper quartile did show a significant relation with social class. The percentage of women without any POP with concentrations over the 75th percentile was higher in class I (61.1%) than in class V (14.7%) (p-value = 0.001). Moreover, the number of POPs detected per person and the number of compounds with concentrations in the upper quartile was statistically significantly different by educational level. The percentage of women with all eight POPs detected was higher in women without formal education (89.5%) than in those with university education (78.8%) (p-value = 0.023). The proportion of women without any POP with concentrations in the 75th percentile was higher in women with university level (54.5%) than in those without formal education (10.5%) (p-value < 0.001).

In women, the highest median serum concentrations of all eight POPs were found in participants in the less privileged occupational social class (class V). Women in the most affluent social class (I) had the lowest concentrations of all eight POPs (Fig. 1 A and B). Differences on median concentrations by social class were statistically significant for all POPs (p-values < 0.05), except for *p,p′*-DDT and PCB 180 (p-values < 0.07). Women without formal education had the highest median POP concentrations (Fig. 1 C and D), whereas the lowest concentrations for *p,p′*-DDE, PCB 118 and 153 were observed in women with university studies, for *p,p′*-DDT, HCB, β-HCH and PCB 138 in women with secondary level education, and for PCB 180 in women with second stage of primary schooling. Differences on median concentrations by educational level were also statistically significant for all POPs (all p-values < 0.05). Intermediate categories of educational level (from first stage of primary schooling to secondary studies) showed a decreasing pattern of POP concentrations; this was not so for intermediate categories of social class (II to IVb).

The full distribution of serum concentrations of *p,p′*-DDE and HCB by social class and education is shown in Fig. 3. In women, there was a progressive flattening of the curves in less affluent classes and lower levels of education. The kurtosis in social classes I–III was hence usually higher than in classes IV–V. This pattern was also true for education: in the university educational level kurtosis was higher than in the group without formal education; e.g., for HCB, kurtosis among women with university studies was over 40 times higher (54.77) than in women without formal education (1.38). In other words, in upper classes and in higher educational levels POP concentrations clustered more around a few values than in the less privileged and in the lowest educational levels. Moreover, the skewness of the distribution of POP levels among women of class I or among women with university studies was often higher than the skewness among class V or among women without formal education; e.g. for HCB, the skewness in women with university studies was 7 times higher than in those without formal education (7.130 and 1.029, respectively) (data not shown).

In women, variability in serum POP concentrations explained by educational level alone was greater than variability explained by occupational social class alone. Educational level explained a minimum of 5.1% (R^2 for *p,p*-DDT) and a maximum of 16.5% (for HCB and β-HCH) of the variability in concentrations (all p-values < 0.001); for social class, the corresponding coefficient of determination (R^2) ranged between 1.3% (for *p,p*-DDT, p-value = 0.235) and 3.4% (for HCB, p-value = 0.004) (data not shown). When social class and parity were considered jointly, the variability explained by these two factors increased to 3.5% (for *p,p*-DDT, p-value = 0.007) and to 13.7% (for HCB, p-values < 0.001). When social class was considered along with BMI, R^2 was 2.6% for PCB 153 and 22.2% for HCB (p-value = 0.040 and < 0.001, respectively). Social class, parity and BMI jointly explained between 7.5% of the variability (of PCB 138) and 27.0% (of HCB) (p-values < 0.001). When age was considered together with social class, parity and BMI, the variability explained increased notably, up to an R^2 of 55.5% for HCB (p-value < 0.001). When educational level was considered together with parity, BMI, and age, the variability explained was 56.3% for HCB (p-value < 0.001). Thus, social class and education each alone explained a small part of the concentrations of POPs. Social class, education, parity, BMI, and age, jointly explained from 14.8% (of the variability of *p,p*-DDT) to 56.1% (of HCB).

Table 2 shows, as an illustration, the influence of all three factors (age, BMI and parity), taken separately, on concentrations (GM, 95% CI) of *p,p′*-DDE by social class and educational level, for both sexes. Non-adjusted multivariate analyses by social class showed that, in women, the highest

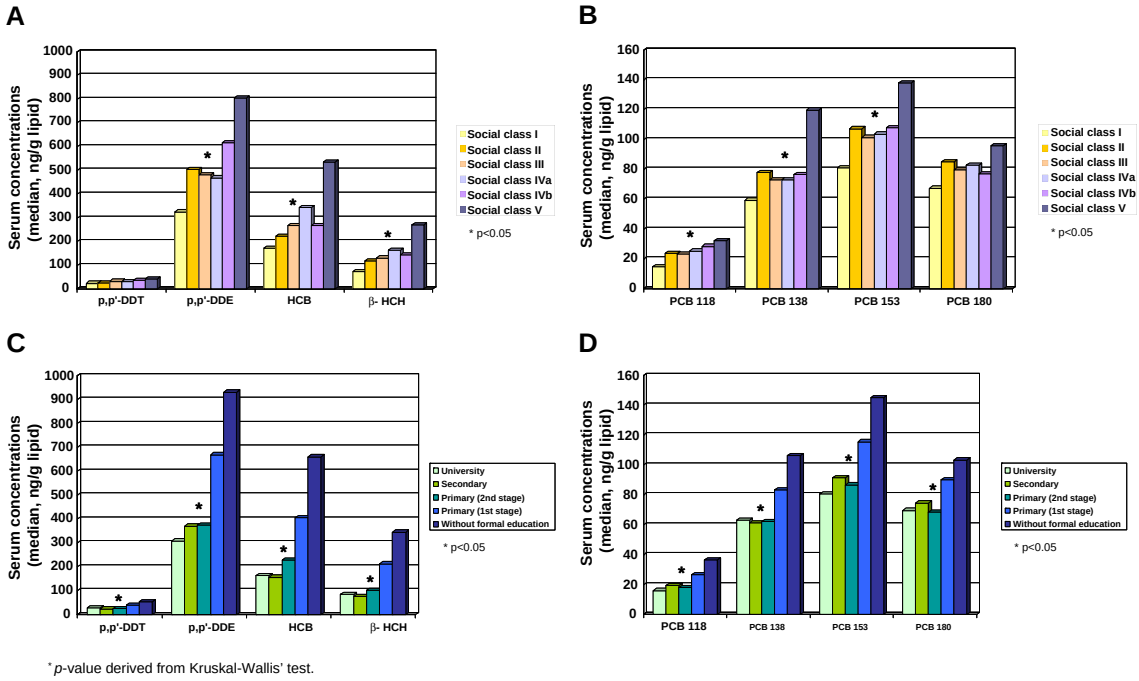

Fig. 1. Serum concentrations of individual organochlorine compounds detected in more than 85% of the participants by occupational social class (A and B) and education (C and D) in women.

serum concentrations were observed in class V (825.5 ng/g), while the lowest concentrations were found in class I (384.5 ng/g), a statistically significant difference (p-value < 0.001). When adjusted for parity, BMI or age separately, the mean concentrations in women in class V tended to decrease (from 834.2 ng/g when adjusted for parity, to 722.4 and to 637.7 ng/g when adjusted for BMI and age, respectively), while

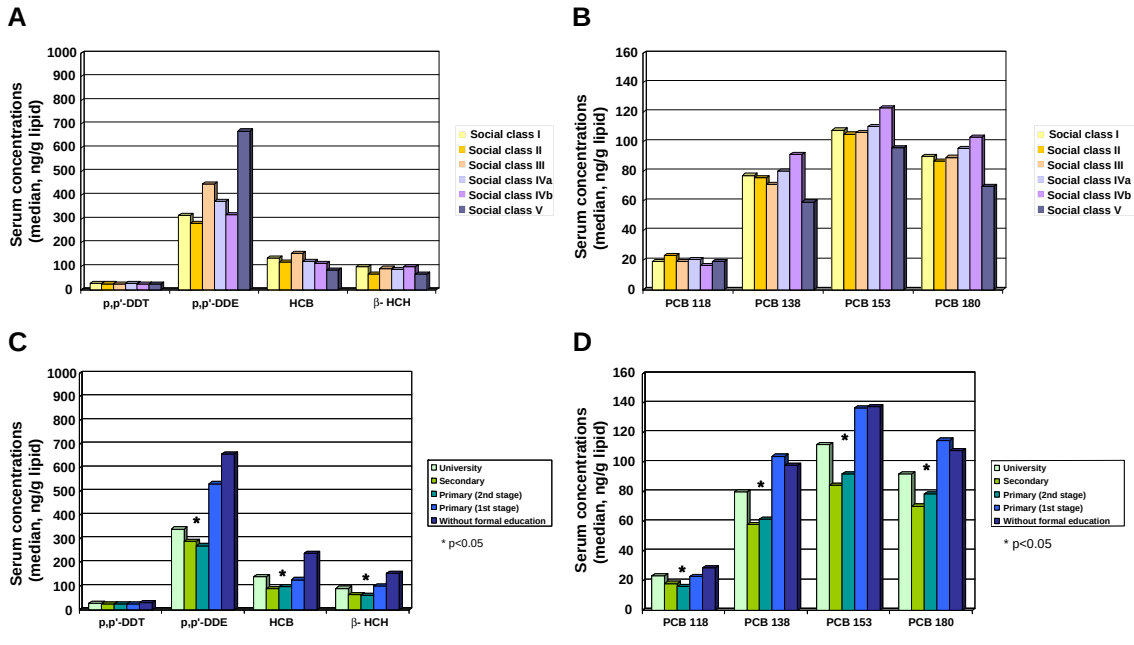

Fig. 2. Serum concentrations of individual organochlorine compounds detected in more than 85% of the participants by occupational social class (A and B) and education (C and D) in men.

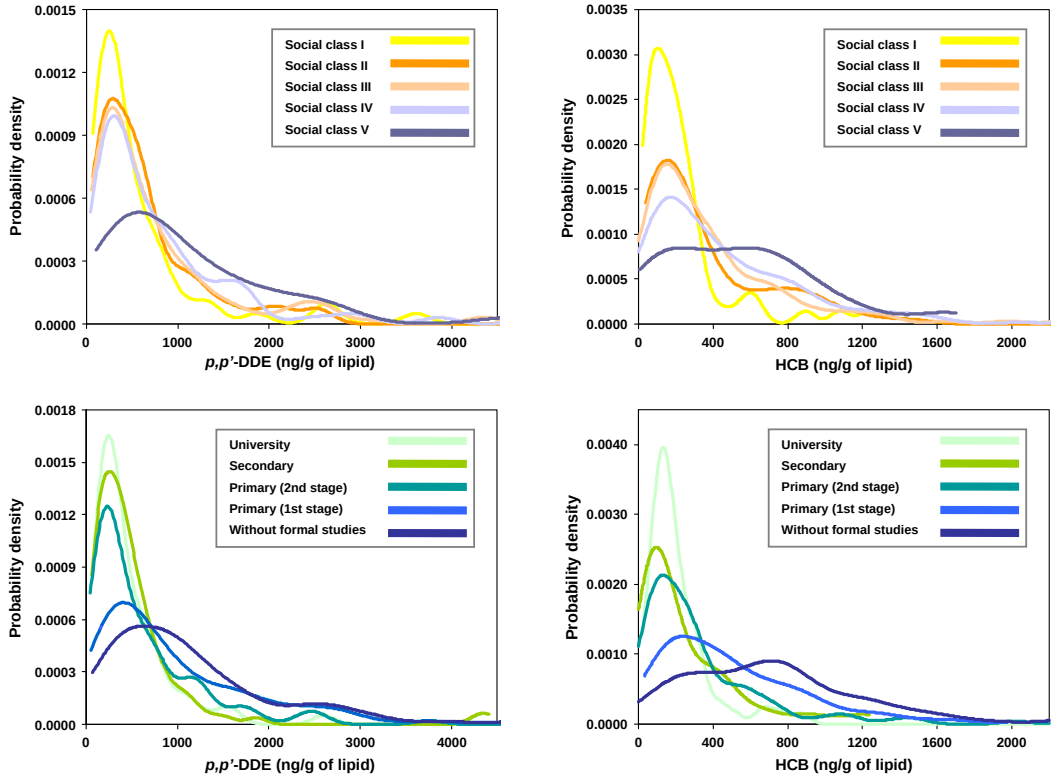

Fig. 3. Distribution of serum concentrations of *p,p′*-DDE and HCB by occupational social class and education in women.

concentrations in class I tended to increase, thus reducing the differences between both classes (and becoming statistically non-significant once adjusted for age). In women, the same pattern was observed when adjusting educational level for the same confounders. Women without formal education had a serum concentration of *p,p′*-DDE about 2.3 times higher than women with university education, with a progressively decreasing difference between the two educational levels when adjusting for parity, BMI, and age, respectively (Table 2). Hence, in women, all statistically significant differences in *p,p′*-DDE concentrations by social class and education disappeared when adjusting for age, whereas they did not when adjusting only for BMI or parity.

As in the example of *p,p′*-DDE in women, significant associations found in crude analyses for the rest of POPs with social class also disappeared when adjusting for age. Models further adjusted for BMI and parity also did not show any statistically significant relationship between social class and POP concentrations, although concentrations of all POPs, except β-HCH, were higher in women in class V than in women in class I (see Supplemental material, Table 2). Age/birth cohort and BMI were the most significant predictors of such concentrations, whereas parity was only inversely associated with HCB and β-HCH (data not shown).

Similarly to the results for occupational social class, in women educational level was no longer associated with any POP concentration when age or birth cohort was taken into account. Models further adjusted for BMI and parity also did not show any statistically significant relationship between education and POP levels, although women with university studies had higher POP concentrations than women without formal studies (Table 3).

When occupational social class and educational level were included simultaneously in the same model along with the rest of potential confounders, class appeared to be positively associated only with concentrations of HCB: women in classes II and III had higher HCB concentrations (268.8 and 265.2 ng/g, respectively) than women in class I (202.8 ng/g) (p-values = 0.044 and 0.041, respectively). Education was positively associated with concentrations of HCB and PCB 118; e.g., women without formal education had about 29% lower HCB concentrations than women with university studies (p-value = 0.031). In models including the joint variable of educational level and social class (along with the rest of potential confounders), women with university studies and in class III had higher concentrations of *p,p′*-DDT than women with university studies and in classes I and II (p-value = 0.010). No other significant differences were observed in the rest of POPs analysed. Models assessing the level of discrepancy between social class and education showed that women with a lower class relative to their education had higher concentrations of *p,p′*-DDT, and PCBs 118 and 153 than women without discrepancy (see Supplemental material, p. 2 and 3).

3.2. Results in men

In men, neither the number of POPs detected per person nor the number of POPs with concentrations in the upper quartile showed significant differences by social class. However, the percentage of men with all eight POPs detected was significantly higher in men without formal education (81.5%) than in men with university studies (77.8%) (p-value = 0.014). Moreover, the percentage of men without any POP at concentrations in the upper quartile was higher in men with university education (44.4%) than in men without formal education (16.7%) (p-value < 0.001) (data not shown).

Table 2
Main sociodemographic predictors of serum concentrations (ng/g lipid) of *p,p′*-DDE, in women and men.

Predictor	Model							
	Crude		Adjusted for age		Adjusted for BMI		Adjusted for parity	
	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)
Women								
Occupational social class[a]								
Social class I	384.5	(297.8–496.5)	477.8	(386.4–590.8)	427.7	(334.7–546.6)	417.6	(325.3–536.1)
Social class II	462.4	(370.6–576.9)	508.6	(423.6–610.5)	482.7	(390.8–596.2)	464.0	(374.3–575.2)
Social class III	486.8	(414.9–571.2)	516.6	(452.7–589.4)	504.2	(432.8–587.3)	506.2	(433.2–591.4)
Social class IVa	507.2	(439.7–585.0)	464.1	(412.4–522.4)	483.9	(422.1–554.8)	480.3	(417.8–552.1)
Social class IVb	576.8	(421.8–788.9)*	535.9	(414.0–693.7)	560.4	(415.8–755.2)	581.0	(427.8–789.0)
Social class V	825.5	(598.2–1139.3)*	637.7	(488.0–833.1)	722.4	(530.3–984.0)*	834.2	(611.5–1137.9)*
Educational level[b]								
University	367.5	(294.0–459.3)	510.9	(418.8–623.4)	404.3	(324.5–503.7)	403.8	(321.5–507.1)
Secondary	356.8	(297.1–428.5)	502.4	(425.5–593.2)	392.4	(327.3–470.5)	377.9	(313.7–455.3)
Primary (II)[c]	418.9	(357.1–491.3)	489.9	(426.0–563.4)	425.3	(364.1–496.8)	425.0	(362.5–498.2)
Primary (I)[d]	660.9	(566.8–770.7)*	545.7	(476.3–625.1)	625.5	(537.9–727.3)*	639.5	(547.4–747.0)*
WFE[e]	847.7	(697.3–1030.6)*	480.4	(397.7–580.2)	755.3	(621.6–917.6)*	773.5	(633.5–944.4)*
Men								
Occupational social class[a]								
Social class I	295.6	(205.9–424.2)	312.8	(228.0–429.0)	302.8	(213.1–430.2)		
Social class II	347.8	(257.0–470.8)	413.0	(316.4–539.1)	361.8	(269.5–485.8)	–	–
Social class III	443.3	(365.6–537.5)	424.3	(358.4–502.3)	424.3	(351.5–512.1)	–	–
Social class IVa	405.8	(338.8–486.2)	383.2	(327.1–448.9)	402.3	(337.5–479.5)	–	–
Social class IVb	366.8	(265.3–507.3)	382.9	(288.3–508.3)	382.2	(278.8–523.9)	–	–
Social class V	522.5	(347.8–785.0)*	541.9	(379.6–773.6)*	562.3	(378.2–836.1)*	–	–
Educational level[b]								
University	384.7	(284.3–520.5)	440.7	(335.2–579.4)	386.2	(287.3–519.2)	–	–
Secondary	314.2	(254.9–387.3)	388.5	(320.2–471.3)	324.3	(264.1–398.2)		
Primary (II)[c]	323.9	(263.9–397.6)	390.4	(323.4–471.3)	336.4	(275.1–411.5)	–	–
Primary (I)[d]	501.1	(410.3–612.0)	403.5	(335.3–485.7)	479.7	(394.1–584.0)	–	–
WFE[e]	618.8	(469.6–815.5)*	411.3	(316.5–534.6)	592.4	(451.8–776.7)*	–	–

GM, geometric mean.
[a] The reference category is social class I.
[b] The reference category is university educational level.
[c] Primary schooling (2nd stage).
[d] Primary schooling (1st stage).
[e] Without formal education.
* p-Value < 0.05.

By contrast with what was found in women, in men statistically significant differences in concentrations of POPs were only observed by educational level, not by occupational social class (Fig. 2). Only concentrations of *p,p*-DDE were higher in men in class V (p-value for differences among median concentrations = 0.149). Moreover, men in the most affluent class (I) no longer had the lowest levels (women in class I had the lowest levels of all compounds). For 3 PCB congeners and HCB, the lowest concentrations were observed in men in class V (Fig. 2A and B). In men differences in median concentrations by educational level were statistically significant for all POPs (p-values < 0.05), except for *p,p′*-DDT (p-value = 0.944). Men without formal education had the highest POP concentrations, except for PCB 138 and PCB 180, for which the highest concentrations were observed in men with first stage of primary schooling. The lowest concentrations of *p,p′*-DDT, HCB, and 3 PCBs were observed in men with secondary education, and those of *p,p′*-DDE, *β*-HCH, and PCB 118 in men with second stage of primary schooling (Fig. 2C and D).

The full distribution of the concentrations of *p,p′*-DDE, PCB 153 and HCB by social class and education did not show the flattening pattern of the curves that was observed in women. Instead, the curves in men trailed all further to the left; thus, in men values of kurtosis and skewness were similar (data not shown).

In men, social class (alone and jointly with BMI or age) explained less variability in POP concentrations than in women. In men, social class and BMI together explained between 0.7% (p-value = 0.842) and 22.1% (p-value < 0.001) of the variability of PCB 180 and HCB, respectively. When age was considered along with social class and BMI, the variability explained reached 39.1% for HCB (p-value < 0.001). When educational level, BMI, and age were all considered in the same model, the R^2 was 39.3% for HCB (p-value < 0.001). Thus, HCB was the compound with the greatest variability explained by social class and education in multivariate-adjusted analyses, in both sexes.

As shown in Table 2, in unadjusted analyses by social class in men the highest mean concentration of *p,p′*-DDE was observed in class V (522.5 ng/g), while the lowest was found in class I (295.6 ng/g), a statistically significant difference (p-value = 0.040), like in women. When adjusted for BMI and age, separately, median concentrations in class V decreased from 562.3 to 541.9 ng/g; in class I they increased from 302.8 to 312.8 ng/g, thus reducing the differences, although maintaining the significance (p-value = 0.022 and 0.024, respectively). On the other hand, in unadjusted analyses by educational level, men without formal education had over 1.6 times greater {median/mean} serum concentrations than men with university education (618.8 and 384.7 ng/g, respectively). When adjusted for BMI, the mean concentrations in men without formal education decreased to 592.4 ng/g, and when adjusted for age, to 411.3 ng/g, showing non-significant differences with men with university studies when adjusted for age. It is relevant to note that some significant differences were always found in men, both in crude and adjusted analyses, while differences in women disappeared when adjusting for age (p-value > 0.05).

As in women, and as in the example of *p,p′*-DDE, in men significant associations found in crude analyses for the rest of POPs with social class and level of education were also mainly explained by age, although to a lesser extent in men than in women. In men, crude analyses showed that occupational social class was only negatively associated with *p,p′*-DDE, as mentioned above, and positively

Table 3
Influence of educational level on concentrations (ng/g lipid) of organochlorine compounds, in women (N = 518) and men (N = 394).

Compound	Women		Men	
	GM	(95% CI)	GM	(95% CI)
1. p,p′-DDT				
University	27.9	(20.4–38.1)	22.5	(15.4–32.9)
Secondary	27.5	(21.2–35.7)	28.0	(21.4–36.5)
Primary (II)	24.0	(19.3–29.9)	23.7	(18.3–30.8)
Primary (I)	31.6	(25.5–39.1)	19.1	(14.8–24.7)
WFE	27.2	(20.3–36.5)	20.2	(14.1–29.0)
2. p,p′-DDE				
University	515.0	(420.8–630.2)	438.3	(334.2–574.9)
Secondary	508.4	(429.6–601.7)	391.3	(323.1–474.0)
Primary (II)	493.7	(429.0–568.1)	395.4	(328.0–476.6)
Primary (I)	546.1	(476.0–626.6)	397.8	(330.9–478.1)
WFE	474.5	(392.8–573.3)	409.9	(316.1–531.6)
3. HCB				
University	284.8	(235.6–344.3)	153.9	(115.5–205.2)
Secondary	252.4	(215.5–295.7)	133.9	(109.3–164.0)
Primary (II)	261.9	(229.5–298.8)	118.6	(97.3–144.6)
Primary (I)	273.1	(240.0–310.8)	80.5	(66.3–97.9)*
WFE	222.9	(186.6–266.2)	102.9	(78.1–135.5)
4. β-HCH				
University	137.6	(111.5–169.8)	96.1	(72.0–128.2)
Secondary	131.8	(110.6–157.1)	80.3	(65.5–98.5)
Primary (II)	133.0	(114.9–153.9)	71.9	(58.9–87.7)
Primary (I)	138.2	(119.8–159.5)	63.7	(52.4–77.5)*
WFE	124.9	(102.6–152.1)	79.7	(60.4–105.1)
5. PCB 118				
University	19.0	(14.6–24.8)	21.9	(15.2–31.3)
Secondary	22.7	(18.2–28.4)	19.3	(14.9–24.9)
Primary (II)	14.6	(12.2–17.6)	12.1	(9.5–15.5)*
Primary (I)	18.7	(15.6–22.4)	14.7	(11.5–18.7)
WFE	17.7	(13.8–22.7)	12.0	(8.5–16.9)*
6. PCB 138				
University	73.6	(59.4–91.3)	74.8	(57.8–96.9)
Secondary	66.8	(55.8–79.9)	61.5	(51.2–73.8)
Primary (II)	58.5	(50.4–68.0)	61.3	(51.3–73.3)
Primary (I)	70.6	(61.0–81.8)	76.4	(64.1–91.1)
WFE	62.6	(51.2–76.5)	57.7	(45.0–73.9)
7. PCB 153				
University	104.4	(85.3–127.7)	116.2	(90.6–148.9)
Secondary	100.2	(84.7–118.5)	90.5	(75.9–107.9)
Primary (II)	85.0	(73.9–97.8)	95.3	(80.3–113.1)
Primary (I)	91.5	(79.8–105.0)	111.6	(94.3–132.1)
WFE	85.9	(71.1–103.7)	83.9	(66.2–106.5)
8. PCB 180				
University	80.0	(68.7–93.2)	102.0	(85.5–121.7)
Secondary	74.7	(65.8–84.8)	81.9	(72.3–92.8)*
Primary (II)	72.9	(65.6–81.1)	89.7	(79.4–101.3)
Primary (I)	81.2	(73.2–90.1)	99.2	(88.0–111.8)
WFE	74.5	(64.5–85.9)	93.7	(79.1–111.0)
9. Sum of PCBs				
University	287.0	(243.6–338.1)	336.7	(279.0–406.3)
Secondary	273.5	(238.6–313.6)	268.4	(235.0–306.5)
Primary (II)	245.0	(218.6–274.6)	274.2	(240.9–312.1)
Primary (I)	280.1	(250.5–313.2)	316.2	(278.4–359.2)
WFE	257.8	(221.1–300.6)	275.9	(230.5–330.3)

GM, geometric mean adjusted by age and BMI. In women, further adjusted by parity.
WFE, without formal education.
*p-Value < 0.05. The reference category is university educational level. In men, *p*-trend for HCB, β-HCH and PCB 118 was 0.001, 0.113 and 0.006, respectively.

associated with HCB; men in class IVb had lower HCB concentrations than men in the most affluent class I (p-value = 0.029) (data not shown). When models also included age and BMI, these associations remained statistically significant; men in the less affluent class had higher *p,p′*-DDE concentrations (563.0 ng/g) than men in class I (315.8 ng/g) (p-value = 0.016); and men in classes IVa and IVb had lower HCB concentrations (103.3 and 85.28 ng/g, respectively) than men in the most privileged class (156.9 ng/g) (p-values = 0.026 and 0.007, respectively). For the rest of POPs concentrations were statistically non-significantly higher in men in class I than in class V (see Supplemental material, Table 2).

Contrary to women, in men the confounding effect of age or birth cohort was not similar for all POPs. As in the example of *p,p′*-DDE and level of education, some associations did not remain significant once adjusted for age. However, some positive associations appeared when models were adjusted for age and also when further adjusted for BMI; e.g., men without formal education and men with first stage of primary schooling had lower HCB concentrations (102.9 and 80.5 ng/g, respectively) than men with university studies (153.9 ng/g) (p-values = 0.051 and <0.001, respectively) (Table 3). When adjusted for age and BMI, concentrations of all POPs were higher in men with university studies than in men without formal studies (statistically significant only for PCB 118); and concentrations of all POPs, except PCB 138, were higher in men with university studies than in men with first stage of primary schooling (statistically significant for HCB and β-HCH) (Table 3).

In men, when social class and educational level were included simultaneously in the same model along with all other factors, social class was negatively associated with concentrations of *p,p′*-DDE. Men in class V had about 2 times greater *p,p′*-DDE concentrations (577.5 ng/g) than men in class I (282.9 ng/g) (p-value = 0.007). As in women, in men education was positively associated with concentrations of HCB and PCB 118; e.g., men with first stage of primary schooling had lower HCB levels (85.8 ng/g) than men with university studies (140.3 ng/g) (p-value = 0.016). In models including the joint variable of educational level and social class, differences were also observed for HCB: men without formal studies and in any of the three groups of social class (I–II/III/IVa–IVb–V) had lower concentrations than men with university studies and in social class I or II (p-values = 0.019, 0.068 and 0.002, respectively) (Table 4). Similar effects were observed for concentrations of β-HCH and PCB 118. For PCB 138, 153 and 180, men with university studies and in social class III had lower concentrations than men with university studies but in the most affluent social classes (I and II) (p-values = <0.001, 0.003 and 0.040, respectively). Also, men with secondary or second stage of primary schooling and in the most affluent (I–II) or in the less affluent (IVa–IVb–V) social classes had lower concentrations than men with university studies and in classes I or II (Table 4). Models including the affinity/discrepancy variable showed that men with higher class relative to their education had lower concentrations of PCB 153 than men without discrepancy between class and education (p = 0.026) (see Supplemental material, p. 2 and 3).

No differences in the DDT/DDE ratio were found across social classes or across levels of education, except in men, in whom those with secondary schooling had a higher DDT/DDE ratio than men with primary schooling (1st stage) or WFE. The DDT/DDE ratio decreased with increasing age, a pattern that was similar in all social classes and educational levels.

Generally, the relationships described above were less evident when manual workers (social classes IV and V) were compared to non-manual workers (classes I to III), and were also less apparent when the level of education was recoded into 3 categories (elementary school or less, secondary, and university) instead of 5, in both sexes (data not shown). Though differences were not statistically significant, the concentration of *p,p′*-DDE was always higher in the less affluent social classes (IVa, IVb, V) than in classes I or II within all three categories of education (Table 4). In models with POP concentrations uncorrected for TL (in ng/mL) and adjusted by age and BMI (and parity, in women), the influence of social class and educational level was very similar to results found with lipid-corrected POP concentrations (ng/g); if models were only adjusted by age (not adjusted by BMI) results also did not change (data not shown). No associations were found in the present study between lipid serum concentrations and social class or educational level.

Table 4
Joint influence of educational level and occupational social class on concentrations (ng/g lipid) of organochlorine compounds, in men (N = 391).

	p,p′-DDT		*p,p′*-DDE		HCB		*β*-HCH	
	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)
University + SC I or II (N = 31)	23.9	(15.2–37.8)	467.4	(338.5–645.6)	161.0	(114.8–226.0)	104.1	(73.5–147.5)
University + SC III (N = 10)	20.0	(8.9–44.9)	282.6	(159.7–500.1)	144.8	(79.5–263.5)	71.3	(38.5–132.0)
University + SC IVa, IVb or V (N = 3)	12.2	(2.8–53.5)	773.0	(272.4–2194)	136.1	(45.6–406.9)	116.8	(37.9–359.9)
Secondary or primary (II) + SC I or II (N = 39)	22.7	(15.0–34.3)	336.1	(250.7–450.4)	150.7	(110.1–204.9)	85.0	(62.0–116.6)
Secondary or primary (II) + SC III (N = 66)	25.5	(18.6–34.9)	464.8	(372.0–580.7)	123.8	(98.0–156.4)	71.7	(56.4–91.1)
Secondary or primary (II) + SC IVa, IVb or V (N = 86)	27.2	(20.4–36.1)	368.5	(301.4–450.4)	116.7	(94.6–144.1)	76.1	(61.3–94.5)
WFE or primary (I) + SC I or II (N = 10)	25.5	(11.4–57.1)	257.1	(145.2–455.1)	70.3	(38.6–128.0)*	44.5	(24.0–82.3)*
WFE or primary (I) + SC III (N = 39)	22.0	(14.4–33.6)	372.0	(275.9–501.7)	104.6	(76.4–143.2)	70.4	(51.0–97.2)
WFE or primary (I) + SC IVa, IVb or V (N = 107)	18.4	(14.2–23.8)	425.5	(355.0–509.9)	86.9	(71.9–105.1)*	69.5	(57.2–84.5)*
	PCB 118		PCB 138		PCB 153		PCB 180	
	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)	GM	(95% CI)
University + SC I or II (N = 31)	23.7	(15.4–36.7)	95.6	(70.4–129.8)	139.7	(103.9–187.9)	113.7	(92.0–140.5)
University + SC III (N = 10)	11.3	(5.2–24.3)	28.3	(16.5–48.6)*	55.7	(33.0–94.0)*	72.5	(49.9–105.5)*
University + SC IVa, IVb or V (N = 3)	28.6	(7.0–116.3)	87.3	(32.5–234.6)	119.8	(46.0–312.1)	74.3	(37.5–147.4)
Secondary or primary (II) + SC I or II (N = 39)	17.2	(11.6–25.5)	48.8	(36.9–64.4)*	73.6	(56.3–96.3)*	76.6	(63.2–92.8)*
Secondary or primary (II) + SC III (N = 66)	16.1	(11.9–21.7)	70.3	(56.9–86.8)	101.7	(82.9–124.7)	91.0	(78.7–105.4)
Secondary or primary (II) + SC IVa, IVb or V (N = 86)	13.0	(9.9–17.0)*	59.1	(48.8–71.4)*	93.1	(77.4–111.9)*	84.7	(74.3–96.6)*
WFE or primary (I) + SC I or II (N = 10)	15.8	(7.3–34.1)	54.3	(31.6–93.3)	89.7	(53.1–151.5)	100.7	(69.3–146.5)
WFE or primary (I) + SC III (N = 39)	13.3	(8.9–19.9)	70.6	(53.2–93.7)	96.4	(73.3–126.9)	100.7	(82.8–122.5)
WFE or primary (I) + SC IVa, IVb or V (N = 107)	14.0	(10.9–17.8)*	71.9	(60.6–85.4)	105.6	(89.4–124.7)	96.5	(85.7–108.7)

GM, geometric mean adjusted for age and BMI. SC, occupational social class. WFE, without formal education.
*p-Value < 0.05. The reference category is University + SC I or II.

4. Discussion

In unadjusted analyses, the percentage of individuals – men and women – with all eight POPs detected was higher in the groups with lower level of education, but there were no differences by social class. The percentage of subjects with one or more POPs with high concentrations was also higher among participants with less education and, among women only, in less affluent social classes (Fig. 4). In women, higher median crude (unadjusted) concentrations of all eight POPs were found with decreasing education and class. By contrast, in men significant differences in concentrations of POPs were only observed by educational level – higher concentrations in men without formal studies – but not by social class: only concentrations of *p,p′*-DDE were higher in men in less affluent social classes. These patterns were largely lost after adjusting for age, especially in women, in whom multivariate analyses showed no association between social class or education and POPs (Fig. 4). In men, after adjusting for age and BMI, education became positively associated with virtually all POP levels (although only a few comparisons were statistically significant), whereas social class was largely unrelated to POP levels (Fig. 4). Results in men are in line with some previous studies, in which education was more related to POP concentrations than social class (Chao et al., 2010; Vrijheid et al., 2012). Higher POP levels in less privileged social classes and lower educational groups were explained by age/birth cohort and BMI to a larger extent than by social class or education.

Importantly, in our population age increased with decreasing affluence and education, a fact seldom appreciated in POP studies (Davies et al., 1972). Therefore, the higher levels of POPs found in less affluent social classes and lower educational levels can partly be attributed to the different age structures of such groups. In a cross-sectional study as this one, the effect of age reflects years of exposure, birth cohort effects, and perhaps changes in metabolic functions related to ageing (such as a putative lower capacity to excrete xenobiotics) (Porta et al., 2008b, 2010, 2012a; Quinn and Wania, 2012; Quinn et al., 2011). Clearly, relative to younger individuals older citizens had more years to accumulate POPs and lived in periods when use of some POPs (e.g., DDT, PCBs) was more extensive. Positive historical changes towards better education and occupations that occurred in countries as Spain in the last decades entail that the younger generations belong to higher occupational classes and educational groups. Hence, policies favouring decreasing historical trends in POP levels would also explain crude differences among social groups (Espina et al., 2013). The effect of age may also partly explain the decrease in statistical significance observed in women when adjusting for parity: women who have more children are commonly older, they lived a longer fertile period. As a result, when adjusting for parity differences between social groups decreased because of the negative relation of age and parity with social class and education.

Age, BMI and parity were not accounted as simple confounders – i.e., as if their effect simply had to be eliminated – but as variables that could be deemed to be inherent to or 'part' of social class and educational level, and which, therefore, contributed to explain the influence on POP concentrations of social class and educational level. In women, differences in age, BMI and parity among social classes and educational groups were significant, whereas in men differences in age and BMI were significant only among educational groups. This may partly explain why in women significant differences in POP levels were found in unadjusted analyses among both social classes and educational groups, while in men unadjusted analyses showed significant differences in POP levels only by educational level, but not by social class. Furthermore, the relationships between age and BMI (and parity, in women) and social class and education partly explain why most of the significant differences in POP levels among classes and educational groups observed in unadjusted analyses dissipated (or some even became positive) after adjusting for age, BMI and parity (Fig. 4).

Differences in POP concentrations by social class may be due to occupational and non-occupational factors (particularly, past and chronic), such as inequalities in exposure to chemicals in the workplace, through diet, in the general environment, or in household conditions (Bergman et al., 2013; García, 1998; Morrens et al., 2012; NRC, National Research Council and Committee on Human Biomonitoring for Environmental Toxicants, 2006; Porta et al., 2008a,b; Wolff, 1985). However, POP contamination affects a large diversity of professions and social groups, due to their numerous applications and widespread presence in fatty foods (Chao et al., 2010; NRC, National Research Council and Committee on Human Biomonitoring for Environmental Toxicants, 2006; Thornton et al., 2002). In the present study, birth place had no influence on the relationship between POP concentrations and social class or education, essentially because of the low proportion of individuals born abroad of Spain, and their homogenous distribution across social classes and

Analysis	Women		Men	
	Education	Social class	Education	Social class
No. POPs detected	(–)	Ø	(–)	Ø
No. POPs High conc.[1]	(–)	(–)	(–)	Ø
[POPs] crude	(–)	(–)	(–)	Ø[3]
[POPs] adjusted[2]	Ø[4]	Ø[5]	(+)[6]	Ø[7]

Did POP concentrations differ among educational levels and social classes?

Ø No, they did not differ significantly.

(–) Yes, there was an inverse relationship; i.e., higher levels in lower groups.

(+) Yes, there was a positive relationship; i.e., higher levels in upper groups.

Fig. 4. Overview of the main findings on the relationships between blood concentrations of POPs and social class and education. Footnotes: [1]Number of POPs detected at high concentrations. [2]Adjusted by age and BMI (in women, further adjusted by parity). [3]The only statistically significant differences were: *p,p′*-DDE was higher in class V than in class I, and HCB was lower in class IVb than in class I. [4]However, all 8 POPs were statistically non-significantly lower in WFE than in university studies. [5]However, all eight POPs showed statistically non-significant inverse trends; i.e., higher levels in lower social classes than in upper classes. [6]In virtually all comparisons (the exception being *p,p′*-DDT), men with university studies had higher concentrations than men with less formal education, and differences were statistically significant for eight comparisons. [7]After adjusting by age and BMI, the only statistically significant differences were: *p,p′*-DDE was higher in class V than in class I, and HCB was lower in classes IVa and IVb than in class I.

educational groups. Similarly, place of residence had no influence on the results.

Both social class and educational level predict health status and social inequalities in health (Davey Smith et al., 1998; Galobardes et al., 2006; Krieger et al., 1997; Martikainen et al., 2007; Morrens et al., 2012). Thus, the observed weak or null association of POP levels with these factors suggests that the effects on health inequalities of social class and education are not mediated by POPs; they also suggest that most effects of POPs on health are independent of socioeconomic position, or that their population health impacts are weak (in spite of the abundant evidence on the contrary mentioned in the Introduction). It is also possible that our cross-sectional design and measures of socioeconomic position were insufficient to capture the complex, invisible and lifelong social influences on human exposure to POPs (Porta, 2004, 2012; Porta et al., 2008b; Quinn and Wania, 2012; Quinn et al., 2011). Occupational social class and educational level have different meanings for different birth cohorts; e.g., in a given social class, older generations often have a lower level of education than the younger ones (Galobardes et al., 2006; Krieger et al., 1997). The small number of chemicals studied, compared with the estimated number that affect humans, also warrants to conduct more complex studies (Porta, 2012).

In the present study, Spearman's correlation between social class and educational level was 0.45 (p-value < 0.001), although in models with the two variables no significant colinearity was apparent. They are interrelated indicators of socioeconomic position inversely related with health gradient (Braveman et al., 2011; Krieger et al., 1997); if possible, they should be disentangled, rather than interchanged, in order to better understand their particular contribution to POP concentrations (Geyer et al., 2006; Morrens et al., 2012). The present study is one of the first to determine the individual and combined effects of social class and educational level on POP concentrations in a representative sample of the general population.

There is scant research on the association between indicators of socioeconomic position and body concentrations of POPs in the general healthy population. Important examples can be found in the German (Becker et al., 2002; Umweltbundesamt, 1985-2006) and U.S. (Department of Health and Human Services, 2009; Patterson et al., 2009) studies; the former analysed such concentrations by socioeconomic status, whereas the latter did so by ethnic groups. Analyses of possible reasons for the associations are even scarcer. Thus, GerEs studies only reported that education, level of income and social status did not significantly influence the exposure of the participants, and other studies in the general population are largely descriptive. Neither income nor education was associated with body concentrations of DDE in a group of New York inner-city African-American pregnant women (N = 152) (L.N. Borrell et al., 2004); income was positively associated with concentrations of PCBs, while education was not. Similar to the adjusted positive associations with educational level found in men in the present study, a study of Flemish adolescents found higher levels of PCBs, HCB and *p,p′*-DDE among participants of higher socioeconomic status (both in crude and adjusted analyses). The authors stated that socially constructed factors, as dietary and lifestyle habits, may play an important role in these relationships (Morrens et al., 2012). Dietary information was not available in our study, but tobacco, alcohol and physical activity were not mediators of the observed relationships. In Spain, the few studies that assessed such relationships included specific populations (Agudo et al., 2009; Jakszyn et al., 2009; Porta et al., 2008a; Zubero et al., 2009) or vulnerable subgroups (Freire et al., 2011; Vrijheid et al., 2012). In Southern Spain, women in social class IV had higher concentrations of HCB than women in classes I–II, and *p,p′*-DDT was higher in classes III and IV than in classes I–II (Freire et al., 2011). In another study of 2081 pregnant women from three Spanish regions, levels of PCBs and HCB were higher in the uppermost classes and educated groups (after adjusting by age, BMI and other factors), while *p,p′*-DDE and β-HCH were not related to social class, nor to education (Vrijheid et al., 2012). Differences among studies could be due to type of sample (placentas (Freire et al., 2011) and serum (Vrijheid et al., 2012, and the present study)), participants (pregnant women (L.N. Borrell et al., 2004; Vrijheid et al., 2012) and a representative sample in our case), place, or pathways of exposure.

In the majority of the general population – which is not occupationally exposed to POPs during significant amounts of time and relevant periods of life – exposure occurs largely through dietary intake, mostly from the fatty components of animal foods (Gasull et al., 2011). Diet patterns commonly differ by age, social class and education (León-Muñoz et al., 2012; López-Azpiazu et al., 2003; Mesas et al., 2012;); social groups may even differ in fat intake (López-Azpiazu et al., 2003), which can be presumed to increase risk of POP exposure. However, it has seldom been tested whether concentrations of POPs and other environmental chemicals differ among such diet patterns.

Surprisingly, positive associations emerged – in men but not in women – between education and POP concentrations after adjusting for age and BMI; i.e., men with higher education had higher levels of PCBs 118 and 180, HCB and β-HCH. This is not obviously explained by dietary patterns in the more educated individuals (León-Muñoz et al., 2012; Mesas et al., 2012). In addition to reasons suggested above, the absence of clear patterns of relationships between blood concentrations of POPs and social class and education may fundamentally be due to the widespread, chronic (lifelong), and largely invisible contamination of human food webs. With few exceptions (Lu et al., 2006; Vrijheid et al., 2012), POPs have not been documented to contaminate more or less the types of foods preferentially consumed by certain socioeconomic groups. However, there is a deep lack of knowledge on this issue: while extensive data show social patterns in food consumption (León-Muñoz et al., 2012; Mesas et al., 2012), little research has connected such evidence with knowledge on socioeconomic patterns of food contamination by POPs and other chemicals. Furthermore, in most countries – and certainly in Southern Europe – awareness of exposure to and contamination from environmental chemical agents as POPs is uncommon, even among groups in the upper socioeconomic positions, whom otherwise try to avoid other – culturally more visible – environmental and lifestyle hazards (e.g., industrial pollution, tobacco, sedentarism).

The Catalan Nutritional Survey (ENCAT) found that the Catalan population had little self-perceived knowledge about the health risks of

dioxins and pesticides (Serra Majem et al., 2006). In the study by Vrijheid et al. (2012), fish intake (which was related to higher body levels of PCBs) was lower among the less affluent class. A cross-sectional study conducted among 11,742 individuals representative of the Spanish population aged ≥18 years found that accordance with the Mediterranean diet (MD) was less frequent (and a less healthy Westernized pattern (WP) more frequent) among the younger, the less educated, and those more sedentary (León-Muñoz et al., 2012). It would thus be important to test – in Spain and elsewhere – whether concentrations of POPs are significantly higher in the main food constituents of the MD or of the WP patterns (and in estimates of each pattern overall), whether long-term adherence to MD and to WP influences body concentrations of POPs, and whether such differences, if any, influence health status in adulthood. After adjusting for sex, age, BMI, energy intake, level of education, tobacco smoking, physical activity, and time watching TV, older age was still strongly associated with higher MD accordance (León-Muñoz et al., 2012). Thus, factors other than the above-mentioned characteristics and lifestyles account for the better MD adherence in older adults. It is possible that older people simply maintain traditional dietary habits acquired in infancy; it is also easier for them to eat at home (León-Muñoz et al., 2012). The same study also found that obesity-related eating behaviours were more prevalent in groups with lower education (Mesas et al., 2012). European surveys indicate that people in the lowest categories of occupation have a higher intake of total fat and of saturated fat than people in the highest category (López-Azpiazu et al., 2003).

Analyses were reported for women and men separately for four main reasons: a) women, especially the oldest, had a lower educational level than men; b) potential confounders were associated with sex; c) concentrations of POPs often differ between sexes (Porta et al., 2010); and d) to integrate a gender perspective (Rohlfs et al., 2000). Other study strengths include the large sample size, the population-based design, the assessment of multiple pollutants of public health relevance, the evaluation of the individual-based relationship between socioeconomic position indicators and body concentrations of POPs, the "dominance approach" used to assign social class, the measure of education in terms of credentials rather than simply years of education (Bonefeld-Jorgensen, 2010), and the combination of the two socioeconomic position indicators in the assessment of human contamination by POPs.

Using the "dominance approach" instead of the "conventional approach", in which only single women retained their own social class in detriment of their husband's when married, may have contributed to avoid underestimation of social class differences in health among women. The attribution of the highest social class of the household assumes that all members of the house share the same economic interests (Sorensen, 1994) regardless of gender (Krieger et al., 1997). Thus, this approach is commonly known as "gender-blind" (Borrell et al., 2004b). Income was not registered in CHIS. However, there commonly exists a positive relationship between the mean household income and level of education, and a connection of social class with education and income. Information on diet and lactation were not available in CHIS.

5. Conclusions

Crude (unadjusted) concentrations were higher in women and men with lower education, and in women, but not men, in the less affluent social class. Educational level influenced blood concentrations of POPs more than occupational social class, especially in men. In women, POP concentrations were mainly explained by age/birth cohort, BMI and parity. In men, while concentrations were also mainly explained by age/birth cohort and BMI, social class showed some positive associations (higher POP levels in upper socioeconomic groups). Important characteristics of socioeconomic groups as age and BMI may largely explain crude differences among such groups in internal contamination by POPs. The absence of clear patterns of relationships between blood concentrations of POPs and indicators of socioeconomic position may fundamentally be due to the widespread, lifelong, and generally invisible contamination of human food webs. Longitudinal studies measuring changes during critical life periods in POP levels and in socioeconomic position could be more able to capture social influences on human exposure to POPs. Decreasing historical trends may also partly explain crude socioeconomic differences apparently due to birth cohort effects. To assess such scenarios it is essential that knowledge and methods from the environmental, health and social sciences become more deeply integrated in innovative studies.

Conflicts of interest

The authors declare they have no competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2013.08.001.

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Supplementary Material

Relative effects of occupational social class and educational level on body concentrations of persistent organic pollutants in a representative sample of the general population of Catalonia, Spain

TABLE OF CONTENTS

1. Supplementary Material, Other results

1.1. Physical activity, tobacco and alcohol consumption

In men, a higher level of physical activity was more frequent in the less affluent social classes than in the upper classes. When correlation coefficients were adjusted by age, physical activity was slightly inversely associated to both social class (rho = −0.163, p-value = 0.001) and to level of education (rho = −0.116, p-value = 0.024). Tobacco and alcohol consumption were not related to social class and educational level in men. In women, physical activity was not related to social class and educational level. Tobacco and alcohol consumption were positively associated with social class and educational level; however, when adjusted by age, only alcohol consumption remained associated with educational level in women (rho = 0.186, p-value <0.001).

Models adjusted by age and body mass index (BMI) showed that men with a high level of physical activity had lower concentrations of PCBs 118, 138, 153, HCB and *β*-HCH than sedentary men. Men with moderate physical activity and women with light physical activity had higher concentrations of PCB 180 than sedentary subjects, when adjusting by age, BMI and parity (in women). In men, adjusted models showed that current smokers had lower concentrations of PCB 118, HCB and *β*-HCH than never smokers, and former smokers had lower concentrations of *p,p'*-DDE and *β*-HCH than never smokers. In women, models adjusted by age, BMI and parity showed that current smokers had lower *p,p'*-DDT concentrations than never smokers, and that women with moderate alcohol consumption had higher concentrations of PCBs 138, 153 and 180 than women non-drinkers.

In spite of the above mentioned associations, including physical activity, tobacco or alcohol consumption in models did not change the results about the relationship between POP concentrations and social class or educational level.

1.2. Affinity / discrepancy or distance between social class and educational level

We assessed the affinity/discrepancy or distance between social class and educational level as follows: we calculated the difference between social class classified in 5 categories (I; II; III; IVa and IVb; V) and educational level, also in 5 categories, thus producing a value that could range between −4 (when an individual was in social class V and had university studies) and 4 (when an individual was in social class I and without formal studies (WFE)); however, the actual maximum value was 3 (i.e., no subject was in social class I and WFE).

The variable was divided in 3 categories: without discrepancy (from −1 to 1); unfavorable occupational social class with respect to the educational level (from −4 to −2) (lower social class than education; e.g., individuals in social class III or IV and with university studies); favorable social class with respect to the educational level (from 2 to 3) (higher social class than education; e.g., individuals in social class I and with primary schooling). 80.8 % of the participants were classified in the reference category (no discrepancy), 11.2% in unfavorable social class vs. education, and 8% in favorable social class vs. education. The level of discrepancy was related to age: individuals born between 1973 and 1984 were more unfavored (50% had values ≤ −1) than individuals born between 1928 and 1942 (50% had values ≥ 1). The level of discrepancy was also related to BMI: individuals with higher BMI had more favorable social class with respect to their educational level.

Most models adjusted by age, BMI and parity (in women) did not show associations between POP concentrations and the level of discrepancy between social class and education, either divided in 3 categories or as a continuous variable. However, men with favorable social class vs. education had lower PCB 153 concentrations than men without discrepancy between class and education ($p = 0.026$); and women with unfavorable class vs. education had higher concentrations of *p,p'*-DDT, PCBs 118 and 153 than women without discrepancy.

Supplemental Material, Table 1. Main sociodemographic characteristics of participants, by education (in women and men).

		Educational level					
	Total	**WFE**	**Primary (I)[a]**	**Primary (II)[b]**	**Secondary**	**University**	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	*p*-value
Women							
Total	518 (99.6)	86 (16.6)	139 (26.8)	129 (24.9)	98 (18.9)	66 (12.7)	
Age (years)							
Mean ± SD	44.4 ± 15.0	59.5 ± 10.9	49.5 ± 13.3	40.2 ± 12.4	35.3 ± 13.2	35.6 ± 10.3	<0.001[c]
Median	44.0	60.0	50.0	41.0	34.0	37.0	<0.001[d]
Min – Max	18 - 74	21 - 74	18 - 74	18 - 67	18 - 69	21 - 72	
BMI[e] (Kg/m^2)							
Mean ± SD	25.9 ± 4.9	28.4 ± 5.6	27.1 ± 5.0	25.6 ± 4.7	23.9 ± 3.8	23.9 ± 3.6	0.001[c]
Median	25.0	27.5	26.3	24.6	23.0	23.3	<0.001[d]
Social class							
V	34 (6.7)	12 (15.0)	14 (10.4)	4 (3.1)	1 (1.0)	3 (4.5)	<0.001[f]
IVb	36 (7.1)	7 (8.8)	8 (5.9)	12 (9.4)	7 (7.2)	2 (3.0)	
IVa	172 (34.1)	40 (50.0)	68 (50.4)	48 (37.8)	14 (14.4)	2 (3.0)	
III	138 (27.3)	19 (23.8)	34 (25.2)	33 (26.0)	39 (40.2)	13 (19.7)	
II	71 (14.1)	2 (2.5)	7 (5.2)	19 (15.0)	23 (23.7)	20 (30.3)	
I	54 (10.7)	0 (0.0)	4 (3.0)	11 (8.7)	13 (13.4)	26 (39.4)	
Parity							
Nulliparity	138 (27.0)	6 (7.0)	16 (11.8)	33 (25.8)	45 (46.9)	38 (58.5)	<0.001[f]
≥1 deliveries	373 (73.0)	80 (93.0)	120 (88.2)	95 (74.2)	51 (53.1)	27 (41.5)	
GM[g]	5.1	5.4	5.5	5.7	4.7	3.6	
Men							
Total	394 (98.7)	54 (13.7)	103 (26.1)	98 (24.9)	94 (23.9)	45 (11.4)	
Age (years)							
Mean ± SD	46.2 ± 15.0	58.3 ± 11.7	52.6 ± 12.5	40.7 ± 15.1	40.0 ± 12.9	42.2 ± 13.8	0.133[c]
Median	46.5	59.5	55.0	39.0	39.5	40.0	<0.001[d]
Min – Max	18 - 74	28 - 74	18 - 74	18 - 74	18 - 70	20 - 71	
BMI[e] (Kg/m^2)							
Mean ± SD	27.0 ± 4.1	27.8 ± 3.6	27.8 ± 4.0	26.3 ± 3.9	26.4 ± 4.7	26.9 ± 3.6	0.147[c]
Median	26.6	27.2	27.1	25.9	25.6	26.5	0.004[d]
Social class							
V	26 (6.6)	5 (9.3)	9 (8.8)	7 (7.2)	5 (5.3)	0 (0.0)	<0.001[f]
IVb	41 (10.5)	8 (14.8)	11 (10.8)	14 (14.4)	8 (8.5)	0 (0.0)	
IVa	129 (33.0)	25 (46.3)	49 (48.0)	31 (32.0)	21 (22.3)	3 (6.8)	
III	115 (29.4)	15 (27.8)	24 (23.5)	30 (30.9)	36 (38.3)	10 (22.7)	
II	47 (12.0)	1 (1.9)	6 (5.9)	11 (11.3)	16 (17.0)	13 (29.5)	
I	33 (8.4)	0 (0.0)	3 (2.9)	4 (4.1)	8 (8.5)	18 (40.9)	

[a] Primary schooling (1st stage). [b] Primary schooling (2nd stage). [c] ANOVA. [d] Kruskal-Wallis' test. [e] BMI: Body Mass Index. [f] Fisher's exact test (two-tail). [g] GM, geometric mean adjusted for age (only for women with ≥1 deliveries).

Supplemental Material, Table 2. Influence of occupational social class on concentrations (ng/g lipid) of organochlorine compounds, in women (N=507) and men (N=395).

Compound	Women		Men	
	GM	(95% CI)	GM	(95% CI)
1. *p,p'*-DDT				
Class I	24.9	(17.7-34.9)	22.1	(14.2-34.4)
Class II	24.5	(18.3-32.7)	24.2	(16.6-35.1)
Class III	29.0	(23.5-35.7)	24.1	(19.0-30.5)
Class IVa	25.9	(21.4-31.3)	22.3	(17.9-27.8)
Class IVb	30.3	(20.0-45.8)	21.1	(14.2-31.3)
Class V	30.4	(19.9-46.6)	20.8	(12.6-34.2)
2. *p,p'*-DDE				
Class I	488.8	(394.1-606.2)	315.8	(230.9-431.9)
Class II	509.4	(423.7-612.6)	417.4	(320.6-543.5)
Class III	519.6	(454.8-593.7)	415.4	(351.3-491.2)
Class IVa	464.5	(412.2-523.4)	382.8	(327.3-447.7)
Class IVb	540.1	(415.6-701.9)	390.5	(294.8-517.2)
Class V	616.9	(471.2-807.8)	563.0	(395.4-801.6)*
3. HCB				
Class I	217.1	(176.7-266.9)	156.9	(112.9-218.0)
Class II	281.7	(236.1-336.1)	127.5	(96.6-168.3)
Class III	262.6	(231.1-298.3)	120.6	(101.1-143.8)
Class IVa	256.3	(228.6-287.3)	103.3	(87.6-121.8)*
Class IVb	245.8	(191.2-315.9)	85.3	(63.5-114.6)*
Class V	225.9	(174.5-292.4)	111.9	(77.2-162.2)
4. *β*-HCH				
Class I	120.0	(95.6-150.5)	95.9	(68.5-134.4)
Class II	149.2	(122.9-181.2)	77.6	(58.4-103.1)
Class III	131.7	(114.5-151.6)	72.1	(60.2-86.4)
Class IVa	131.6	(116.1-149.3)	73.3	(61.9-86.8)
Class IVb	123.9	(94.0-163.4)	74.4	(55.0-100.7)
Class V	103.6	(77.9-137.6)	70.8	(48.4-103.7)
5. PCB 118				
Class I	15.5	(11.6-20.7)	16.0	(10.5-24.4)
Class II	17.6	(13.8-22.5)	22.1	(15.5-31.5)
Class III	20.3	(17.0-24.3)	14.7	(11.8-18.5)
Class IVa	16.7	(14.3-19.6)	14.6	(11.9-18.0)
Class IVb	21.8	(15.3-30.9)	12.6	(8.6-18.3)
Class V	17.9	(12.5-25.7)	12.4	(7.7-20.0)

GM, geometric mean adjusted by age and BMI. In women, further adjusted by parity.
* *p*-value<0.05. The reference category is social class I. In men, *p*-trend for *p,p'*-DDE, HCB and PCB 118 was 0.161, 0.009 and 0.067, respectively.

[Continued next page]

Supplemental Material, Table 2 (Continued)

Compound	Women		Men	
	GM	(95% CI)	GM	(95% CI)
6. PCB 138				
Class I	62.7	(49.7-79.1)	63.9	(47.1-86.6)
Class II	70.7	(57.9-86.2)	66.1	(51.1-85.4)
Class III	68.3	(59.1-78.8)	64.9	(55.1-76.4)
Class IVa	58.0	(51.0-65.9)	69.4	(59.6-80.9)
Class IVb	75.5	(56.9-100.2)	67.5	(51.4-88.7)
Class V	79.8	(59.7-106.8)	55.7	(39.5-78.5)
7. PCB 153				
Class I	85.8	(69.0-106.7)	100.0	(74.7-133.8)
Class II	97.3	(80.7-117.3)	96.3	(75.3-123.2)
Class III	95.5	(83.4-109.3)	94.7	(81.0-110.8)
Class IVa	83.3	(73.8-94.1)	106.1	(91.7-122.8)
Class IVb	106.6	(81.8-139.1)	98.7	(76.0-128.3)
Class V	102.6	(78.1-134.8)	84.4	(60.7-117.3)
8. PCB 180				
Class I	70.8	(60.1-83.3)	90.6	(73.5-111.6)
Class II	80.1	(69.6-92.1)	95.7	(80.3-114.1)
Class III	80.0	(72.3-88.4)	92.0	(82.3-102.9)
Class IVa	71.1	(65.0-77.9)	92.3	(83.1-102.4)
Class IVb	82.4	(67.6-100.5)	97.2	(80.6-117.3)
Class V	85.9	(70.0-105.3)	81.0	(64.0-102.5)
9. Sum of PCBs				
Class I	247.1	(207.3-294.6)	285.7	(229.0-356.4)
Class II	283.8	(244.1-329.9)	305.3	(253.4-368.0)
Class III	281.6	(252.6-314.0)	285.5	(253.6-321.4)
Class IVa	240.7	(218.3-265.3)	295.1	(264.2-329.7)
Class IVb	297.9	(240.5-369.0)	297.8	(244.2-363.2)
Class V	305.5	(245.1-380.7)	255.9	(199.4-328.5)

GM, geometric mean adjusted by age and BMI. In women, further adjusted by parity.

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Number of persistent organic pollutants detected at high concentrations in a general population

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ABSTRACT

Background: Surveys of human exposure to environmental chemicals do not integrate the number of compounds detected per person and the concentration of each compound. This leaves untested relevant exposure scenarios, such as whether individuals with low concentrations of some compounds have high concentrations of the other compounds.
Objective: To analyze the number of persistent organic pollutants (POPs) detected at high concentrations.
Methods: Serum concentrations of 19 POPs were analyzed by gas chromatography with electron-capture detection in a representative sample of the general population of Catalonia, Spain (N = 919).
Results: Over 58% of participants had concentrations in the top quartile of ≥1 of the eight most prevalent POPs, and 34% of ≥3 POPs. 83% of women 60 to 74 years old had concentrations of ≥3 POPs in the top quartile; 56% of women 60 to 74 years had *p,p′*-DDE, HCB and β-HCH all in their respective top quartiles, and 48% had concentrations of ≥6 POPs in the top quartile. Over 30% of subjects had concentrations in the top decile of 1 to 5 of the eight most prevalent POPs. Half of the population had levels of 1 to 5 POPs >500 ng/g. Less than 4% had all eight POPs in the lowest quartile.
Conclusions: More than half of the study population had concentrations in the top quartile of ≥1 POPs. Significant subgroups of the population accumulate POP mixtures at high concentrations. POP concentrations appear low in most of the population only when each individual compound is looked at separately.

1. Introduction

Studies monitoring human exposure to persistent organic pollutants (POPs) and other environmental chemical agents have traditionally addressed with difficulties the well-known fact that populations are contaminated by mixtures of chemicals at very different concentrations; in particular, analyses of the population distribution of the concentrations of a given compound usually show that most citizens have much lower concentrations than a certain minority (DHHS, 2009; Health Canada, 2010; NRC, 2006; Patterson et al., 2009; Porta et al., 2008, 2010; Thornton et al., 2002). It is indeed important to assess the full population distribution of the concentrations of environmental chemicals and, as also recommended by a committee from the National Research Council, the number of chemicals detected per person (NRC, 2006). Yet, biomonitoring studies commonly report separately the number of compounds detected per person (if at all), and the concentration of each individual compound (DHHS, 2009; Health Canada, 2010; Patterson et al., 2009; Porta et al., 2008, 2010; Thornton et al., 2002; Woodruff et al., 2011). Reasonably, the emphasis is usually on the latter: the number of compounds detected per person may be misleading, since it does not account for the corresponding concentrations, among other reasons. Yet, the analysis of the concentrations chemical-by-chemical does not tackle adequately the accumulation of multiple chemicals (Gladen et al., 2003; Kortenkamp et al., 2009; Porta et al., 2008, in press). Combination effects may result from pollutants each of which produces small effects, if they are present in sufficiently large numbers. The existence of mixture effects (e.g., additive, synergistic, antagonistic) depends on the number of contaminants in the mixture, their respective concentrations, and the concentration–response curves. Two crucial factors for combination effects to occur are the number of chemicals and their concentrations (Kortenkamp et al., 2009; NRC, 2008).

So far, population surveys of human exposure to chemicals have not attempted to arithmetically integrate the two types of indicators — number of compounds detected per person and concentration of each

Abbreviations: BMI, body mass index; CHIS, Catalan Health Interview Survey; CI, confidence interval; DDD, dichlorodiphenyldichloroethane; DDE, dichlorodiphenyldichloroethene; DDT, dichlorodiphenyltrichloroethane; GM, geometric mean; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; PCBs, polychlorinated biphenyls; PeCB, pentachlorobenzene; POPs, persistent organic pollutants; TL, total serum lipids.

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compound. This gap hinders exposure assessment and leaves untested a relevant question (with two reciprocal dimensions): in a given population, *a)* do all individuals who have low concentrations of some compounds have low concentrations of the other compounds detected, and all individuals with high concentrations of some compounds have high concentrations of the other compounds detected? or *b)* do some individuals who have low concentrations of some compounds have high concentrations of the other compounds detected and, therefore, some individuals with high concentrations of some compounds have low concentrations of the other compounds detected? Here, we develop and apply some new indicators – notably, the 'number of chemicals detected at high concentrations' – and show that the answer is *b)*.

2. Materials and methods

2.1. Study population

The study population was described in detail elsewhere (DSGC, 2004; Porta et al., 2009, 2010). Briefly, participants in the Catalan Health Interview Survey (CHIS) aged 18–74 years old were offered to take part in a health examination, which included a physical exam, a supplementary interview, and the collection of urine and blood samples. A total of 1374 individuals – who gave specific written informed consent – participated during 2002 in the health examination. Trained nurses recorded the weight and height, and the corresponding Body Mass Index (BMI) was computed (Porta et al., 2010). Participants were asked to fast for 12 h before blood extraction. Information on blood lipids and ≥1 mL of serum (for organochlorine analyses) was available from 919 participants. There were no significant differences between these 919 subjects and the remaining participants in the health examination with respect to age, sex, BMI, and education (Porta et al., 2010). Sociodemographic variables (sex, age, educational level, occupational social class, birth place) were obtained from the CHIS interview. The lower educational category of subjects without formal studies included the illiterate. The occupational social class was based on Goldthorpe's scheme (Porta et al., 2009); class was hence assigned through the current or last occupation of the head of the household, whom in 46.3% of cases was the participant himself. The classification includes 5 well-established main social groups: I, Managers of companies with ≥10 employees, senior technical staff, free professionals; II, Managers of companies with <10 employees, intermediate occupations; III, Administrative personnel and financial management supporting professionals, self employed professionals, supervisors of manual workers, other skilled non-manual workers; IV, Skilled and partly skilled manual workers; and V, Unskilled manual workers.

2.2. Analytical chemical methods

Laboratory methods have previously been described (DSGC, 2004; Porta et al., 2009, 2010). The following 19 POPs were analyzed in serum: *o,p′*-DDT, *p,p′*-DDT, *o,p′*-DDE, *p,p′*-DDE, *o,p′*-DDD, *p,p′*-DDD, PeCB, HCB, α-HCH, β-HCH, γ-HCH and δ-HCH; and PCB congeners 28, 52, 101, 118, 138, 153, and 180. Gas chromatography analyses were performed with an Agilent Technologies model GC-6890N provided with an electron-capture detection and a 60 m, 0.25 mm i.d. DB-5 column (film thickness 0.25 μm). Analyses were carried out in the Department of Environmental Chemistry (IIQAB-CSIC) in Barcelona, Spain. Limits of detection and quantification ranged from 0.0023 ng/mL and 0.0069 ng/mL, respectively, for PCB 101, to 0.0235 ng/mL and 0.0706 ng/mL, respectively, for γ-HCH; they were 0.0156 ng/mL and 0.0468 ng/mL for *p,p′*-DDE, 0.0135 ng/mL and 0.0406 ng/mL for PCB 138, and 0.0111 ng/mL and 0.0334 ng/mL for HCB (Porta et al., 2009). When a sample had a concentration of a compound below the detection threshold, it was assigned the mid-value of this limit; when a POP was detected but under the quantification threshold, the mid-value between detection and quantification limits was used (Porta et al., 2009, 2010). Eight of the 19 POPs analyzed were detected (each) in >85% of subjects: four organochlorine pesticides or related compounds (*p,p′*-DDT, *p,p′*-DDE, HCB, β-HCH), and four PCBs (congeners 118, 138, 153 and 180). Thus, these eight are the most common or prevalent POPs, while the other eleven are the least prevalent POPs; the percentage of detection for the eleven compounds ranged between 12% and 64%. Therefore, all 19 POPs were detected in the study sample; the smallest number of POPs detected in one person was 3, and the largest, 19. Ten or more compounds were detected in 73% of the population (Porta et al., 2009, 2010). Total cholesterol and triglyceride levels were determined enzymatically, using serum obtained in the health examination (DSGC, 2004). Total serum lipids (TL) were calculated by the Standard formula 2, based on total cholesterol and triglycerides (Bernert et al., 2007). POP concentrations were individually corrected for TL by dividing the crude serum POP concentration by TL.

2.3. Statistical analyses

We created the variable 'number of POPs at high concentrations' as follows: for each subject we added the number of POPs whose serum concentrations were equal to or greater than a selected cutoff point. To be conservative, in the main analyses we included only the eight POPs that had been detected (each) in >85% of the study subjects. Thus, values of the variable 'number of POPs at high concentrations' ranged between 0 and 8. Ancillary analyses included compounds detected in >25% of subjects. Finally, other analyses included all 19 POPs, with quartiles defined after imputing values to non-detects and to compounds detected but not quantified (see Supplemental material, p. 2).

We used two types of definitions of 'high concentrations' based on two types of cutoff points:

a) Compound- and population-specific percentiles, based on the POP distributions previously published (Porta et al., 2010); for the main statistical analyses the main cutoff point selected was percentile 75 (the upper quartile).
b) A particular serum concentration, applied to all compounds (e.g., 250 ng/g, 500 ng/g); such level can be considered high in different populations (e.g., the 95th percentile for a prevalent compound in the U.S. general population).

To calculate the sum of orders or sum of category ranking of the eight most prevalent POPs, each POP was categorized in quartiles and the category number of each POP was summed, producing a value ranging between eight (when the eight POPs had concentrations in the lowest quartile) and 32 (when the eight POPs had concentrations in the top quartile).

Univariate statistics were computed as customary (Porta et al., 2010). The highest correlations were observed between PCB congeners 138 and 153, 153 and 180, 138 and 180, and HCB and β-HCH (all Spearman's $\rho > 0.8$ and $p < 0.001$) (Porta et al., 2010). The percentage of participants with concentrations in the top quartile of ≥1 POPs is positively influenced by the number of compounds considered, and inversely influenced by the magnitude of the correlations between the pairs of compounds (see Supplemental material, p. 2 and Fig. 1). For comparisons between continuous variables, Student's *t* test and Mann–Whitney's *U* tests were used. When a tendency was observed, the Jonckheere–Terpstra test for linear trend was used. The level of statistical significance was set at 0.05 and all tests are two tailed.

3. Results

Over 58% of the 919 participants had concentrations of ≥1 of the eight most prevalent POPs equal to or greater than percentile 75 (Table 1), while 43.7% had ≥2 POPs, and 33.9% had ≥3 POPs in such top quartile (36.7% of women and 30.3% of men). One in five subjects had concentrations of two PCBs in the upper quartile; e.g., 21.9% of

participants had both PCB 138 and PCB 153 in their respective upper quartiles. Simultaneous high concentrations of PCBs 138, 153 and 180 (i.e., all three congeners in their respective upper quartile) were observed in 18.4% of subjects; and of *p,p′*-DDE, HCB and β-HCH, in 13.4%. There was substantial mixture of the two chemical classes at high concentrations: 74.1% of subjects with concentrations of ≥1 of the four PCBs in the upper quartile also had ≥1 of the four pesticides in the upper quartile, and 58.2% of subjects with concentrations of ≥1 of the four pesticides in the upper quartile also had ≥1 of the four PCBs in the upper quartile.

The proportion of women, subjects over 44 years old, and obese individuals was higher in participants with concentrations of ≥1 of the eight most prevalent POPs in the upper quartile than in participants without any of such compounds at high concentrations (all $p<0.001$, except for sex, $p=0.121$). There were also statistically significant differences between the two groups by occupational social class, educational level and birth place (all $p<0.01$) (Table 1).

Of the 538 subjects with high concentrations of ≥1 of the most prevalent POPs, 25% had only one POP at high concentrations, while 30% had 5 or more POPs at such levels (see Supplemental material, Table 1). There were significant differences in the number of the most prevalent POPs with high concentrations by sex, age, BMI and occupational social class (all $p<0.015$). 78.5% of women with high concentrations of at least one of the most common POPs had ≥2 compounds at high concentrations, whereas for men this percentage was 69.4%. The number of POPs at high concentrations showed a positive linear relation with age and with BMI (both p for trend <0.001). Among subjects with high concentrations of ≥1 of the most prevalent POPs, 66.1% of subjects with normal weight, 76.3% of subjects overweight and 83.2% of obese subjects had ≥2 POPs with concentrations in the upper quartile. 7.5% of subjects of the less affluent occupational social class (V) had all eight most prevalent POPs at high concentrations, while none of the participants of the most affluent class (I) had all such POPs at high levels (see Supplemental material, Table 1). Significant differences in the number of most prevalent POPs at high concentrations were also found for parity, educational level, birth place and area of residence (results not shown).

Ten or more of the 19 POPs analyzed were detected in 73% of the individuals; this percentage was 79.9% in participants with high concentrations of at least one of the most prevalent POPs, and 63.3% in subjects without any of such POPs at high concentrations. In general, the percentage of participants with ≥1 of the most prevalent POPs in the upper quartile was greater in subjects with a higher number of compounds detected, but the relationship was not linear: 31% of subjects in whom 7 compounds were detected had at least one of the eight most prevalent POPs in the top quartile; the corresponding percentages among subjects with 10, 13, 14 and 16 compounds detected were 54%, 77%, 64% and 70%, respectively (see Supplemental material, Fig. 2).

The 11 least prevalent POPs also commonly contaminated subjects with high levels of the eight most prevalent POPs: as compared to participants without any of the eight most prevalent POPs at high concentrations, participants with high concentrations of ≥1 of the eight most prevalent POPs also had higher percentages of detection of 9 of the 11 least prevalent POPs, differences being statistically significant for *o,p′*-DDT, *p,p′*-DDD, PeCB and α-HCH (see Supplemental material, Table 2). 74.9% of subjects with high concentrations of ≥1 of the most prevalent POPs had between 1 and 6 of the least prevalent POPs detected; and 15.6% had 7 or more. *o,p′*-DDT was detected in 65.2% of participants who also had simultaneous high concentrations of PCBs 138 and 153, and in 73.8% of participants with simultaneous high concentrations of both HCB and β-HCH.

Fig. 1 shows the number of POPs with concentrations in the upper quartile by age and sex groups. The proportion of subjects with concentrations of ≥1 of the eight most common POPs in the top quartile increased from over 20% among the 18–29 year-olds, to over 60% and 80% for men and women 45 to 59 years old, respectively, and to over 80% among 60 to 74 year old subjects. The largest differences between women and men were seen in the oldest group, in which 95% of women had high concentrations of ≥1 of the most prevalent POPs, and 48.4% had high concentrations of ≥6 such POPs; the corresponding percentages for men were 85% and 25%, respectively (Fig. 1). 55.8% of women 60 to 74 years old had high concentrations of *p,p′*-DDE, HCB and β-HCH simultaneously, and 53.7% of PCB 118, HCB and β-HCH.

Results obtained by alternative definitions of 'high concentration' are shown in Table 2. Over 30% of subjects had concentrations in the top decile of 1 to 5 of the eight most prevalent POPs. 49.5% of the population had concentrations greater than 500 ng/g of 1 to 5 of the eight POPs. The geometric mean of the number of prevalent POPs at high concentrations ranged only from 2.7 for percentile 75 to 2.0 for percentile 90 (Table 2).

The sum of orders for the eight most prevalent POPs was eight in only 3.8% of the subjects; i.e., less than 4% of subjects had concentrations of all eight POPs in the lowest quartile. Among participants with ≥3 POPs in the top quartile, 26.3% were not in the top quartile of the sum of orders. 20.3% of participants had concentrations of ≥1 POPs in the top quartile and simultaneously concentrations of ≥1 POPs in the lowest quartile. This 'discordance' was inversely associated to BMI (adjusted by age and sex): participants with a lower BMI were more likely to have POPs in the upper and lower quartiles simultaneously (p for trend = 0.019); subjects with higher BMI tended to have concentrations of virtually all POPs in the upper and middle quartiles.

We next considered the 13 POPs that had been detected in >25% of subjects (the eight most prevalent POPs and *o,p′*-DDT, *o,p′*-DDD, *p,p′*-DDD, δ-HCH and γ-HCH): 82.9% of the participants had concentrations of ≥1 of these POPs in the upper quartile, and 68.2% had ≥2. When we considered all 19 POPs analyzed in the study, the corresponding percentages increased to 89.4% and to 80.6%, respectively.

Table 1
Main characteristics of subjects with and without serum concentrations in the upper quartile of one or more of the eight most prevalent POPs analyzed.

Characteristics	Total	Concentrations of ≥1 of the most prevalent POPs in the upper quartile		
		Yes	No	*p* value
	N (%)	N (%)	N (%)	
All participants	919	538 (58.5)	381 (41.5)	
Sex				
Men	399 (43.4)	222 (41.3)	177 (46.5)	0.121[a]
Women	520 (56.6)	316 (58.7)	204 (53.5)	
Age (years)				
Mean ± SD	45.2 ± 15.0	51.7 ± 13.6	36.1 ± 12.0	<0.001[b]
Median	45.0	53.0	36.0	<0.001[c]
18–29	175 (19.0)	43 (8.0)	132 (34.6)	<0.001[d]
30–44	272 (29.6)	113 (21.0)	159 (41.7)	
45–59	288 (31.4)	214 (39.8)	74 (19.4)	
60–74	184 (20.0)	168 (31.2)	16 (4.2)	
BMI (kg/m^2)				
Mean ± SD	26.4 ± 4.6	27.3 ± 4.8	25.1 ± 3.9	<0.001[b]
Median	25.9	26.7	24.6	<0.001[c]
Normal range (18.5–24.9)	381 (41.5)	177 (32.9)	204 (53.5)	<0.001[d]
Overweight (25.0–29.9)	348 (37.9)	219 (40.7)	129 (33.9)	
Obese (≥30)	180 (19.6)	137 (25.5)	43 (11.3)	
Occupational social class[e]				
V (less affluent)	75 (8.4)	53 (10.2)	22 (5.9)	0.003[a]
IV	420 (47.1)	236 (45.6)	184 (49.2)	
III	229 (25.7)	147 (28.4)	82 (21.9)	
II	94 (10.5)	49 (9.5)	45 (12.0)	
I (most affluent)	74 (8.3)	33 (6.4)	41 (11.0)	
Educational level[f]				
Without formal studies	140 (15.4)	122 (22.8)	18 (4.8)	<0.001[d]
Primary schooling (1st stage)	242 (26.5)	161 (30.1)	81 (21.4)	
Primary schooling (2nd stage)	227 (24.9)	109 (20.4)	118 (31.2)	
Secondary	192 (21.1)	87 (16.3)	105 (27.8)	
University	111 (12.2)	55 (10.3)	56 (14.8)	
Birth place				
Catalonia	656 (71.8)	358 (66.8)	298 (78.8)	<0.001[a]
Rest of Spain	231 (25.3)	163 (30.4)	68 (18.0)	
Other	27 (3.0)	15 (2.8)	12 (3.2)	

[a] Fisher's exact test (two-tail).
[b] Student's *t*-test (two-tailed).
[c] Mann–Whitney's *U* test (two-tailed).
[d] Mantel–Haenszel's χ^2 test for linear trend.
[e] Assigned through the current or last occupation of the head of the household.
[f] Primary schooling (1st stage): elementary not completed; Primary schooling (2nd stage): elementary completed.

4. Discussion

More than half of the study population had concentrations in the top quartile of ≥1 of the eight most commonly detected POPs, 34% had ≥3 such compounds in their respective top dose quartiles, and 32% ≥1 POPs in the top decile. Less than 4% of subjects had concentrations of all eight POPs in the lowest quartile. To our knowledge this type of findings has never been reported before. They are partly in contrast with the notion that human POP concentrations are low in the vast majority of the population: such view holds only when each individual compound is looked at separately.

Significant subgroups of the general population are contaminated by POP mixtures at high concentrations; e.g., women 60 to 74 years. A higher proportion of women than men had concentrations of POPs in the top quartile, and the gap increased with age.

To be methodologically cautious, we focused on eight POPs, each of which had been detected in >85% of the study subjects. Yet, 16% of subjects with high concentrations of ≥1 of such eight contaminants also had between 7 and 11 of the 11 least prevalent POPs detected. We studied only 19 organochlorines, a figure that is low,

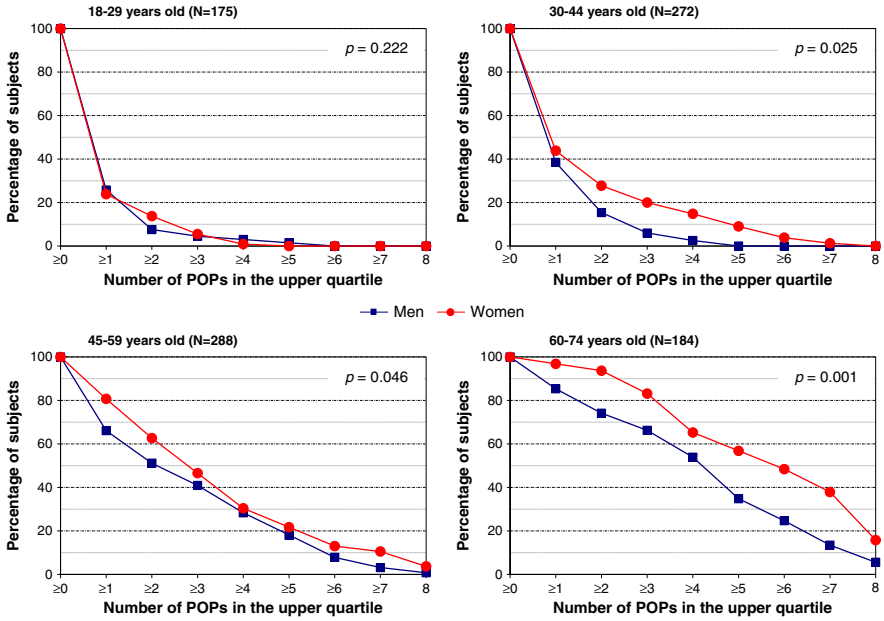

Fig. 1. Cumulative percentage of subjects with serum concentrations of the eight most prevalent POPs in the upper quartile, by age and sex (*p*-value derived from Pearson's Chi-square test).

albeit similar to other initial surveys in representative samples of a general population; e.g., 27 compounds were included in the first US National Report on Human Exposure to Environmental Chemicals (NRC, 2006; Porta et al., 2008). Surveys have not yet estimated a common range of chemicals that humans may accumulate over the life-course. Case-series (Watson, 2005; Weinhold, 2003) provide anecdotal evidence. In 155 volunteers from the United Kingdom, the median and highest number of chemicals found were 27 and 49, respectively (out of 78 substances analyzed) (WWF, 2003). A study of 541 pregnant women from Spain detected ≥8 POPs per person (out of 16 analyzed) in 43% of women; the median was 7 compounds detected per woman (Llop et al., 2010). In a US nationally representative assessment of 268 pregnant women's exposure to 163 chemicals, essentially all women were contaminated by ≥43 different chemicals; the median number of organochlorine pesticides detected was 6 (out of 13 analyzed); across chemical classes, the median number ranged from 8 (out of 17 chemical analytes) to 50 (out of 71 chemical analytes) (Woodruff et al., 2011). Our 19 organochlorines belonged only to two chemical classes (pesticide-related organochlorines and PCBs). If a higher number of classes are studied, findings might be more culturally sensitive or worrisome – from a population perspective – than those here reported (Haines et al., 2011; NRC, 2006; Thornton et al., 2002). Concordance or discordance of exposure patterns with mixtures may depend on the mixtures, exposure pathways and metabolism (e.g., subjects with common exposure pathways are likely to be more concordant). In individuals who have a mix of high and low POP levels, such 'discordance' could be a source of exposure misclassification in studies that assess only a few POPs,

Table 2
Frequency of subjects with high concentrations of the eight most frequently detected POPs according to different definitions of 'high concentration'.

Cutoff point of 'high concentration'	Number of the most prevalent POPs at 'high concentrations'					
	0	≥1	≥2	1 to 5	6 to 8	GM (95% CI)[a]
	N (%)	N (%)	N (%)	N (%)	N (%)	
Different cutoff point for each compound						
≥Percentile 75 (top quartile)	381 (41.5)	538 (58.5)	402 (43.7)	433 (47.1)	105 (11.4)	2.7 (2.6–2.9)
≥Percentile 80 (top quintile)	439 (47.8)	480 (52.2)	327 (35.6)	404 (44.0)	76 (8.3)	2.4 (2.3–2.6)
≥Percentile 90 (top decile)	622 (67.7)	297 (32.3)	179 (19.5)	281 (30.6)	16 (1.7)	2.0 (1.9–2.2)
Same cutoff point for all compounds						
≥50 ng/g of lipid[b]	3 (0.3)	916 (99.7)	875 (95.2)	335 (36.5)	581 (63.2)	4.9 (4.8–5.1)
≥100 ng/g of lipid[c]	32 (3.5)	887 (96.5)	739 (80.4)	655 (71.3)	232 (25.2)	3.1 (3.0–3.3)
≥250 ng/g of lipid[d]	231 (25.1)	688 (74.9)	399 (43.4)	669 (72.8)	19 (2.1)	1.8 (1.8–1.9)
≥500 ng/g of lipid[e]	463 (50.4)	456 (49.6)	181 (19.7)	455 (49.5)	1 (0.1)	1.4 (1.4–1.5)
≥750 ng/g of lipid	608 (66.2)	311 (33.8)	92 (10.0)	311 (33.8)	0 (0.0)	1.3 (1.2–1.3)

[a] GM: Geometric Mean; calculated for subjects with ≥1 of the eight most prevalent POPs at 'high concentrations' according to each cutoff point for 'high concentration'.
[b] Percentile 95 of the serum concentration of β-HCH in the US Fourth National Report on Human Exposure to Environmental Chemicals was 56.5 ng/g (Patterson et al., 2009; DHHS, 2009).
[c] Percentile 95 of the serum concentration of PCB 153 in the US Fourth National Report was 97.1 ng/g.
[d] Percentile 75 of the serum concentration of *p,p′*-DDE in the Report on Human Biomonitoring of Environmental Chemicals in Canada was 285 ng/g (Health Canada, 2010).
[e] In the present study the median value of *p,p′*-DDE (the compound with highest concentrations) was 436.28 ng/g of lipid. Percentile 75 of the serum concentration of *p,p′*-DDE in the US Fourth National Report was 509 ng/g.

especially when there is toxicological overlap among compounds. In our study, participants with a lower BMI were more likely to have POPs in the upper and lower quartiles simultaneously; they could thus be at greatest risk for exposure misclassification in studies with a limited set of analytes.

Few studies based on representative samples of the general population have assessed a large number of compounds — up to 91 in Canada (Health Canada, 2010), and 212 in the US Fourth National Report on Human Exposure to Environmental Chemicals (DHHS, 2009). However, for ethical and logistic reasons, not all compounds were studied in the same individuals. Nevertheless, the information available on different sets of compounds and individuals could be pooled to model the distribution of the number of contaminants and chemical classes that commonly contaminate individuals at different concentrations (Porta et al., in press).

Although a positive association between the number of POPs detected and the number of common POPs at high concentrations could be expected, the association was moderate in strength and not linear. The percentage of subjects with ≥1 of the POPs at high concentrations was higher when the POPs considered were poorly correlated with each other than when the POPs were highly correlated. The number of POPs at high concentrations was related to variables that are often associated with concentrations of POPs when each compound is analyzed separately (sex, age, BMI). The indicators presented may complement other estimates of POP body burden in biomonitoring surveys (DHHS, 2009; Health Canada, 2010; NRC, 2006; Patterson et al., 2009; Porta et al., 2008, 2010; Thornton et al., 2002).

If viewed in isolation, the number of compounds detected can be misleading; e.g., it is highly dependent on how many PCB or polybrominated diphenyl ether congeners are measured. However, there are sound ways to look at such number. Both the number of compounds at certain concentrations and the specific mixtures of compounds are worth exploring in several settings. While we propose that the study indicators could be used primarily in population surveys, they might also be relevant in some etiologic and mechanistic studies. Some such studies computed risks of adverse effects associated with levels of POPs above the 95th or other extreme percentiles (De Roos et al., 2005). Other studies used a *sum of orders* (Lee and Jacobs, 2006; Ukropec et al., 2010), which is specific to each study population; also, subjects with many POPs at low concentrations have scores similar to subjects with a low number of POPs at high concentrations, which may not be justified. While sum of orders and other summatories of concentrations of chemicals may be relevant in some mechanistic scenarios (Glynn et al., 2003; Henkler and Luch, 2011; Hernández et al., 2009; Hou et al., in press; Kortenkamp et al., 2009; Lee et al. 2009; Myers et al., 2009; Patterson et al., 2009), such approaches do not offer the advantages of our indicators. The latter also allow to group chemicals according to their ability to induce similar effects or to act through similar mechanisms at higher and lower doses.

There is no universal cutoff point to define high concentrations of POPs in humans: choices depend on context and purpose. In the present study the primary definition of 'high concentration' (percentile 75) was compound-specific and internal or specific to the study population. We also used definitions of 'high concentration' independent of the study population; thus, for instance, half of participants had concentrations of 1 to 5 POPs greater than 500 ng/g (Table 2). Some of our cutoff points were similar to US reference values as percentile 95 (P95) of β-HCH and PCB 153, or percentile 75 (P75) of *p,p′*-DDE (see footnotes in Table 2). In the present study P75 of the eight most prevalent POPs were between 2- and 20-times higher than the corresponding P75 in the US Fourth National Report (DHHS, 2009; Patterson et al., 2009). In fact, our P75 were often higher than the P95 in the US; e.g., in the present study P75 of *p,p′*-DDT (57,9 ng/g) tripled P95 of *p,p′*-DDT in the US (19.5 ng/g); P75 of β-HCH (252 ng/g) was over 4 times higher than P95 of β-HCH in the US (56.5 ng/g); and P75 of HCB (415 ng/g) was over 14 times higher than P95 of HCB in the US (28.9 ng/g) (DHHS, 2009; Patterson et al., 2009). Therefore, concentrations that we qualified as 'high' were indeed rather high as compared with the US. They also are high compared with population-based studies in Canada (Health Canada, 2010), New Zealand (Bates et al., 2005) and other countries that report blood levels corrected by lipids (Porta et al., 2008).

Findings of this study do not imply that compounds will cause adverse health effects when present above a given absolute concentration or percentile. Nor do they mean that effects at low doses are irrelevant: several environmental chemicals have been shown to increase risk at low concentrations (Alonso-Magdalena et al., 2011; Casals-Casas and Desvergne, 2011; De Roos et al., 2005; Diamanti-Kandarakis et al., 2009; Henkler and Luch, 2011; Hernández et al., 2009; Hou et al., in press; Jirtle and Skinner, 2007; Kortenkamp et al., 2009; Lee and Jacobs, 2006; Myers et al., 2009; NRC, 2008; Ukropec et al., 2010). Nevertheless, our primary targets were not etiologic and mechanistic studies, but biomonitoring studies (NRC, 2006). Although we simply added the number of POPs at high concentrations, the present results do not suggest whether dose addition, independent action, or some other method is the most appropriate for cumulative risk assessment (NRC, 2008); empirical uses of the study indicators in a variety of populations will clarify these issues.

5. Conclusions

Significant subgroups of the general population accumulate POP mixtures at high concentrations. It is misleading to state that most of the population has low concentrations of POPs. POP concentrations appear low in most of the population only when each individual compound is looked at separately. Based on our methods and findings, studies could analyze more systematically the number and type of compounds detected at high concentrations, integrate these indicators with traditional measures of exposure, analyze the characteristics and causes of the mixtures of contaminants at high concentrations, their coexistence with mixtures at low concentrations, and their joint health effects.

Conflict of interest

The authors declare that they have no competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.envint.2012.02.005.

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Supplementary Material

Number of persistent organic pollutants detected at high concentrations in a general population

TABLE OF CONTENTS:

1 Supplemental Material, Methods

1.1 Statistical analyses

The minimum value of the percentage of participants with ≥1 of the eight most prevalent POPs in the upper quartile will always be 25%, while the maximum value depends on the number of compounds considered (see Supplemental Material, Figure 1). The percentage will be higher when the POPs considered are poorly correlated with each other than when the POPs are highly correlated. Thus, if two compounds are completely uncorrelated ($\rho = 0$) about 50% of participants will have one or both POPs in the upper quartile. By contrast, if the two compounds are completely correlated ($\rho = 1$) 25% of subjects will have ≥2 POPs in the upper quartile. When ≥4 POPs are considered, the percentage will be near 100% only if the compounds are highly uncorrelated. In the Figure, the black line represents the proportion of participants with concentrations of ≥1 POPs in the upper quartile if these POPs are completely uncorrelated. Values close to this line indicate that the POPs are poorly correlated and values above this line indicate that POPs are negatively correlated. The black point is the percentage of participants in our study with concentrations of ≥1 POPs in the upper quartile. The green line represents the percentage of participants with ≥1 POPs in the upper quartile when the pairs of POPs considered are poorly correlated with each other. The blue line is the percentage when the pairs are highly correlated. The green line starts with the two compounds less correlated; the next compound added is the compound less correlated with these two compounds of the other six, and so on (Supplementary Material, Figure 1). Thus, when four POPs were considered (six correlations), the percentage of participants with ≥1 of the POPs in the upper quartile was 53.3% when the compounds were poorly correlated, and 38.2% when they were highly correlated. When six POPs were considered (15 correlations), the percentages were 58.9% and 50.9%, respectively.

2. Supplementary Material, Tables

Supplemental Material, Table 1 Characteristics of subjects with concentrations of one or more of the eight most prevalent POPs in the upper quartile

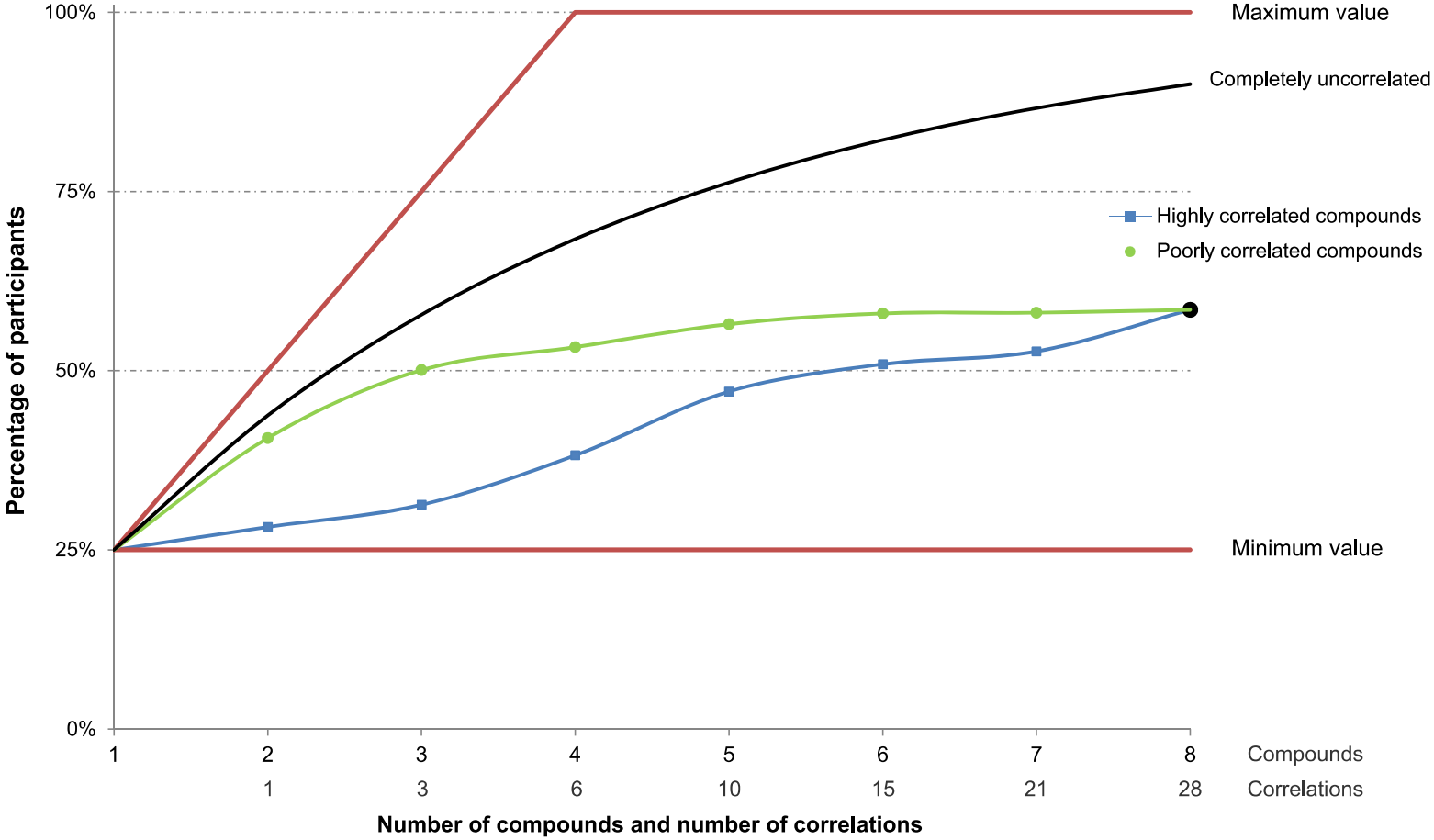
Characteristics	Total	Number of the most prevalent POPs with serum concentrations in the upper quartile								
		8	7	6	5	4	3	2	1	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	*p* value[1]
Total	538 (58.5)	27 (5.0)	44 (8.2)	34 (6.3)	56 (10.4)	63 (11.7)	88 (16.4)	90 (16.7)	136 (25.3)	
(Cumulative %)		(5.0)	(13.2)	(19.5)	(29.9)	(41.6)	(58.0)	(74.7)	(100)	
Sex										0.013
Men	222 (41.3)	6 (2.7)	10 (4.5)	16 (7.2)	26 (11.7)	31 (14.0)	32 (14.4)	33 (14.9)	68 (30.6)	
Women	316 (58.7)	21 (6.6)	34 (10.8)	18 (5.7)	30 (9.5)	32 (10.1)	56 (17.7)	57 (18.0)	68 (21.5)	
Age (years)										
Median	53.0	65.0	62.0	61.5	56.0	57.0	53.0	49.5	42.0	<0.001[2]
18-29	43 (8.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	2 (4.7)	6 (14.0)	11 (25.6)	23 (53.5)	<0.001
30-44	113 (21.0)	0 (0.0)	2 (1.8)	4 (3.5)	11 (9.7)	9 (8.0)	12 (10.6)	23 (20.4)	52 (46.0)	
45-59	214 (39.8)	7 (3.3)	14 (6.5)	10 (4.7)	27 (12.6)	27 (12.6)	42 (19.6)	39 (18.2)	48 (22.4)	
60-74	168 (31.2)	20 (11.9)	28 (16.7)	20 (11.9)	17 (10.1)	25 (14.9)	28 (16.7)	17 (10.1)	13 (7.7)	
BMI (Kg/m^2)										
Median	26.7	29.1	29.3	27.0	27.6	27.3	26.9	26.0	25.6	<0.001[2]
Normal range	177 (32.9)	3 (1.7)	9 (5.1)	8 (4.5)	13 (7.3)	15 (8.5)	32 (18.1)	37 (20.9)	60 (33.9)	<0.001
Overweight	219 (40.7)	12 (5.5)	16 (7.3)	17 (7.8)	26 (11.9)	30 (13.7)	31 (14.2)	35 (16.1)	52 (23.7)	
Obese	137 (25.5)	12 (8.8)	19 (13.9)	9 (6.6)	17 (12.4)	17 (12.4)	22 (16.1)	18 (13.1)	23 (16.8)	
Occupational social class[a]										<0.001[3]
V (less affluent)	53 (10.2)	4 (7.5)	8 (15.1)	1 (1.9)	7 (13.2)	7 (13.2)	5 (9.4)	8 (15.1)	13 (24.5)	
IV	236 (45.6)	12 (5.1)	19 (8.1)	15 (6.4)	21 (8.9)	29 (12.3)	44 (18.6)	37 (15.7)	59 (25.0)	
III	147 (28.4)	8 (5.4)	8 (5.4)	9 (6.1)	17 (11.6)	17 (11.6)	24 (16.3)	27 (18.4)	37 (25.2)	
II	49 (9.5)	2 (4.1)	2 (4.1)	5 (10.2)	8 (16.3)	7 (14.3)	4 (8.2)	7 (14.3)	14 (28.6)	
I (most affluent)	33 (6.4)	0 (0.0)	4 (12.1)	2 (6.1)	2 (6.1)	1 (3.0)	4 (12.1)	9 (27.3)	11 (33.3)	

[1] Unless otherwise specified, *p* value derived from Mantel–Haenszel's χ^2 test for linear trend.
[2] Jonckheere-Terpstra test for linear trend.
[3] Fisher's exact test (two-tail).
[a] Social class was assigned through the current or last occupation of the head of the household.

Supplemental Material, Table 2 Frequency of detection of the eleven least prevalent POPs by concentrations in the upper quartile of one or more of the eight most prevalent POPs analysed

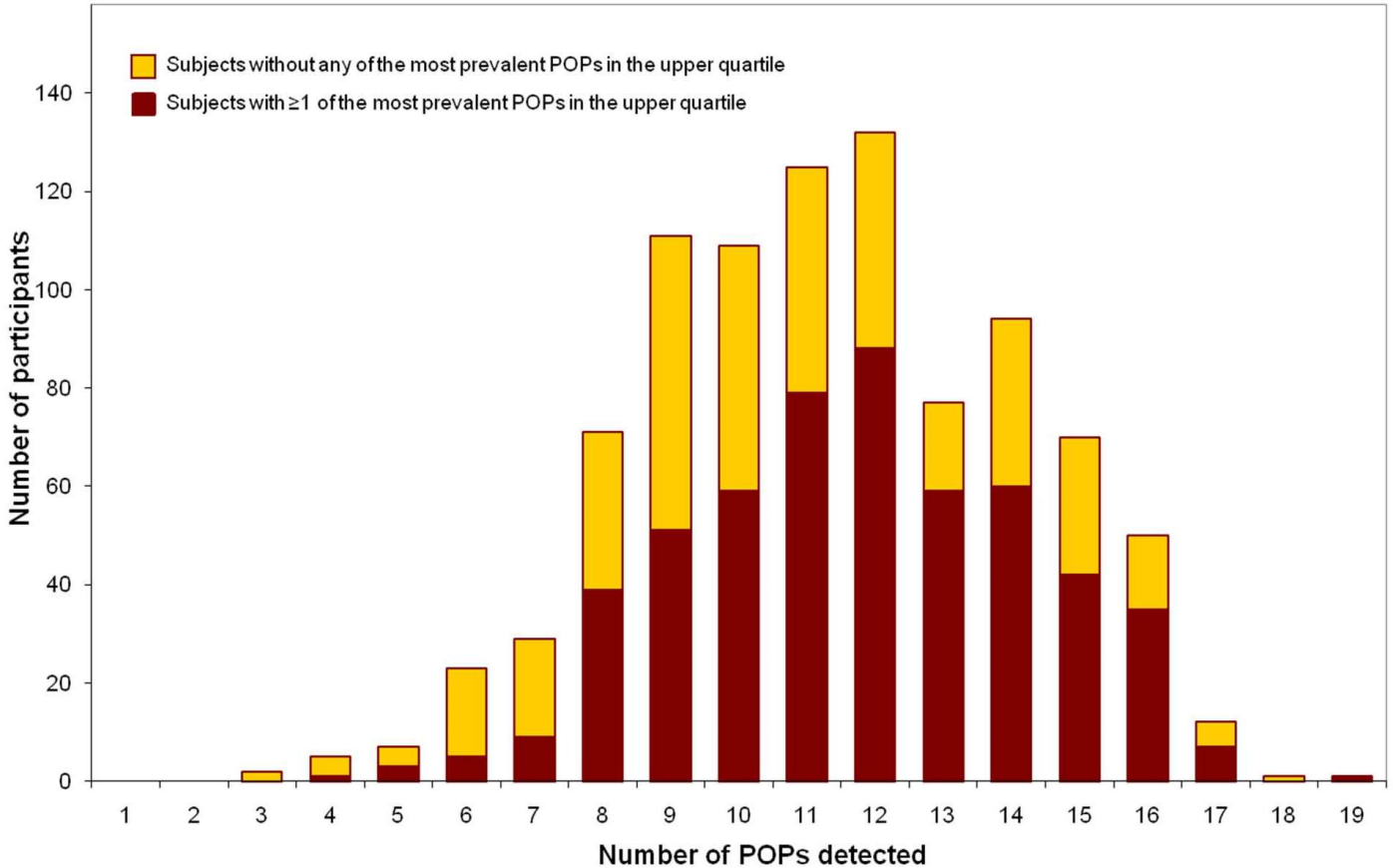
Least prevalent POPs	Total	Concentrations of ≥1 of the most prevalent POPs in the upper quartile		
		Yes	No	
	N (%)	N (%)	N (%)	*p*-value[1]
Total	919 (100)	538 (58.5)	381 (41.5)	
***o,p'*-DDT**				<0.001
Not detected	343 (37.3)	165 (48.1)	178 (51.9)	
Detected	576 (62.7)	373 (64.8)	203 (35.2)	
***o,p'*-DDE**				0.483
Not detected	695 (75.6)	402 (57.8)	293 (42.2)	
Detected	224 (24.4)	136 (60.7)	88 (39.3)	
***o,p'*-DDD**				0.733
Not detected	366 (39.8)	217 (59.3)	149 (40.7)	
Detected	553 (60.2)	321 (58.0)	232 (42.0)	
***p,p'*-DDD**				0.004
Not detected	406 (44.2)	216 (53.2)	190 (46.8)	
Detected	513 (55.8)	322 (62.8)	191 (37.2)	
PCB 28				0.269
Not detected	704 (76.6)	405 (57.5)	299 (42.5)	
Detected	215 (23.4)	133 (61.9)	82 (38.1)	
PCB 52				0.135
Not detected	800 (87.1)	476 (59.5)	324 (40.5)	
Detected	119 (12.9)	62 (52.1)	57 (47.9)	
PCB 101				0.422
Not detected	802 (87.3)	465 (58.0)	337 (42.0)	
Detected	117 (12.7)	73 (62.4)	44 (37.6)	
PeCB				<0.001
Not detected	749 (81.5)	417 (55.7)	332 (44.3)	
Detected	170 (18.5)	121 (71.2)	49 (28.8)	
α-HCH				<0.001
Not detected	695 (75.6)	370 (53.2)	325 (46.8)	
Detected	224 (24.4)	168 (75.0)	56 (25.0)	
γ-HCH				0.105
Not detected	520 (56.6)	292 (56.2)	228 (43.8)	
Detected	399 (43.4)	246 (61.7)	153 (38.3)	
δ-HCH				0.497
Not detected	674 (73.3)	390 (57.9)	284 (42.1)	
Detected	245 (26.7)	148 (60.4)	97 (39.6)	

[1] Fisher's exact test (2-tailed).



Supplementary Material, Figure 1 Percentage of participants with ≥1 of the eight most prevalent POPs in the upper quartile by number of compounds and magnitude of the correlations between the pairs of compounds considered.

The minimum percentage of participants with concentrations in the top quartile of ≥1 POPs will always be 25%, while the maximum depends on the number of compounds considered. The black line represents the proportion of participants with concentrations of ≥1 POPs in the upper quartile if the POPs are completely uncorrelated. The green line represents the percentage of participants with ≥1 POPs in the upper quartile when the pairs of POPs considered are poorly correlated with each other. The blue line is the percentage when the pairs are highly correlated.



Supplementary Material, Figure 2 Distribution of the number of POPs detected in the study participants with or without any of the eight most prevalent POPs in the upper quartile

Article A6

Títol: Blood Concentrations of Persistent Organic Pollutants and Prediabetes and Diabetes in the General Population of Catalonia.

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Blood Concentrations of Persistent Organic Pollutants and Prediabetes and Diabetes in the General Population of Catalonia

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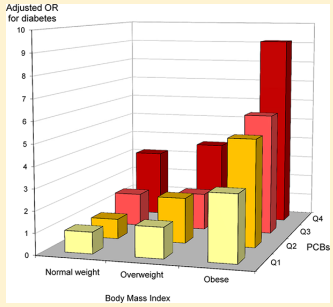
Supporting Information

ABSTRACT: The aim was to analyze the effects of body mass index (BMI), low-dose exposure, mixtures of persistent organic pollutants (POPs), and lipid adjustment on the relationship between POP concentrations and diabetes and prediabetes in the general adult population of Catalonia (Spain). Serum concentrations of POPs were measured by gas chromatography with electron-capture detection in 886 participants in a health interview survey. The highest concentrations of all POPs analyzed were found in subjects who had diabetes. Levels were also higher in individuals with prediabetes than in subjects without the disorder. In models adjusted by age, sex and BMI, the prevalence of diabetes and prediabetes increased in a dose-dependent manner across quartiles of PCBs 118, 138, 153, and 180, and HCB. When models were further adjusted for lipids, the associations were slightly lower and statistically significant, the ORs for the upper quartile ranging from 2.0 to 2.8 (all *p*-values for linear trend <0.05). Concentrations of *p,p′*-DDT, *p,p′*-DDE and *β*-HCH were not associated with diabetes or prediabetes. Increasing concentrations of PCBs and HCB were positively associated with diabetes and prediabetes. Only part of the association was due to age and BMI. Findings support the hypothesis that exposure to POPs may be a diabetogenic factor in both obese and nonobese individuals.



INTRODUCTION

In recent years more than 90 studies have reported associations between type 2 diabetes and body concentrations of persistent organic pollutants (POPs) and other chemical agents.[1,2] Some of such studies were prospective and ruled out "reverse causality" and disease progression bias.[2−7] POPs are synthetic chemicals highly lipophilic and resistant to degradation that bioaccumulate in living organisms and the environment; virtually all humans accumulate POPs throughout the life-course,[8−10] sometimes at high concentrations.[11] The significant increase in the incidence of type 2 diabetes worldwide warrants considering the potential role of environmental factors along with well-established risk factors as obesity, inactivity, high energy intake and genetic susceptibility.[1−7,12−14] Experimental studies provide evidence on possible mechanisms linking glucose metabolism disorders and POP exposure at concentrations similar to those commonly found in humans, suggesting, notably, that some POPs may interfere with insulin production, pancreatic beta-cell function, and insulin resistance.[1,15−18]

In spite of the evidence linking type 2 diabetes and POP exposure, important questions remain unclear.[1] In the present study we focus on (a) the role of possible confounders, effect modifiers or mediators as body mass index and lipids, both highly associated with type 2 diabetes and POP levels;[1,12,19] (b) the possible low-dose effects of POPs and the shapes of the dose−response curves;[6,20] (c) the effects of exposure to mixtures of POPs;[20] and (d) the relationship between POP concentrations and prediabetic status.[21] Furthermore, the population of Catalonia has higher levels of POPs than other populations,[9] which further increases the relevance of

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examining in this population relationships that have been assessed in previous studies.

Therefore, the aim of the present study was to analyze the relationship between POP serum concentrations and type 2 diabetes and prediabetes in the general adult population of Catalonia (Spain), as well as to elucidate the potential confounding or modifying effects on such relationship of BMI, lipids, low-dose exposure, and mixtures of POPs.

MATERIALS AND METHODS

Study Population. The study population has been described in detail elsewhere.[22] Briefly, participants in the Catalan Health Interview Survey (CHIS) aged 18−74 years were offered to take part in a health examination, which included a physical exam, a supplementary interview, and the collection of urine and blood samples. A total of 1374 individuals—who gave specific written informed consent—participated during 2002 in the health examination. Trained nurses recorded the weight and height, and the corresponding body mass index (BMI) was computed (measured weight (kg) divided by measured height squared (m^2)).[23] Information on blood concentrations of lipids and at least 1 mL of serum (for POP analyses) was available from 919 participants.[22] The present report is based on 886 participants with data available on POP serum concentrations and on diabetes status (see below). There were no statistically significant differences between the 886 individuals and the remaining participants in the health examination with respect to age, sex, BMI, diabetes status, educational level, and occupational social class.[22]

Diabetes Status. A capillary blood sample obtained during the health examination was used to determine glucose concentration in whole blood. The fasting plasma glucose concentration was then calculated by multiplying the whole blood glucose by 1.12.[24,25] Following previous epidemiologic studies,[2,25−29] and recommendations of the American Diabetes Association,[30] the World Health Organization,[31] and a National Toxicology Program Workshop,[1] participants were considered to have diabetes if (a) their fasting plasma glucose was ≥126 mg/dL, or (b) they answered affirmatively to the question "Do you have or did a doctor tell you that you have diabetes?" (only four individuals were classified as diabetic because they answered affirmatively to the question while they reported no current use of insulin or antidiabetic medication and their fasting plasma glucose was <110 mg/dL), or (c) they reported a current use of insulin or antidiabetic medication. Subjects were classified as having prediabetes (or impaired fasting glycemia) if their fasting plasma glucose was between 110 and 125 mg/dL.[1,30,31] Of participants reporting not to have diabetes and not to use insulin or antidiabetic medication, we excluded seven subjects missing blood glucose concentrations, six subjects with whole blood glucose concentration ≤55 mg/dL, 16 nonfasting subjects with whole blood glucose concentration >100 mg/dL, and four pregnant women, leaving the mentioned 886 participants.

Analysis of Serum Concentrations of POPs and Lipids. Laboratory methods have also previously been described in detail.[22] The following 19 POPs were analyzed in serum: *o,p′*-DDT (dichlorodiphenyltrichloroethane), *p,p′*-DDT, *o,p′*-DDE (dichlorodiphenyldichloroethene), *p,p′*-DDE, *o,p′*-DDD (dichlorodiphenyldichloroethane), *p,p′*-DDD; PCB (polychlorinated biphenyls) congeners 28, 52, 101, 118, 138, 153, and 180; PeCB (pentachlorobenzene), HCB (hexachlorobenzene), *α*-HCH (hexachlorocyclohexane), *β*-HCH, *γ*-HCH, and *δ*-HCH. Gas chromatography (GC) analyses were performed with an Agilent Technologies model GC-6890N provided with an ECD and a 60 m, 0.25 mm i.d. DB-5 column (J&W Scientific, Folsom, CA; film thickness 0.25 μm). Analyses were carried out in the Department of Environmental Chemistry (IIQAB-CSIC) in Barcelona, Spain.[22] Limits of quantification ranged from 0.0069 ng/mL for PCB 101 to 0.0706 ng/mL for *γ*-HCH. The calculation of the limits of detection and quantification was based on the analysis of proficiency testing materials, an external quality assessment for selected pollutants, and the study of the signal/noise ratio of chromatograms obtained from GC-ECD injection.[32] When a sample had a concentration of a compound below the detection threshold, it was assigned the midvalue of this limit; when a POP was detected but under the quantification threshold, the midvalue between detection and quantification limits was used.[22,23] Main statistical analyses were limited to the eight compounds that were detected in >85% of participants: *p,p′*-DDT, *p,p′*-DDE, PCB congeners 118, 138, 153, and 180, HCB and *β*-HCH.[22] Total cholesterol and triglycerides levels were determined enzymatically (Txad-Pap and CIN-UV methods, respectively), using serum obtained in the health examination.[22] Total serum lipids (TL) were calculated by the standard short formula (or Standard formula 2) based on total cholesterol and triglycerides,[34,35] and POP concentrations were individually corrected for TL by dividing the crude serum POP concentration by TL.

Statistical Analysis. Univariate statistics were computed as customary.[36] Fisher's exact test for homogeneity was applied to assess the relationship between two categorical variables. To assess differences on POP concentrations by diabetes status Student's *t*-test and Mann−Whitney's *U*-test were used. To estimate the magnitude of the associations between POPs and diabetes and prediabetes, multivariate-adjusted odds ratios (ORs) and their corresponding 95% confidence intervals (CI) were calculated by unconditional logistic regression[37] with progressive degrees of adjustment, including (1) crude models, with unadjusted POP concentrations (in ng/mL); (2) models adjusted for socio-demographic variables (including age, sex, and BMI); (3) models further adjusted for total cholesterol and triglycerides; and (4) models using TL-corrected POPs (in ng/g lipid). Including arterial pressure in the models (as mean value or as hypertension, dichotomous) did not significantly change the results; thus, it was not included in the final models. POP concentrations were introduced in the regression model as quartiles categories; we also evaluated the increase in the odds comparing the 80th and the 20th percentiles of POP concentrations from regression models with log-transformed POPs concentrations. We assessed linear relations by testing the log−linear POPs concentrations coefficients using the Wald test and the multivariate analogue of Mantel's extension test for linear trend. We evaluated nonlinear relations using restricted quadratic splines with knots at the 20th, 50th, and 80th percentiles of each POP distribution.[37] The *p*-value for nonlinear trend was estimated by testing the nonlinear spline terms using Wald's test for multiple coefficients. The joint effects of POPs and BMI were explored graphically, in stratified analyses, and by including in the model the two main terms and the interaction term.[36] In order to evaluate POPs mixtures we calculated the sum of orders or sum of category ranking of the eight most prevalent POPs mentioned above. Each POP was thus categorized in quartiles and the category number of each POP was summed, producing a value ranging between 8 (when all eight POPs had concentrations in the lowest quartile) and

Table 1. Main Characteristics of the Study Subjects by Diabetes Status

characteristic	total	normal subjects	subjects with prediabetes	subjects with diabetes	$P^{a,b}$	$P^{c,b}$
number of subjects (%)	886 (100)	541 (61.1)	202 (22.8)	143 (16.1)		
age (years)[d]	45.1 ± 15.0	40.9 ± 14.3	48.6 ± 13.4	55.8 ± 13.1	<0.001	<0.001
median	45.0	40.0	49.0	59.0		
sex (% of males)	42.9	36.8	50.5	55.2	0.001[f]	<0.001[f]
body mass index (kg/m^2)[d]	26.4 ± 4.6	25.1 ± 4.0	27.9 ± 4.5	29.0 ± 5.2	<0.001	<0.001
median	25.8	24.5	27.5	28.3		
underweight (<18.5) (%)	1.1	1.7	0.5	0.0	<0.001[f]	<0.001[f]
normal range (18.5−24.9)	41.9	53.6	25.2	21.0		
overweight (25.0−29.9)	37.6	33.5	46.5	40.6		
obese (≥30)	19.4	11.3	27.7	38.5		
total cholesterol (mg/dL)[d]	196 ± 40	190 ± 40	207 ± 37	206 ± 43		
median	192	185	204	205	<0.001	<0.001
triglycerides (mg/dL)[d]	95 ± 61	82 ± 52	114 ± 75	118 ± 60		
median	80	70	96	105	<0.001	<0.001
PCB 118 (ng/mL)[e]	0.099	0.076	0.138	0.170	<0.001	<0.001
(95% CI)	(0.091−0.108)	(0.068−0.085)	(0.117−0.162)	(0.143−0.202)		
median	0.133	0.105	0.179	0.208		
PCB 138 (ng/mL)[e]	0.389	0.312	0.501	0.632	<0.001	<0.001
(95% CI)	(0.364−0.417)	(0.284−0.342)	(0.446−0.563)	(0.555−0.719)		
median	0.451	0.360	0.546	0.640		
PCB 153 (ng/mL)[e]	0.564	0.453	0.720	0.912	<0.001	<0.001
(95% CI)	(0.529−0.601)	(0.416−0.494)	(0.645−0.802)	(0.799−1.040)		
median	0.625	0.519	0.753	0.916		
PCB 180 (ng/mL)[e]	0.492	0.413	0.592	0.732	<0.001	<0.001
(95% CI)	(0.467−0.517)	(0.387−0.441)	(0.538−0.651)	(0.654−0.818)		
median	0.501	0.426	0.618	0.735		
HCB (ng/mL)[e]	1.068	0.825	1.368	1.995	<0.001	<0.001
(95% CI)	(0.980−1.164)	(0.738−0.922)	(1.148−1.631)	(1.677−2.373)		
median	1.201	0.855	1.496	2.385		
β-HCH (ng/mL)[e]	0.615	0.463	0.819	1.204	<0.001	<0.001
(95% CI)	(0.564−0.670)	(0.415−0.516)	(0.693−0.967)	(0.990−1.465)		
median	0.668	0.464	0.896	1.483		
p,p′-DDT (ng/mL)[e]	0.148	0.131	0.160	0.212	0.076	<0.001
(95% CI)	(0.136−0.162)	(0.117−0.147)	(0.134−0.190)	(0.170−0.265)		
median	0.176	0.157	0.206	0.211		
p,p′-DDE (ng/mL)[e]	2.703	2.240	3.216	4.300	<0.001	<0.001
(95% CI)	(2.520−2.899)	(2.056−2.441)	(2.763−3.743)	(3.629−5.096)		
median	2.604	1.974	3.128	4.447		

[a]Subjects with prediabetes vs normal subjects. The differences between pairs of medians were all statistically significant ($p < 0.001$), except for *p,p′*-DDT ($p = 0.035$) (Mann−Whitney's *U*-test, two-tail). [b]Unless otherwise specified, *p* value derived from Student's *t*-test. [c]Subjects with diabetes vs normal subjects. The differences between pairs of medians were all statistically significant ($p \leq 0.001$, Mann−Whitney's U-test, two-tail). [d]Values are mean ± SD. [e]Values are geometric mean and 95% CI of the geometric mean. [f]Fisher's exact test (excluding "underweight" for BMI).

32 (when all eight POPs had concentrations in the top quartile).[11] Similarly, we calculated the sum of orders of the four PCBs, and the sum of the four PCBs by adding congener-specific values. We also created the variable "number of POPs at high concentrations": for each subject we added the number of POPs whose serum concentrations were equal to or greater than percentile 75.[11] The level of statistical significance was set at 0.05 and all tests are two tailed. Analyses were conducted using SPSS version 12.0 (SPSS Inc., Chicago, IL) and R version 2.7.2 (2008).

RESULTS

Of the 886 participants, 143 (16%) were classified as diabetics and 202 (23%) as prediabetics. Participants with diabetes and prediabetes were older, more often men, and had a higher BMI than participants without the disorder (Table 1). Concentrations of total cholesterol and triglycerides were also significantly higher in prediabetics and diabetics than in the other participants. Concentrations of all POPs analyzed were significantly lower in nondiabetic participants than in prediabetics, and in the latter than in diabetics (Table 1). For instance, the median concentration of PCB 118 was 1.7 and 2 times higher in prediabetics and diabetics, respectively, than in individuals without diabetes; for HCB the corresponding values were 1.7 and 2.8 (*p*-values <0.001).

Diabetes. Multivariate analyses showed that concentrations of PCBs and HCB were positively associated with diabetes after adjusting for age, sex, and BMI, although the magnitude of the associations was substantially lower than in crude models (Table 2, model 1). The ORs for the upper quartile of PCBs and HCB ranged between 2.3 and 3.2 (all *p*-values for linear trend <0.02) (Table 2). When models were further adjusted for total cholesterol and triglycerides, such associations were slightly lower but still statistically significant: the ORs for the

Table 2. Associations between Concentrations of Organochlorine Compounds and Diabetes[a]

		crude model			model 1			model 2		
compounds (ng/mL)	diabetes/normal[b]	OR	(95% Cl)	*P*	OR	(95% Cl)	*P*	OR	(95% Cl)	*P*
PCB118										
≤0.060	16/167	1.0		<0.001	1.0		0.018	1.0		0.048
0.060−0.135	27/162	1.7	(0.9−3.3)		1.4	(0.7−2.9)		1.4	(0.7−2.9)	
0.135−0.242	40/126	3.3	(1.8−6.2)		1.7	(0.9−3.5)		1.7	(0.8−3.4)	
>0.242	60/86	7.3	(4.0−13.4)		2.3	(1.1−4.8)		2.1	(1.0−4.4)	
80th vs 20th percentile		4.1	(2.5−6.7)	<0.001[c]	1.7	(1.1−2.6)	0.027[c]	1.6	(1.0−2.4)	0.055[c]
PCB 138										
≤0.258	13/179	1.0		<0.001	1.0		0.002	1.0		0.004
0.259−0.451	21/152	1.9	(0.9−3.9)		1.1	(0.5−2.5)		1.1	(0.5−2.5)	
0.452−0.722	44/121	5.0	(2.6−9.7)		1.7	(0.8−3.7)		1.6	(0.7−3.4)	
>0.722	65/89	10.1	(5.3−19.2)		2.9	(1.3−6.2)		2.7	(1.2−5.8)	
80th vs 20th percentile		3.6	(2.4−5.4)	<0.001[c]	1.6	(1.1−2.4)	0.025[c]	1.5	(1.0−2.3)	0.050[c]
PCB 153										
≤0.361	12/178	1.0		<0.001	1.0		0.006	1.0		0.017
0.362−0.626	25/151	2.5	(1.2−5.1)		1.6	(0.7−3.5)		1.6	(0.7−3.5)	
0.627−0.978	41/121	5.0	(2.5−10.0)		1.8	(0.8−4.0)		1.7	(0.8−3.8)	
>0.978	65/91	10.6	(5.4−20.6)		2.9	(1.3−6.4)		2.6	(1.2−5.9)	
80th vs 20th percentile		3.8	(2.5−5.8)	<0.001[c]	1.7	(1.2−2.5)	0.006[c]	1.6	(1.2−2.4)	0.007[c]
PCB 180										
≤0.314	12/179	1.0		<0.001	1.0		0.007	1.0		0.023
0.315−0.503	29/152	2.8	(1.4−5.8)		1.1	(0.5−2.4)		1.0	(0.5−2.2)	
0.504−0.783	37/113	4.9	(2.4−9.8)		1.6	(0.7−3.5)		1.5	(0.7−3.2)	
>0.783	65/97	10.0	(5.1−19.4)		2.3	(1.0−5.3)		2.0	(0.9−4.6)	
80th vs 20th percentile		3.4	(2.5−4.7)	<0.001[c]	1.7	(1.2−2.5)	0.007[c]	1.6	(1.1−2.4)	0.018[c]
HCB										
≤0.509	14/181	1.0		<0.001	1.0		0.011	1.0		0.028
0.510−1.193	26/140	2.4	(1.2−4.8)		1.4	(0.7−3.1)		1.4	(0.7−3.1)	
1.194−2.610	36/124	3.8	(1.9−7.2)		1.9	(0.9−4.2)		1.9	(0.8−4.1)	
>2.610	67/96	9.0	(4.8−16.9)		3.2	(1.3−8.1)		2.8	(1.1−7.1)	
80th vs 20th percentile		3.8	(2.6−5.6)	<0.001[c]	1.8	(1.0−3.2)	0.043[c]	1.7	(0.9−2.9)	0.078[c]
β-HCH										
≤0.288	16/171	1.0		<0.001	1.0		0.536[c]	1.0		0.665[c]
0.289−0.670	22/156	1.5	(0.8−3.0)		0.8	(0.4−1.8)		0.8	(0.4−1.7)	
0.671−1.547	40/120	3.6	(1.9−6.7)		1.1	(0.5−2.4)		1.0	(0.5−2.2)	
>1.547	65/94	7.4	(4.0−13.5)		1.4	(0.6−3.4)		1.2	(0.5−3.0)	
80th vs 20th percentile		4.2	(2.7−6.4)	<0.001[c]	1.7	(0.9−2.9)	0.080[c]	1.5	(0.9−2.6)	0.146[c]
***p,p′*-DDT**										
≤0.086	25/150	1.0		0.005	1.0		0.303[c]	1.0		0.213[c]
0.087−0.178	37/144	1.5	(0.9−2.7)		1.2	(0.6−2.2)		1.2	(0.6−2.2)	
0.179−0.349	37/125	1.8	(1.0−3.1)		0.8	(0.4−1.5)		0.8	(0.4−1.5)	
>0.349	44/122	2.2	(1.3−3.7)		0.7	(0.3−1.3)		0.6	(0.3−1.2)	
80th vs 20th percentile		1.7	(1.3−2.2)	<0.001[c]	1.0	(0.7−1.3)	0.816[c]	0.9	(0.7−1.2)	0.616[c]
p,p′-DDE										
≤1.24	17/172	1.0		<0.001	1.0		0.787[c]	1.0		0.840[c]
1.25−2.63	29/139	2.1	(1.1−4.0)		1.3	(0.7−2.8)		1.3	(0.6−2.6)	
2.64−5.56	41/122	3.4	(1.8−6.3)		1.0	(0.5−2.1)		1.0	(0.5−2.0)	
>5.56	56/108	5.2	(2.9−9.5)		1.1	(0.5−2.3)		1.0	(0.5−2.1)	
80th vs 20th percentile		3.1	(2.2−4.3)	<0.001[c]	1.1	(0.7−1.8)	0.611[c]	1.1	(0.7−1.7)	0.812[c]

Table 2. continued

		crude model			model 1			model 2		
compounds (ng/mL)	diabetes/normal[b]	OR	(95% CI)	*P*	OR	(95% CI)	*P*	OR	(95% CI)	*P*
Sum of PCBs										
≤1.03	13/183	1.0		<0.001	1.0		0.004	1.0		0.013
1.04−1.76	25/149	2.4	(1.2−4.8)		1.2	(0.5−2.5)		1.2	(0.5−2.6)	
1.76−2.72	41/122	4.7	(2.4−9.2)		1.5	(0.7−3.3)		1.4	(0.7−3.2)	
>2.73	64/87	10.4	(5.4−19.8)		2.7	(1.2−5.9)		2.4	(1.1−5.4)	
80th vs 20th percentile		1.7	(1.2−2.6)	0.007[c]	1.8	(1.2−2.7)	0.003[c]	1.7	(1.1−2.6)	0.010[c]
Sum of Orders PCBs										
4−6	13/186	1.0		<0.001	1.0		0.007[c]	1.0		0.018[c]
7−10	28/162	2.5	(1.2−4.9)		1.3	(0.6−2.9)		1.3	(0.6−2.9)	
11−13	36/114	4.5	(2.3−8.9)		1.4	(0.7−3.1)		1.3	(0.6−3.0)	
14−16	66/79	12.0	(6.2−22.9)		3.1	(1.4−6.8)		2.8	(1.3−6.3)	
80th vs 20th percentile		9.7	(5.3−17.8)	<0.001[c]	2.8	(1.4−5.5)	0.004[c]	2.5	(1.2−4.9)	0.010[c]
Sum of Orders All POPs										
8−14	11/197	1.0		<0.001[c]	1.0		0.017[c]	1.0		0.020[c]
15−20	35/135	4.6	(2.3−9.5)		2.4	(1.1−5.1)	0.004[d]	2.4	(1.1−5.3)	0.003[d]
21−26	32/127	4.5	(2.2−9.3)		1.3	(0.5−2.9)		1.2	(0.5−2.8)	
27−32	65/82	14.2	(7.1−28.3)		2.5	(1.1−6.1)		2.3	(0.9−5.5)	
80th vs 20th percentile		7.2	(4.5−11.6)	<0.001[c]	2.2	(1.2−4.0)	0.015[c]	1.9	(1.0−3.5)	0.041[c]
Number of POPs at High Concentrations										
0	26/279	1.0		<0.001	1.0		0.017[c]	1.0		0.016[c]
1−2	34/131	2.8	(1.6−4.8)		1.4	(0.8−2.7)		1.4	(0.8−2.7)	
3−4	29/78	4.0	(2.2−7.2)		1.0	(0.5−2.1)		0.8	(0.4−1.8)	
5−6	31/33	10.1	(5.3−19.0)		2.9	(1.3−6.4)		2.8	(1.2−6.2)	
7−8	23/20	12.3	(6.0−25.4)		2.4	(0.9−5.8)		1.9	(0.7−4.8)	
80th vs 20th percentile		3.6	(2.0−6.7)	<0.001[c]	1.7	(0.9−3.4)	0.126[c]	1.5	(0.7−3.0)	0.283[c]
Dioxin-Like PCBs (PCBs 28, 118)										
≤0.0727	16/167	1.0		<0.001	1.0		0.306[c]	1.0		0.391[c]
0.0727−0.1561	33/156	2.2	(1.2−4.2)		1.6	(0.8−3.3)		1.6	(0.8−3.3)	
0.1561 −0.268	42/120	3.7	(2.0−6.8)		2.0	(1.0−4.1)		1.9	(0.9−3.8)	
>0.268	52/98	5.5	(3.0−10.2)		1.6	(0.8−3.3)		1.5	(0.7−3.1)	
80th vs 20th percentile		2.9	(2.0−4.2)	<0.001[c]	1.3	(0.9−1.9)	0.127[c]	1.2	(0.9−1.8)	0.242[c]
Nondioxin-Like PCBs (PCBs 52, 101, 138, 153, 180)										
≤0.931	13/176	1.0		<0.001	1.0		0.004	1.0		0.012
0.931 −1.5975	24/157	2.1	(1.0−4.2)		1.0	(0.5−2.3)		1.0	(0.5−2.2)	
1.5975−2.468	42/115	4.9	(2.5−9.6)		1.7	(0.8−3.6)		1.6	(0.7−3.5)	
>2.468	64/93	9.3	(4.9−17.8)		2.5	(1.1−5.4)		2.2	(1.0−4.9)	
80th vs 20th percentile		3.9	(2.8−5.5)	<0.001[c]	1.8	(1.2−2.7)	0.003[c]	1.7	(1.1−2.5)	0.009[c]

[a]OR: Odds ratio. CI: Confidence interval. Model 1: adjusted by sex, age and BMI. Model 2: further adjusted by total cholesterol and triglycerides. Number of POPs at high concentrations: number of POPs whose serum concentrations were ≥percentile 75. Unless otherwise specified, *p* value derived from multivariate analogue of Mantel's extension test for linear trend. [b]Number of participants with diabetes/number of normal participants. [c]Wald's test. [d]*p* value for cubic model.

upper quartile of PCBs and HCB ranged between 2.0 and 2.8 (all *p*-values for linear trend <0.05) (Table 2, model 2). In spline regression models for PCBs, the dose−response relation was monotonic and increasingly positive (Figure 1). The *p*-values for the nonlinear components in the restricted quadratic spline terms were all ≥0.785. The adjusted ORs comparing participants in the 80th vs the 20th percentiles of PCBs concentrations were all ≥1.5 (*p*-values ≤0.055) (Table 2). In models using POPs individually corrected by total lipids (i.e., in ng/g lipid), the OR point estimates were further attenuated but consistent with the main analysis, and confidence intervals became wider, except for PCB 118 (OR for the upper quartile = 1.9, *p*-trend = 0.048) (Supporting Information (SI) Table S1).

Diabetes was also associated with different mixtures of POPs, as the sum of PCBs and the sum of orders of PCBs (Table 2); thus, for instance, participants in the upper category of the sum of orders of PCBs (who had between two and all four PCBs with concentrations in the upper quartile) were about three times more likely to have diabetes than subjects in the lowest category (Table 2). The sum of orders of all POPs was also positively associated with diabetes, and in this case a cubic trend was observed: the ORs were 2.4, 1.2, and 2.3 (Table 2)

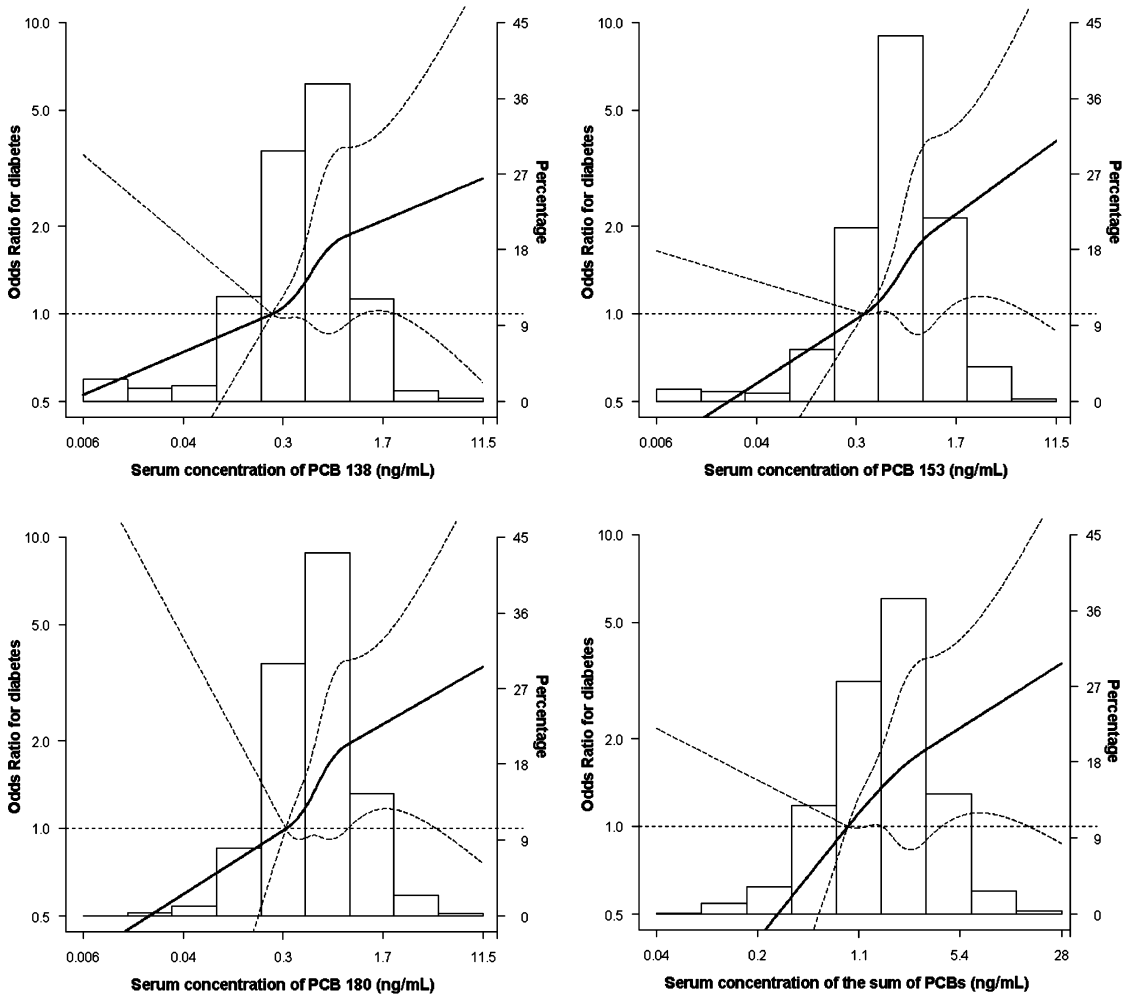
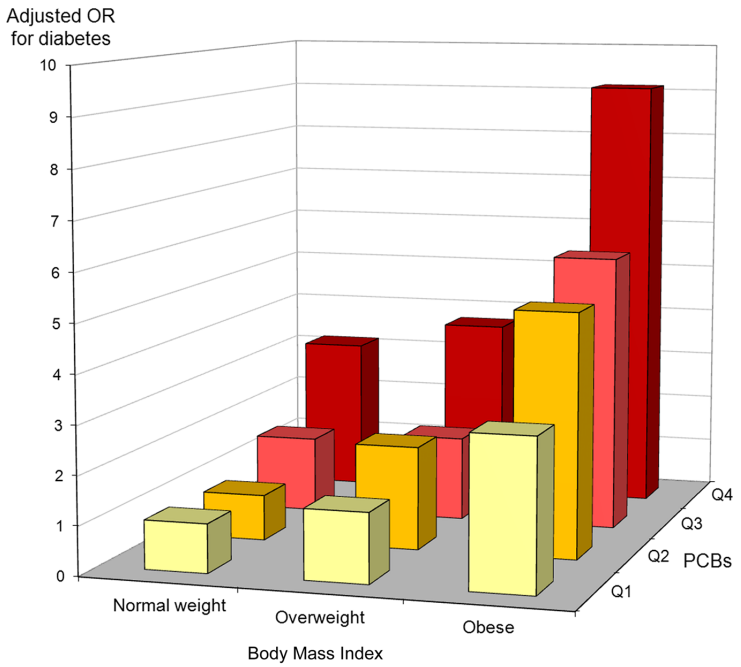


Figure 1. Odds ratios and 95% confidence intervals for the association between diabetes and blood concentrations of PCBs. Odds ratios (solid lines) and 95% confidence intervals (curved dashed lines) were based on restricted quadratic splines for log-transformed PCB concentrations with knots at the 20th, 50th, and 80th percentiles. Models adjusted for age, sex, BMI, total cholesterol, and triglycerides. The reference value was set at the 20th percentile of PCB distribution. Vertical bars represent the histogram of PCB distribution.

(p-value for cubic trend = 0.003). For obese individuals the corresponding ORs increased to 5.7, 3.5, and 7.2 (p-value for cubic trend = 0.115). When PCBs were classified as dioxin-like and non dioxin-like, only the latter showed a statistically significant association with diabetes (Table 2). The OR of diabetes for the upper quartile of PCBs phenobarbital-type inducers was 2.6 (95% CI: 1.2−5.9, p-trend 0.004); for moderately chlorinated PCBs it was 2.4 (95% CI: 1.1−5.3, p-trend 0.015). PCBs 28, 52, and 101 were detected in less than 23% of the study subjects and showed no association with diabetes, nor with prediabetes.

Concerning effect modification by BMI, the positive associations between PCBs (and HCB) and diabetes were of similar magnitude in subjects with normal weight, overweight and obese; p-values for the POP−BMI interaction ranged between 0.328 and 0.995. Thus, no statistically significant interactions were found between BMI and POP concentrations on the prevalence of diabetes. The only possible exception was PCB 118: the OR of diabetes for the upper quartile of PCB 118 was 1.0 for participants with normal BMI, 3.4 for subjects overweight, and 4.5 for obese (p for interaction = 0.514, model adjusted by age, sex, cholesterol and triglycerides) (SI Table S2). Importantly, among individuals with normal weight the prevalence of diabetes increased as well with increasing concentrations of HCB and of PCBs 138, 153, and 180 (SI Table S2).

Next, all ORs were computed taking as the reference category individuals with normal weight and with the of sum of orders of PCBs in the lowest quartile: with respect to this category, the prevalence of diabetes was 9 times higher among subjects with obesity and the sum of orders of PCBs in the top quartile (OR = 9.1, 95% CI: 2.5−33) (Figure 2). The positive association between BMI and diabetes was of a similar magnitude in all quartiles of all POPs; for example, the



	Normal weight		Overweight		Obese	
	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
Q1	128	1.0 –	62	1.4 (0.4 – 5.1)	9	3.1 (0.5 – 21)
Q2	100	0.9 (0.3 – 3.5)	53	2.1 (0.6 – 7.1)	37	5.0 (1.5 – 17)
Q3	58	1.6 (0.4 – 5.5)	60	1.7 (0.5 – 5.8)	32	5.7 (1.6 – 20)
Q4	43	3.2 (0.9 – 11)	64	3.7 (1.1 – 12)	38	9.1 (2.5 – 33)

Figure 2. Interaction between body mass index (BMI) and serum concentrations of PCBs on the prevalence of diabetes. PCBs: Sum of orders of PCBs 118, 138, 153, and 180. All odds ratios (OR) are computed with Q1 and normal weight as the reference category (OR = 1.0), with models adjusted by age, sex, total cholesterol, and triglycerides.

increase in the prevalence of diabetes with increasing BMI was similar in subjects with lower and higher concentrations of PCBs (Figure 2).

Concerning effect modification by lipids, the positive associations between PCBs (and HCB) and diabetes were of similar magnitude and statistical significance in subjects with cholesterol (and triglycerides) in the normal range of concentrations than in all subjects; the number of subjects with abnormally high cholesterol (and triglycerides) was insufficient to assess the associations.

The relationship between HCB (and PCBs) and diabetes appeared to be weakly mediated by triglycerides, and the relationship between triglycerides and diabetes was only partly due to HCB (and to PCBs) (SI, Table S3). The relationship between HCB and diabetes was also weakly mediated by BMI, and that between BMI and diabetes was weakly mediated by HCB; a similar conclusion can be applied to PCB 118.

Prediabetes. Similar to what we observed for diabetes, participants with higher concentrations of PCBs were more likely to have prediabetes, after adjusting for age, sex, and BMI, as well as for total cholesterol and triglycerides. ORs for participants with PCB concentrations in the top quartile ranged between 2.1 (95% CI: 1.2−3.7) and 2.3 (95% CI: 1.2−4.2) (all *p*-values for linear trend <0.021) (Table 3). In dose−response analyses based on restricted quadratic splines, we observed positive and linear associations with increasing PCB concentrations, with no evidence of nonlinearity (SI Figure S1). The *p*-values for the nonlinear spline terms for PCBs 118, 138, 153, and 180 were 0.459, 0.715, 0.965, and 0.108, respectively. The adjusted ORs comparing participants in the 80th vs the 20th percentiles of PCBs concentrations were all ≥1.5 (*p*-values <0.02) (Table 3). When POP concentrations were individually corrected by total lipids the ORs for prediabetes became attenuated and with wider confidence intervals, except for PCB 118 (OR for the upper quartile = 1.9, *p*-value for linear trend = 0.013) (SI Table S1), as also observed in models for diabetes. The sum of orders of PCBs was also associated with prediabetes: individuals in the upper category were 3 times more likely to have prediabetes than those in the lowest category. Both dioxin-like and non dioxin-like PCBs were significantly associated with prediabetes (Table 3). The OR of prediabetes for the upper quartile of PCBs phenobarbital-type inducers was 2.7 (95% CI: 1.4−5.0, *p*-trend 0.001); for moderately chlorinated PCBs it was 3.0 (95% CI: 1.6−5.6, *p*-

Table 3. Associations between Concentrations of Organochlorine Compounds and Prediabetes[a]

		crude model			model 1			model 2		
compounds (ng/mL)	prediabetes/Normal[b]	OR	(95% Cl)	*P*	OR	(95% Cl)	*P*	OR	(95% Cl)	*P*
PCB 118										
≤0.060	39/167	1.0		<0.001[c]	1.0		0.004[c]	1.0		0.007[c]
0.060−0.135	35/162	0.9	(0.6−1.5)		0.9	(0.5−1.5)		0.9	(0.5−1.5)	
0.135−0.242	55/126	1.9	(1.2−3.0)		1.4	(0.8−2.3)		1.3	(0.8−2.2)	
>0.242	73/86	3.6	(2.3−5.8)		2.2	(1.3−3.8)		2.1	(1.2−3.7)	
80th vs 20th percentile		2.5	(1.7−3.5)	<0.001[c]	1.7	(1.2−2.5)	0.005[c]	1.6	(1.1−2.4)	0.010[c]
PCB 138										
≤0.258	33/179	1.0		<0.001	1.0		0.002	1.0		0.009
0.259−0.451	47/152	1.7	(1.0−2.8)		1.5	(0.9−2.5)		1.4	(0.8−2.4)	
0.452−0.722	55/121	2.5	(1.5−4.0)		1.7	(1.0−2.9)		1.5	(0.9−2.7)	
>0.722	67/89	4.1	(2.5−6.7)		2.5	(1.4−4.6)		2.3	(1.2−4.2)	
80th vs 20th percentile		2.1	(1.6−2.9)	<0.001[c]	1.6	(1.2−2.2)	0.005[c]	1.5	(1.0−2.0)	0.017[c]
PCB 153										
≤0.361	34/178	1.0		<0.001	1.0		0.004	1.0		0.021
0.362−0.626	44/151	1.5	(0.9−2.5)		1.4	(0.8−2.3)		1.3	(0.8−2.3)	
0.627−0.978	58/121	2.5	(1.5−4.1)		1.7	(1.0−3.0)		1.5	(0.9−2.7)	
>0.978	66/91	3.8	(2.3−6.2)		2.4	(1.3−4.3)		2.1	(1.1−3.8)	
80th vs 20th percentile		2.2	(1.7−2.9)	<0.001[c]	1.7	(1.2−2.3)	0.001[c]	1.5	(1.1−2.1)	0.007[c]
PCB 180										
≤0.314	31/179	1.0		<0.001	1.0		0.005[c]	1.0		0.035[c]
0.315−0.503	43/152	1.6	(1.0−2.7)		1.4	(0.8−2.4)		1.3	(0.8−2.3)	
0.504−0.783	67/113	3.4	(2.1 −5.6)		2.5	(1.4−4.4)		2.2	(1.2−3.9)	
>0.783	61/97	3.6	(2.2−6.0)		2.4	(1.3−4.5)		2.1	(1.1−3.9)	
80th vs 20th percentile		2.2	(1.6−2.9)	<0.001[c]	1.7	(1.2−2.5)	0.002[c]	1.6	(1.1−2.3)	0.015[c]
HCB										
≤0.509	29/181	1.0		<0.001	1.0		0.060	1.0		0.166[c]
0.510−1.193	51/140	2.3	(1.4−3.8)		1.9	(1.1−3.3)		1.7	(1.0−3.0)	
1.194−2.610	61/124	3.1	(1.9−5.1)		2.1	(1.1−3.8)		1.9	(1.0−3.4)	
>2.610	61/96	4.0	(2.4−6.6)		2.1	(1.0−4.4)		1.6	(0.7−3.5)	
80th vs 20th percentile		2.0	(1.4−2.8)	<0.001[c]	1.2	(0.8−2.0)	0.435[c]	1.1	(0.7−1.8)	0.754[c]
β-HCH										
≤0.288	37/171	1.0		<0.001	1.0		0.350	1.0		0.914[c]
0.289−0.670	43/156	1.3	(0.8−2.1)		1.0	(0.6−1.6)		0.9	(0.5−1.5)	
0.671−1.547	58/120	2.2	(1.4−3.6)		1.2	(0.7−2.1)		1.1	(0.6−1.9)	
>1.547	64/94	3.1	(2.0−5.1)		1.3	(0.7−2.7)		1.1	(0.5−2.2)	
80th vs 20th percentile		2.2	(1.6−3.0)	<0.001[c]	1.4	(0.9−2.2)	0.119[c]	1.3	(0.8−1.9)	0.295[c]
p,p '-DDT										
≤0.086	47/150	1.0		0.128[c]	1.0		0.270[c]	1.0		0.251[c]
0.087−0.178	44/144	1.0	(0.6−1.6)		0.7	(0.5−1.2)		0.7	(0.4−1.2)	
0.179−0.349	61/125	1.6	(1.0−2.4)		1.0	(0.6−1.6)		1.0	(0.6−1.6)	
>0.349	50/122	1.3	(0.8−2.1)		0.7	(0.4−1.1)		0.6	(0.4−1.1)	
80th vs 20th percentile		1.2	(1.0−1.5)	0.076[c]	0.9	(0.7−1.1)	0.297[c]	0.9	(0.7−1.1)	0.285[c]
p,p'-DDE										
≤1.24	32/172	1.0		<0.001	1.0		0.336[c]	1.0		0.346[c]
1.25−2.63	56/139	2.2	(1.3−3.5)		1.6	(0.9−2.6)		1.5	(0.9−2.5)	
2.64−5.56	58/122	2.6	(1.6−4.2)		1.3	(0.7−2.3)		1.2	(0.7−2.1)	
>5.56	56/108	2.8	(1.7−4.6)		1.1	(0.6−2.1)		1.0	(0.5−1.9)	
80th vs 20th percentile		1.9	(1.4−2.5)	<0.001[b]	1.1	(0.7−1.5)	0.784[c]	1.0	(0.7−1.4)	0.950[c]

Table 3. continued

		crude model			model 1			model 2		
compounds (ng/mL)	prediabetes/Normal[b]	OR	(95% Cl)	*P*	OR	(95% Cl)	*P*	OR	(95% Cl)	*P*
Sum of PCBs										
≤1.03	29/183	1.0		<0.001	1.0		<0.001	1.0		0.001
1.04−1.76	47/149	2.0	(1.2−3.3)		1.6	(0.9−2.8)		1.6	(0.9−2.8)	
1.76−2.72	56/122	2.9	(1.8−4.8)		2.1	(1.2−3.8)		1.9	(1.1−3.4)	
>2.73	70/87	5.1	(3.1−8.4)		3.5	(1.9−6.4)		3.0	(1.6−5.7)	
80th vs 20th percentile		1.6	(1.1−2.3)	0.009[c]	1.8	(1.2−2.5)	0.002[c]	1.6	(1.1−2.3)	0.012[c]
Sum of Orders PCBs										
4−6	29/186	1.0		<0.001	1.0		<0.001	1.0		0.001
7−10	55/162	2.2	(1.3−3.6)		1.8	(1.0−3.0)		1.7	(1.0−2.9)	
11−13	50/114	2.8	(1.7−4.7)		2.0	(1.1−3.5)		1.8	(1.0−3.2)	
14−16	68/79	5.5	(3.3−9.2)		3.4	(1.8−6.3)		3.0	(1.6−5.6)	
80th vs 20th percentile		3.7	(2.4−5.6)	<0.001[c]	2.4	(1.4−4.1)	0.001[c]	2.1	(1.2−3.7)	0.007[c]
Sum of Orders All POPs										
8−14	33/197	1.0		<0.001	1.0		0.077[c]	1.0		0.160[c]
15−20	49/135	2.2	(1.3−3.5)		1.7	(1.0−2.9)		1.7	(1.0−3.0)	
21−26	56/127	2.6	(1.6−4.3)		1.6	(0.9−2.9)		1.5	(0.8−2.8)	
27−32	64/82	4.7	(2.8−7.6)		2.4	(1.2−4.6)		2.0	(1.0−4.0)	
80th vs 20th percentile		2.9	(2.1−4.2)	<0.001[c]	1.8	(1.1−3.1)	0.021[c]	1.6	(1.0−2.8)	0.073[c]
Number of POPs at High Concentrations										
0	71/279	1.0		<0.001	1.0		0.323[c]	1.0		0.459[c]
1−2	46/131	1.4	(0.9−2.1)		0.9	(0.6−1.4)		0.9	(0.6−1.5)	
3−4	38/78	1.9	(1.2−3.1)		1.0	(0.6−1.7)		0.9	(0.5−1.5)	
5−6	25/33	3.0	(1.7−5.3)		1.6	(0.8−3.1)		1.4	(0.7−2.9)	
7−8	22/20	4.3	(2.2−8.4)		1.8	(0.8−4.0)		1.6	(0.7−3.5)	
80th vs 20th percentile		2.4	(1.4−4.2)	0.002[c]	2.0	(1.0−3.9)	0.036[c]	1.7	(0.9−3.4)	0.116[c]
Dioxin-Like PCBs (PCBs 28, 118)										
≤0.0727	38/167	1.0		<0.001[c]	1.0		0.007[c]	1.0		0.015[c]
0.0727−0.1561	33/156	0.9	(0.6−1.6)		0.8	(0.5−1.4)		0.8	(0.5−1.4)	
0.1561 −0.268	60/120	2.2	(1.4−3.5)		1.7	(1.0−2.8)		1.6	(0.9−2.8)	
>0.268	71/98	3.2	(2.0−5.1)		1.8	(1.1−3.1)		1.8	(0.7−4.2)	
80th vs 20th percentile		2.1	(1.6−2.9)	<0.001[c]	1.5	(1.1−2.1)	0.011[c]	1.5	(1.1−2.0)	0.019[c]
Nondioxin-Like PCBs (PCBs 52, 101, 138, 153, 180)										
≤0.931	32/176	1.0		<0.001	1.0		<0.001	1.0		0.003
0.931 −1.5975	41/157	1.4	(0.9−2.4)		1.3	(0.7−2.2)		1.2	(0.7−2.1)	
1.5975−2.468	65/115	3.1	(1.9−5.0)		2.3	(1.3−4.0)		2.0	(1.2−3.6)	
>2.468	64/93	3.8	(2.3−6.2)		2.6	(1.4−4.8)		2.3	(1.2−4.2)	
80th vs 20th percentile		2.2	(1.7−3.0)	<0.001[c]	1.7	(1.2−2.4)	0.003[c]	1.5	(1.1−2.2)	0.016[c]

[a]OR: Odds ratio. CI: Confidence interval. Model 1: adjusted by sex, age and BMI. Model 2: further adjusted by total cholesterol and triglycerides. Number of POPs at high concentrations: number of POPs whose serum concentrations were ≥percentile 75. [b]Number of participants with prediabetes/number of normal participants. Unless otherwise specified, *p* value derived from multivariate analogue of Mantel's extension test for linear trend. [c]Wald's test.

trend 0.006). The association of prediabetes with HCB was marginally significant when adjusting by age, sex, and BMI (*p*-value for linear trend = 0.060); it was not significant when it was further adjusted for total cholesterol and triglycerides (Table 3).

Contrary to what was found for diabetes, the relationship between prediabetes and all four PCBs and HCB was always stronger among normal-weight than among obese participants (SI Table S4). *P*-values for the interactions ranged between 0.044 for PCB 138 and 0.403 for HCB. The positive association between BMI and prediabetes was always stronger among participants with PCBs or HCB concentrations in the lowest quartile; for example, the ORs of prediabetes for obese individuals (compared to normal-weight individuals) in the lowest and highest quartiles of PCB 138 were 14.0 and 3.0, respectively.

When we excluded patients taking insulin or antidiabetic medication, and subjects who answered affirmatively to the question "Do you have or did a doctor tell you that you have diabetes" (N = 61), statistically significant associations were observed among the remaining subjects (N = 825) between fasting plasma glucose and concentrations of PCBs 138, 153,

and 180 (adjusting by age, sex, BMI, cholesterol and triglycerides).

DISCUSSION

The prevalence of diabetes and prediabetes was substantially higher in population groups with higher concentrations of all the 8 most prevalent POPs analyzed. However, virtually all the association between diabetes and some POPs (*p,p′*-DDT, *p,p′*-DDE and *β*-HCH) was due to the confounding effects of age, sex and BMI. For PCBs 118, 138, 153, and 180, and HCB, only part of the association was due to age, sex, and BMI: in models adjusted by these three factors, the prevalence of diabetes and prediabetes continued to increase in a dose-dependent manner across quartiles of the PCBs and HCB, with odds ratios of diabetes between 2.3 and 3.2 for the upper quartile of POPs. These multivariate analyses were performed with crude (i.e., lipid-uncorrected) values of POPs; when models were further adjusted for total cholesterol and triglycerides, the associations were slightly lower and remained statistically significant: the ORs for the upper quartile ranged between 2.0 and 2.8 (all *p*-values for linear trend <0.05). In models with POPs individually corrected by lipids, ORs were further attenuated and nonsignificant, except for PCB 118. Importantly, coexposure to both obesity and POPs was a strong determinant of diabetes, with a 9-fold increased odds of having diabetes comparing participants in the highest exposure quartiles with those in the lowest exposure quartiles of obesity and PCBs.

Two previous studies found the strongest associations between type 2 diabetes and concentrations of *p,p′*-DDE and PCB 153 among overweight and obese individuals.[27,28] One of them found no diabetes-POPs association among normal-weight subjects,[27] while the other study also found the association among normal-weight subjects.[28] In the present study stronger associations of PCB 118 with diabetes were observed among obese and overweight individuals than among individuals with normal weight, although precision was low and the interaction was not statistically significant. Positive associations between the remaining POPs and diabetes were of similar magnitude in subjects with normal weight, overweight, and obese.

We also assessed the possible interaction between POP levels and BMI on the prevalence of prediabetes. We found that the relationship between prediabetes and serum concentrations of PCBs and HCB tended to be stronger in normal-weight individuals than in overweight and obese individuals.

Therefore, when the association between POPs and prediabetes was different across BMI categories, the association was stronger in normal-weight subjects than in the other BMI categories. By contrast, when the association between POPs and diabetes was different across BMI categories, the association was stronger in obese subjects than in the other BMI categories. This contrasting patterns might reflect a sequence of events that only longitudinal studies with repeated individual measures will properly assess.

Our results are generally in accordance with most prospective[1,3,4,6,7] and cross-sectional[1,21,25,27−29] studies on POPs and diabetes, which found positive associations between concentrations of PCBs and the disease. Moreover, most of these studies found a linear dose−response relationship between PCBs and diabetes risk.[3,7,21,27,28] In contrast with some,[5,21,27−29] but not all reports, we observed no association between concentrations of *p,p′*-DDT and *p,p′*-DDE and diabetes. The associations that we observed between PCBs, HCB, and prediabetes are consistent with two previous studies.[21,25]

Some[6]—but not all[1]—studies have shown nonlinear relationships (nonmonotonic, quadratic) between POPs and diabetes or metabolic syndrome. In the present study results from both quartiles and spline models favored linear dose—response relationships, although only exposure in the higher quartiles of some POPs was significantly associated with diabetes and prediabetes. Differences among studies in the shape of dose—response curves could be due to differences in population characteristics, confounding factors, and interactions.

The population of Catalonia has higher levels of POPs than other populations, such as Germany, the US, Canada or New Zealand;[9,38,39] for example, the geometric mean of *p,p′*-DDE, PCBs 153 and 180, HCB and *β*-HCH for the Catalan population was 458, 96, 83, 181, and 104 ng/g lipid, respectively, whereas for the U.S. population ≥20 years the corresponding values are 268, 24, 19, 16, and 8 ng/g lipid, respectively;[38] and in Catalonia the percentile 75 (P75) of the eight most prevalent POPs is between 2- and 20-times higher than the corresponding P75 in the U.S. The high levels of POPs in our study further increase the relevance of examining in this population relationships between diabetes and POPs that have been assessed in previous studies.

We assessed effects of POP mixtures through the sum of the seven PCBs analyzed and the sum of orders of PCBs, the sum of orders of all POPs and the number of POPs at high concentrations.[11] Similarly to previous findings,[21] individuals in the highest category of the sum of orders of PCBs had a higher risk of prediabetes than that of each individual PCB. This effect was not observed in diabetes or for the other measures of POP mixtures. Other studies also found the sum of PCBs[7,25] and the sum of orders of various POPs[27] associated with diabetes. By contrast with dioxin-like PCBs, nondioxin like PCBs were associated with diabetes, as were phenobarbital-type inducers PCBs.

The current state of knowledge does not permit to state which measure of serum POP concentrations—lipid-corrected or uncorrected—is more valid when studying the influence of POPs on the risk of diabetes and other diseases.[1,33] POPs are highly lipophilic, and their serum concentrations are hence closely related to serum lipid levels. Perhaps crucially, some POPs might alter lipid profiles.[6,33,34,40] From its early stages, diabetes is associated with changes in serum lipids (increased triglycerides, decreased HDL cholesterol).[19] A change in blood lipid contents will disturb the dynamic equilibrium between POP concentrations in blood and body tissues. These questions are of particular concern in cross-sectional studies, although our subjects were fasting when blood was drawn.[22,33] There are reasons to correct for lipids as well as reasons to think that such correction may be an overadjustment that underestimates true associations between diabetes and POPs.[6,26]

In addition to its moderate sample size, which limited statistical power in quartile and interaction models, our study has other limitations. Venous blood samples collected during the health examination would have been more appropriate to measure glucose levels than the capillary blood samples that were also collected in the CHIS and used in the present report; logistic limitations in sample processing prevented obtaining valid glucose measures in venous blood. Other epidemiologic studies also used capillary blood samples to define diabetes status,[25,41] and our participants were considered to have

diabetes and prediabetes following established recommendations.[1,30,31]

The cross-sectional design of this and previous studies requires caution when assessing causal relationships.[13] Certainly, findings are in accordance with results of experimental[15−18] and observational studies,[1−7] some of which had a prospective design[2−7] that allowed to rule out disease progression bias.[1] Moreover, some studies provided evidence on possible mechanisms of PCBs, dioxins and other POPs on beta-cell function and insulin resistance.[15−18] The associations we found with POP levels and prediabetes are also suggestive of a causal relationship with diabetes. Findings might also have mechanistic implications for other diseases in which diabetes is a risk factor: the toxic effects of some POP mixtures (neuroendocrine, inflammatory, immunosuppressive)[1,2,8,10,17,18,20,38] may lie beneath some associations between diabetes or obesity and some cancers and inflammatory disorders.[42]

Findings support the hypothesis that exposure to POPs may be a diabetogenic factor in both obese and nonobese individuals. Coexposure to obesity and POPs could contribute to explain the population burden of diabetes. Findings must be confirmed by prospective studies in other populations exposed to a variety of obesogenic factors. Nevertheless, results add to the existing evidence supporting policies that decrease human exposure to POPs.

■ ASSOCIATED CONTENT

Supporting Information

Additional information on Methods, Tables, and Figures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

ADA	American Diabetes Association
CI	confidence interval
DDD	dichlorodiphenyldichloroethane
DDE	dichlorodiphenyldichloroethene
DDT	dichlorodiphenyltrichloroethane
HCB	hexachlorobenzene
HCH	hexachlorocyclohexane
PCBs	polychlorinated biphenyls
PeCB	pentachlorobenzene
POPs	persistent organic pollutants
CHIS	Catalan Health Interview Survey
WHO	World Health Organization
BMI	body mass index

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NOTE ADDED AFTER ASAP PUBLICATION

Due to a production error, Figure 2 was modified in the version of this paper published June 20, 2012. The correct version published June 27, 2012.

Supporting Information

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Blood Concentrations of Persistent Organic Pollutants and Prediabetes and Diabetes in the General Population of Catalonia

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Table S2. Associations between concentrations of organochlorine compounds and diabetes stratified by BMI.

Table S3. Assessing the concentration of triglycerides as partial mediator of the relationship between hexachlorobenzene and diabetes.

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Figure S1. Odds ratios and 95% confidence intervals for the association between prediabetes and blood concentrations of PCBs.

Methods

Recruitment and study population. Catalonia, an autonomous region in the North-east of Spain, had a population of 6,506,440 inhabitants in 2002. As part of its mission to monitor health status and use of health services, that year the Department of Health of the Catalan government conducted a new health interview survey. The main objective of the Catalan Health Interview Survey (CHIS) was to obtain information on perceived health, health-related behaviors, and use of health services. The selection of a representative sample of the non-institutionalized population followed a complex design, including a multiple-stage random sampling strategy. In the first sampling stage municipalities (for the city of Barcelona, districts) were selected from the eight health areas of Catalonia, according to their population size (eight strata). Based on the size of the municipality (or district), at the second sampling stage a random sample from the census was used to select individuals using proportional probabilities. The target population of CHIS were all non-institutionalized residents in Catalonia in 2001. Face to face interviews were conducted at home by trained staff from October 2001 to April 2002. At the end of the CHIS interview, participants 18-74 year old were offered to take part in a health examination, which included a physical exam, a supplementary interview, and the collection of urine and blood samples. Among those who explicitly consented to participate, a sample was randomly selected, contacted by phone and given an appointment at the primary health centre nearest to their home. Participation was voluntary and no economic compensation was offered. Participants were asked to fast for twelve hours before blood extraction. The blood sample was drawn by venipuncture, kept refrigerated, and centrifuged within four hours. Serum was first stored frozen at –20ºC to determine immunologic, biochemical and nutritional parameters. Once these analyses were completed, the remaining serum was kept frozen at –80ºC until 2006, when POP concentrations were analyzed.

Table S1. Associations between lipid-corrected organochlorine compounds (ng/g lipid) and diabetes and prediabetes.

Compounds (ng/g lipid)	Diabetes / Normal[a]	OR	(95% CI)	P	Prediabetes / Normal[b]	OR	(95% CI)	P
PCB 118								
≤ 10.43	17 / 166	1.0		0.048	39 / 166	1.0		0.013
10.44-22.99	28 / 156	1.3	(0.7-2.7)		42 / 156	1.0	(0.6-1.7)	
23.00-38.24	41 / 122	2.0	(1.0-4.0)		53 / 122	1.4	(0.9-2.4)	
> 38.24	57 / 97	1.9	(0.9-3.9)		68 / 97	1.9	(1.1-3.2)	
PCB 138								
≤ 43.98	15 / 170	1.0		0.405[c]	39 / 170	1.0		0.112
43.99-74.09	28 / 145	1.2	(0.6-2.5)		46 / 145	1.2	(0.7-2.0)	
74.10-118.51	45 / 120	1.8	(0.9-3.6)		53 / 120	1.4	(0.8-2.3)	
> 118.52	55 / 106	1.4	(0.7-3.0)		64 / 106	1.5	(0.9-2.7)	
PCB 153								
≤ 64.97	14 / 165	1.0		0.060	44 / 165	1.0		0.357[c]
64.98-104.11	28 / 150	1.1	(0.5-2.4)		42 / 150	0.9	(0.5-1.4)	
104.12-162.34	41 / 125	1.6	(0.8-3.5)		54 / 125	1.1	(0.7-1.9)	
> 162.34	60 / 101	1.8	(0.8-4.0)		62 / 101	1.4	(0.8-2.4)	
PCB 180								
≤ 54.96	21 / 163	1.0		0.219[c]	37 / 163	1.0		0.079
54.97-85.34	29 / 145	0.7	(0.3-1.4)		51 / 145	1.2	(0.7-2.1)	
85.35-126.65	33 / 130	0.8	(0.4-1.6)		54 / 130	1.4	(0.8-2.5)	
> 126.65	60 / 103	1.2	(0.6-2.5)		60 / 103	1.7	(0.9-3.0)	
HCB								
≤ 86.39	14 / 173	1.0		0.103	36 / 173	1.0		0.147[c]
86.40-200.94	28 / 143	1.6	(0.8-3.5)		47 / 143	1.3	(0.7-2.2)	
200.95-415.12	40 / 115	2.0	(0.9-4.4)		63 / 115	1.6	(0.9-2.8)	
> 415.12	61 / 110	2.1	(0.9-5.3)		56 / 110	0.9	(0.5-2.0)	
β-HCH								
≤ 52.20	18 / 163	1.0		0.308	42 / 163	1.0		0.809
52.21-110.68	18 / 159	0.6	(0.3-1.4)		44 / 159	0.8	(0.5-1.3)	
110.69-251.40	44 / 115	1.2	(0.6-2.5)		58 / 115	0.9	(0.5-1.6)	
> 251.40	63 / 104	1.2	(0.5-2.7)		58 / 104	0.8	(0.4-1.5)	
***p,p'*-DDT**								
≤ 13.68	30 / 142	1.0		0.024	49 / 142	1.0		0.120
13.69-30.02	36 / 139	0.9	(0.5-1.6)		48 / 139	0.8	(0.5-1.3)	
30.03-57.72	34 / 136	0.6	(0.3-1.1)		54 / 136	0.8	(0.5-1.3)	
> 57.72	43 / 124	0.5	(0.3-1.0)		51 / 124	0.6	(0.4-1.1)	
***p,p'*-DDE**								
≤ 222.65	22 / 160	1.0		0.880[c]	39 / 160	1.0		0.196[c]
222.66-433.74	27 / 145	1.1	(0.5-2.1)		52 / 145	1.1	(0.7-1.9)	
433.75-910.90	35 / 124	0.8	(0.4-1.7)		62 / 124	1.2	(0.7-2.0)	
> 910.90	59 / 112	0.9	(0.4-1.8)		49 / 112	0.7	(0.4-1.3)	

[a] Number of participants with diabetes / number of normal participants.
[b] Number of participants with prediabetes / number of normal participants.
OR: Odds ratio. CI: Confidence interval.
Models adjusted by sex, age and BMI.
Unless otherwise specified, p value derived from multivariate analogue of Mantel's extension test for linear trend.
[c] Wald's test.

Table S2. Associations between concentrations of organochlorine compounds and diabetes stratified by BMI.

Compounds (ng/mL)	Categories of BMI: Normal range (N = 329) OR	(IC 95%)	P	Overweight (N = 239) OR	(IC 95%)	P	Obese (N = 116) OR	(IC 95%)	P	$P_{interaction}$
PCB 118										
≤ 0.060	1.0		0.628 [a]	1.0		0.022	1.0		0.214 [a]	0.514
0.060-0.135	0.8	(0.2-2.4)		1.5	(0.5-4.8)		5.7	(0.7-44.7)		
0.135-0.242	1.6	(0.5-4.6)		2.3	(0.8-7.0)		2.3	(0.3-17.4)		
> 0.242	1.0	(0.3-3.9)		3.4	(1.1-10.2)		4.5	(0.6-35.0)		
PCB 138										
≤ 0.258	1.0		0.266 [a]	1.0		0.035	1.0		0.496	0.977
0.259-0.451	0.7	(0.2-2.8)		1.1	(0.3-3.6)		1.9	(0.3-12.8)		
0.452-0.722	1.3	(0.3-5.2)		1.9	(0.6-5.8)		1.7	(0.3-11.2)		
> 0.722	2.4	(0.6-9.9)		2.8	(0.9-8.6)		2.3	(0.3-15.8)		
PCB 153										
≤ 0.361	1.0		0.246	1.0		0.077	1.0		0.389	0.995
0.362-0.626	1.1	(0.3-4.3)		1.8	(0.5-6.1)		1.6	(0.3-9.6)		
0.627-0.978	1.7	(0.4-7.3)		1.7	(0.5-5.6)		2.0	(0.4-11.3)		
> 0.978	2.1	(0.5-9.5)		2.9	(0.9-9.6)		2.2	(0.4-13.5)		
PCB 180										
≤ 0.314	1.0		0.338 [a]	1.0		0.134	1.0		0.999 [a]	0.976
0.315-0.503	0.6	(0.1-3.0)		1.0	(0.3-3.6)		1.0	(0.2-5.2)		
0.504-0.783	1.4	(0.3-6.2)		1.6	(0.5-5.4)		1.1	(0.2-5.7)		
> 0.783	2.2	(0.5-10.0)		2.0	(0.6-6.7)		1.1	(0.2-6.8)		
Sum of orders PCBs										
4-6	1.0		0.013	1.0		0.009	1.0		0.790 [a]	0.975
7-10	0.7	(0.2-2.9)		1.5	(0.5-4.8)		1.6	(0.3-10.6)		
11-13	1.3	(0.3-5.3)		1.4	(0.4-4.3)		1.8	(0.3-12.1)		
14-16	2.6	(0.6-11.2)		3.0	(1.0-9.5)		2.5	(0.4-18.0)		
HCB										
≤ 0.509	1.0		0.086	1.0		0.070	1.0		0.290	0.668
0.510-1.193	2.6	(0.7-9.2)		0.9	(0.3-3.0)		1.2	(0.1-21.9)		
1.194-2.610	3.9	(1.0-15.0)		1.4	(0.4-4.4)		1.5	(0.1-22.8)		
> 2.610	3.9	(0.7-20.2)		3.5	(0.8-15.7)		2.4	(0.2-38.8)		
β-HCH										
≤ 0.288	1.0		0.667 [a]	1.0		0.198 [a]	1.0		0.611 [a]	0.328
0.289-0.670	1.6	(0.5-5.7)		0.3	(0.1-1.1)		1.0	(0.1-9.9)		
0.671-1.547	2.3	(0.6-8.9)		0.5	(0.2-1.8)		1.0	(0.1-8.8)		
> 1.547	1.8	(0.4-9.3)		0.8	(0.2-3.1)		2.1	(0.2-18.6)		
***p,p'*-DDT**										
≤ 0.086	1.0		0.030	1.0		0.639 [a]	1.0		0.718 [a]	0.456
0.087-0.178	1.1	(0.4-2.8)		1.6	(0.5-4.7)		1.3	(0.3-5.6)		
0.179-0.349	0.6	(0.2-1.9)		1.3	(0.4-3.7)		0.8	(0.2-3.5)		
> 0.349	0.2	(0.0-0.9)		0.9	(0.3-2.8)		1.6	(0.4-6.0)		
***p,p'*-DDE**										
≤ 1.24	1.0		0.949 [a]	1.0		0.749 [a]	1.0		0.267 [a]	0.475
1.25-2.63	1.2	(0.4-3.9)		1.0	(0.3-3.2)		1.8	(0.3-11.8)		
2.64-5.56	0.9	(0.2-3.1)		1.3	(0.4-4.2)		0.7	(0.1-3.8)		
> 5.56	1.0	(0.3-3.6)		0.8	(0.2-2.9)		1.7	(0.3-9.6)		

All models adjusted by sex, age, total cholesterol and triglycerides.
Unless otherwise specified, p value derived from multivariate analogue of Mantel's extension test for linear trend.
[a] Wald's test.

Table S3. Assessing the concentration of triglycerides as partial mediator of the relationship between hexachlorobenzene and diabetes.

Model Exposures	OR	(IC 95%)	P
Model 1			
Age	1.1	(1.1-1.1)	<0.001[a]
Sex (male)	1.9	(1.3-2.9)	0.002[a]
Triglycerides			
<150	1.0		<0.001[a]
≥150	3.6	(2.1-6.1)	
Model 2			
Age	1.0	(1.0-1.1)	<0.001[a]
Sex (male)	4.0	(2.4-6.7)	<0.001[a]
Hexachlorobenzene			
≤ 0.509	1.0		<0.001
0.510 – 1.193	2.0	(0.9-4.2)	
1.194 – 2.610	3.0	(1.4-6.4)	
>2.610	6.8	(2.9-16.0)	
Model 3			
Age	1.1	(1.0-1.1)	<0.001[a]
Sex (male)	3.4	(2.0-5.8)	<0.001[a]
Triglycerides			
<150	1.0		<0.001[a]
≥150	3.0	(1.7-5.3)	
Hexachlorobenzene			
≤ 0.509	1.0		<0.001
0.510 – 1.193	1.9	(0.9-4.0)	
1.194 – 2.610	2.7	(1.3-5.8)	
>2.610	5.4	(2.3-13.1)	

OR: Odds ratio. CI: Confidence interval. [a] Wald's test. Units: Hexachlorobenzene, ng/mL; triglycerides, mg/dL. Models adjusted by age and sex. In Model 3, ORs for Hexachlorobenzene and triglycerides are mutually adjusted for. Unless otherwise specified, p value derived from multivariate analogue of Mantel's extension test for linear trend.

Models above assess the concentration of triglycerides as partial mediator of the relationship between hexachlorobenzene (HCB) and diabetes. In order to be a mediator, the potential mediator (triglycerides) has to be associated with both the exposure of interest (HCB) and the outcome (diabetes). Spearman's correlation coefficient (ρ) between triglycerides and HCB was 0.22 ($p < 0.001$). When adjusted for age and sex, HCB was positively associated with levels of triglycerides ($p < 0.001$) (model not shown). Triglycerides were also positively associated with diabetes (Model 1, Table S3). The OR of diabetes for the upper quartile of HCB decreased from 6.8 (Model 2) to 5.4 (Model 3) when triglycerides were adjusted for. The OR of diabetes for increased triglycerides decreased from 3.6 (Model 1) to 3.0 (Model 3). These findings support the notion that the relationship between HCB and diabetes is only weakly mediated by triglycerides, and that the relationship between triglycerides and diabetes is only weakly due to HCB.

Analyses assessing triglycerides as possible mediators were also performed for the rest of POPs; similar results were obtained for some PCBs. Concentrations of PCBs 118, 138 and 153 were also associated with triglycerides (ρ about 0.21, $p < 0.001$); the ORs for the association of these PCB and diabetes were slightly attenuated when triglycerides were included in the models; the ORs for the association of the triglycerides and diabetes were also slightly attenuated. Again, these findings support the notion that the relationship between PCBs and diabetes is only weakly mediated by triglycerides, and that the relationship between triglycerides and diabetes is only weakly due to PCBs.

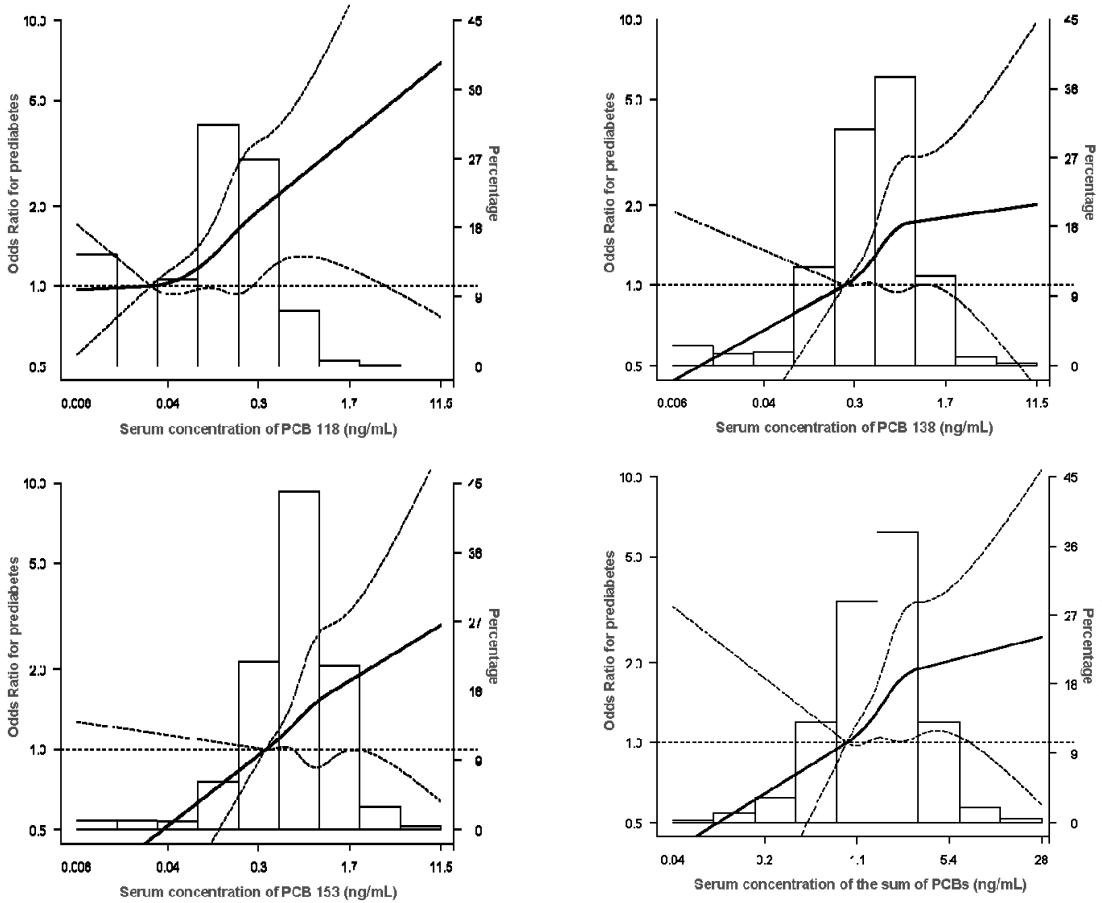
We also performed analyses assessing BMI as a possible mediator of the relationship between PCBs and HCB and diabetes. The ρ between BMI and HCB was 0.47, and between BMI and PCB 118, 0.31 (both $p < 0.001$). When adjusting for age and sex, only HCB and PCB 118 were positively and statistically significantly associated with BMI (p-values < 0.001). BMI was also associated with diabetes (OR for overweight vs. normal-weight = 1.6, 95% CI: 1.0-2.7; and OR for obese vs. normal-weight = 4.5, 95% CI: 2.6-8.0). The OR of diabetes for the upper quartile of HCB decreased from 6.8 to 3.7 when BMI was adjusted for. Similarly, the OR for the upper quartile of PCB 118 decreased from 3.2 to 2.4 when BMI was adjusted for. The ORs for BMI were also somewhat attenuated (OR for obese in model with HCB = 3.2, OR for obese in model with PCB 118 = 3.9; both ORs are to be compared with the OR of 4.5 just mentioned above). Results suggest that the relationship between HCB and diabetes is only weakly mediated by BMI, and that the relationship between BMI and diabetes is only weakly due to HCB. A similar conclusion can be applied to PCB 118.

Table S4. Associations between concentrations of organochlorine compounds and prediabetes stratified by BMI.

Compounds (ng/mL)	Categories of BMI: Normal range (N = 351) OR	(IC 95%)	P	Overweight (N = 275) OR	(IC 95%)	P	Obese (N = 117) OR	(IC 95%)	P	$P_{interaction}$
PCB 118										
≤ 0.060	1.0		0.005	1.0		0.303 [a]	1.0		0.144 [a]	0.370
0.060-0.135	1.1	(0.4-2.6)		0.9	(0.4-1.9)		0.4	(0.1-2.0)		
0.135-0.242	2.9	(1.2-6.7)		1.1	(0.5-2.5)		0.5	(0.2-1.9)		
> 0.242	3.0	(1.1-8.2)		1.7	(0.8-3.8)		1.5	(0.4-5.5)		
PCB 138										
≤ 0.258	1.0		0.021	1.0		0.019	1.0		0.038 [a]	0.044
0.259-0.451	1.9	(0.8-4.7)		2.2	(0.9-5.4)		0.2	(0.1-0.9)		
0.452-0.722	2.7	(1.0-7.3)		2.6	(1.1-6.4)		0.2	(0.1-0.7)		
> 0.722	3.5	(1.2-10.4)		3.3	(1.3-8.4)		0.5	(0.1-2.0)		
PCB 153										
≤ 0.361	1.0		0.023	1.0		0.071	1.0		0.177 [a]	0.175
0.362-0.626	1.7	(0.7-4.2)		2.1	(0.9-4.9)		0.3	(0.1-1.1)		
0.627-0.978	2.9	(1.1-7.9)		1.9	(0.8-4.6)		0.3	(0.1-1.1)		
> 0.978	3.3	(1.1-10.0)		2.6	(1.0-6.4)		0.6	(0.1-2.5)		
PCB 180										
≤ 0.314	1.0		0.017	1.0		0.065	1.0		0.159 [a]	0.104
0.315-0.503	3.1	(1.2-8.5)		1.5	(0.6-3.7)		0.3	(0.1-1.0)		
0.504-0.783	4.9	(1.7-14.1)		2.7	(1.1-6.4)		0.4	(0.1-1.4)		
> 0.783	4.1	(1.2-14.1)		2.2	(0.9-5.5)		0.6	(0.1-2.8)		
Sum of orders PCBs										
4-6	1.0		0.013	1.0		0.009	1.0		0.078 [a]	0.089
7-10	2.2	(0.9-5.4)		3.0	(1.2-7.4)		0.3	(0.1-1.1)		
11-13	2.7	(1.0-7.6)		2.9	(1.2-7.4)		0.3	(0.1-1.1)		
14-16	4.2	(1.4-12.9)		4.3	(1.6-11.5)		0.7	(0.2-3.2)		
HCB										
≤ 0.509	1.0		0.091 [a]	1.0		0.138 [a]	1.0		0.900 [a]	0.403
0.510-1.193	2.8	(1.2-6.4)		1.8	(0.7-4.6)		0.6	(0.1-3.5)		
1.194-2.610	1.6	(0.5-4.6)		2.9	(1.1-7.3)		0.7	(0.1-3.9)		
> 2.610	2.7	(0.8-9.6)		2.0	(0.6-6.8)		0.5	(0.1-3.8)		
β-HCH										
≤ 0.288	1.0		0.909 [a]	1.0		0.707 [a]	1.0		0.830 [a]	0.882
0.289-0.670	1.1	(0.5-2.4)		0.8	(0.3-1.8)		0.8	(0.2-4.0)		
0.671-1.547	1.0	(0.4-2.6)		1.1	(0.5-2.6)		1.2	(0.2-6.7)		
> 1.547	1.4	(0.4-4.7)		1.3	(0.5-3.6)		0.8	(0.1-5.2)		
***p,p'*-DDT**										
≤ 0.086	1.0		0.131 [a]	1.0		0.852 [a]	1.0		0.960 [a]	0.834
0.087-0.178	0.6	(0.2-1.4)		0.9	(0.4-1.9)		0.7	(0.2-2.7)		
0.179-0.349	1.4	(0.7-3.1)		0.9	(0.4-1.9)		0.9	(0.2-3.2)		
> 0.349	0.5	(0.2-1.5)		0.7	(0.3-1.6)		0.8	(0.2-2.8)		
***p,p'*-DDE**										
≤ 1.24	1.0		0.543 [a]	1.0		0.106 [a]	1.0		0.029 [a]	0.031
1.25-2.63	1.7	(0.7-3.7)		1.2	(0.5-2.8)		3.5	(0.7-17.5)		
2.64-5.56	1.0	(0.3-2.7)		1.9	(0.8-4.3)		0.6	(0.1-3.2)		
> 5.56	1.2	(0.4-3.5)		0.8	(0.3-2.1)		1.8	(0.3-10.4)		

All models adjusted by sex, age, total cholesterol and triglycerides.
Unless otherwise specified, p value derived from multivariate analogue of Mantel's extension test for linear trend.
[a] Wald's test.

Figure S1. Odds ratios and 95% confidence intervals for the association between prediabetes and blood concentrations of PCBs.



Odds ratios (solid lines) and 95% confidence intervals (curved dashed lines) were based on restricted quadratic splines for log-transformed PCB concentrations with knots at the 20th, 50th and 80th percentiles. Models adjusted for age, sex, BMI, total cholesterol and triglycerides. The reference value was set at the 20th percentile of PCB distribution. Vertical bars represent the histogram of PCB distribution.

Annex B. Llistat de publicacions i altres documents i materials científics elaborats pel Grup de Recerca en Epidemiologia Clínica i Molecular del Càncer (GRECMC PSMar) sobre els Compostos Tòxics Persistents (CTPs) i altres agents químics ambientals

Des de fa més de 20 anys, el Grup de Recerca en Epidemiologia Clínica i Molecular del Càncer (GRECMC) del Parc de Salut Mar (PSMar), liderat pel Dr. Miquel Porta, desenvolupa una línia de recerca sòlida, reconeguda a nivell internacional, sobre els compostos tòxics persistents (CTPs) i altres contaminants ambientals. Com en alguna altra ocasió, en el present annex d'aquesta tesi ens ha semblat adient presentar, actualitzat, un llistat que recull la major part de publicacions científiques –i alguns dels altres documents i materials científics relacionats amb aquestes exposicions ambientals– als que ha donat lloc aquesta recerca al llarg dels anys. A banda dels documents llistats a continuació convé esmentar que la recerca també ha generat nombroses intervencions de qualitat en institucions locals i globals, mitjans de comunicació, organitzacions ciutadanes i xarxes socials. Alguns exemples d'aquests i altres materials del grup es poden consultar a: https://www.imim.cat/programesrecerca/epidemiologia/grecm.html. D'altres es poden trobar fàcilment amb els buscadors habituals. El llistat que segueix exclou les publicacions científiques i altres documents relacionats amb les altres línies de recerca del GRECMC.

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Annex C. Activitats científiques de la doctoranda

Durant el procés de realització de la tesi s'han dut a terme diverses activitats científiques addicionals com les que es detallen a continuació. Les dades actualitzades sobre l'activitat científica de la doctoranda es poden consultar a: https://orcid.org/0000-0003-4546-3650.

Comunicacions a congressos

M. Gasull, C. Castell, N. Pallarès, C. Miret, J. Pumarega, T. López, J. Salas-Salvadó, DH. Lee, A. Goday, et al. Blood concentrations of persistent organic pollutants and unhealthy metabolic phenotypes in normal-weight, overweight and obese individuals. Gac Sanit 2017; 31 Supl : 251. XXXV Reunión Científica de la Sociedad Española de Epidemiología: (SEE) y XII Congresso da Associação Portuguesa de Epidemiologia (APE). Barcelona, 6-8 setembre 2017. *Comunicació oral*

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E. Puigdomènech, M. Gasull, M. Rodríguez-Sanz, J. Pumarega, C. Rebato, C. Borrell, M. Porta. 2008. Análisis de las concentraciones de compuestos orgánicos persistentes en la encuesta de salud de barcelona de 2006: diseño, proceso de reclutamiento y porcentajes de respuesta. Gac Sanit 2008; 22 (Espec Congr): 117-8. XXVI Reunión Científica de la Sociedad Española de Epidemiología. Girona, 15-17 d'Octubre de 2008. *Comunicació oral*

Elaboració de projectes de recerca i sol·licituds d'ajuts

La doctoranda ha participat activament en l'elaboració de diversos projectes de recerca i sol·licituds d'ajuts, diversos dels quals han obtingut finançament. En són un exemple el projecte que dona continuïtat a la recerca de la present tesi (vegeu l'apartat 5.4. del capítol de *Discussió*) i el projecte *'Concentracions sanguínies de compostos organoclorats, estils de vida i risc de càncer de pàncrees en la cohort EPIC'* finançat per La Marató de TV3.
També ha participat activament en la coordinació del treball de camp i altres aspectes d'aquests i altres projectes del grup.

Participació en cursos d'especialització metodològica i assistència a seminaris

Alguns dels cursos d'especialització metodològica que ha realitzat la doctoranda són:

Causal Diagrams: Draw Your Assumptions Before Your Conclusions.
Course of study offered by HarvardX, an online learning initiative of Harvard University through edX
(octubre 2017 – març 2018)

Getting published in journals.
Programa Intervals del Parc de Recerca Biomèdica de Barcelona (PRBB)
(juny 2016)

Curs d'Introducció a l'anàlisi i maneig de dades amb el programa R.
Àrea de Formació Continuada de l'Institut Hospital del Mar d'Investigacions Mèdiques (IMIM)
(febrer – març 2012)

Assisteix regularment als seminaris impartits per experts estatals i internacionals organitzats tant pel Programa d'Epidemiologia i Salut Pública (EPISAP) de l'IMIM com pel PRBB o per altres institucions. Assisteix anualment al *Retreat* que organitza l'IMIM i participa en els seminaris interns del GRECMC.

Tasques docents

Ha col·laborat en diverses activitats docents a la UD PSMar (Unitat Docent del Parc Salut Mar) de la Universitat Autònoma de Barcelona i actualment n'és professora associada. Participa en la docència de les assignatures 'Epidemiologia i Demografia Sanitaria' i 'Medicina Preventiva i Salut Pública' de 3er i 6è curs, respectivament, del Grau de Medicina conjunt de les Universitats Autònoma de Barcelona i Pompeu Fabra. També ha col·laborat en tasques docents del Màster en Salut Pública impartit per les mateixes universitats.

Revisió d'articles

Ha estat revisora per les següents revistes científiques internacionals (*peer-review*):
European Journal of Epidemiology, *Environment International*, *Environmental Research*, *Archives of Environmental Contamination and Toxicology*, *Reviews on Environmental Health* i *Journal of Human and Ecological Risk Assessment*.

Altres afiliacions

La doctoranda és membre de la 'Sociedad Española de Epidemiología' (SEE) des de l'any 2008 i del 'Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública' (CIBERESP). També forma part de la xarxa 'NCDs (Non-communicable diseases) Risk Factor Collaboration'.

IMIM

Parc de Salut MAR Barcelona

Institut Hospital del Mar d'Investigacions Mèdiques

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