Exposición prenatal a contaminantes

TÓXICOS AMBIENTALES EN RECIÉN NACIDOS DE LA ISLA DE LA PALMA

DOCTORADO EN INVESTIGACIÓN APLICADA
A LAS CIENCIAS SANITARIAS

Las Palmas de Gran Canaria | junio de 2020

Raúl Cabrera Rodríguez

UNIVERSIDAD DE LAS PALMAS
DE GRAN CANARIA

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D. JUAN FRANCISCO LORO FERRER, COORDINADOR DEL PROGRAMA DE DOCTORADO DE INVESTIGACIÓN APLICADA A LAS CIENCIAS SANITARIAS DE LA UNIVERSIDAD DE LAS PALMAS DE GRAN CANARIA,

INFORMA,

Que la Comisión Académica del Programa de Doctorado, en su sesión de fecha _____ tomó el acuerdo de dar el consentimiento para su tramitación, a la tesis doctoral titulada *"Exposición prenatal a contaminantes tóxicos ambientales en recién nacidos de la isla de La Palma"* presentada por el doctorando D. Raúl Cabrera Rodríguez y dirigida por el Doctor Luis Alberto Henríquez Hernández y la Doctora Maira Almeida González.

Y para que así conste, y a efectos de lo previsto en el Artº 11 del Reglamento de Estudios de Doctorado (BOULPGC 7/10/2016) de la Universidad de Las Palmas de Gran Canaria, firmo la presente en Las Palmas de Gran Canaria, a ___ de junio de 2020.

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ESCUELA DE DOCTORADO

Programa de doctorado de Investigación Aplicada a las Ciencias Sanitarias

Exposición prenatal a contaminantes tóxicos ambientales en recién nacidos en la isla de La Palma

· Tesis Doctoral presentada por D. Raúl Cabrera Rodríguez.

· Dirigida por el Dr. D. Luis Alberto Henríquez Hernández.

· Dirigida por la Dra. Dª Maira Almeida González.

El Director,	**La Directora,**	**El Doctorando,**
(firma)	(firma)	(firma)

Las Palmas de Gran Canaria, a de junio de 2020.

UNIVERSIDAD DE LAS PALMAS
DE GRAN CANARIA

D. LUIS ALBERTO HENRÍQUEZ HERNÁNDEZ, PROFESOR TITULAR DEL DEPARTAMENTO DE CIENCIAS CLÍNICAS, FACULTAD DE CIENCIAS DE LA SALUD DE LA UNIVERSIDAD DE LAS PALMAS DE GRAN CANARIA,

CERTIFICA,

Que el trabajo de investigación titulado *"Exposición prenatal a contaminantes tóxicos ambientales "*, ha sido realizado por D. Raúl Cabrera Rodríguez en el Departamento de Ciencias Clínicas de la Universidad de Las Palmas, bajo su dirección y asesoramiento técnico y científico, y que una vez revisada la presente Memoria, la encuentra apta para su defensa ante tribunal.

Y para que así conste, y surta los efectos oportunos, extiende el presente certificado en Las Palmas de Gran Canaria , a ____ de junio de 2020.

D. Luis Alberto Henríquez Hernández,

(firma)

UNIVERSIDAD DE LAS PALMAS
DE GRAN CANARIA

DÑA. MAIRA ALMEIDA GONZÁLEZ, PROFESORA ASOCIADA DE TOXICOLOGÍA DEL DEPARTAMENTO DE CIENCIAS CLÍNICAS, FACULTAD DE CIENCIAS DE LA SALUD DE LA UNIVERSIDAD DE LAS PALMAS DE GRAN CANARIA,

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Dña. Maira Almeida González,

(firma)

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Introducción

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1.1. La contaminación química ambiental

La humanidad ha experimentado un cambio progresivo desde sus orígenes hasta la actualidad, pero sin duda, la mayor transformación se ha producido en los dos últimos siglos. Desde la Revolución Industrial del Siglo XVIII hasta nuestros días, se han producido múltiples avances tecnológicos que han requerido la extracción de diferentes elementos de la corteza terrestre y la producción de un sinfín de materiales y sustancias químicas previamente inexistentes que se han puesto en contacto con el ser humano de forma progresiva.

Las nuevas formas de energía (gas, petróleo, electricidad) han requerido el desarrollo de industrias paralelas con el empleo de múltiples productos químicos y su liberación al medio ambiente. De igual manera, los nuevos métodos de transporte (ferrocarril, avión, automóvil) se han desarrollado de forma exponencial ocasionando mayor contaminación ambiental.

Por otro lado, la revolución agrícola de finales del siglo XIX, también denominada revolución verde, ha propiciado la producción masiva de insumos agrícolas, principalmente abonos nitrogenados y múltiples familias de pesticidas, que se han liberado de forma incontrolada al medio ambiente.

Finalmente, en los últimos 25 años, la revolución tecnológica ha supuesto la producción continua de múltiples instrumentos electrónicos con materiales previamente desconocidos y la generación de basura electrónica que se libera continuamente al medio ambiente. Dicha revolución ha venido acompañada del cambio en los hábitos del consumo, con la necesidad de poseer el último modelo de instrumento tecnológico, desechando continuamente los modelos anteriores. Esto unido a la obsolescencia programa de múltiples dispositivos electrónicos, genera anualmente la eliminación al medio ambiente de millones de toneladas de chatarra electrónica.

En muchos casos, desconocemos los efectos a largo plazo sobre la salud de los múltiples productos químicos que forman parte de nuestro estilo de vida, porque, en la actualidad, estas sustancias se utilizan en todo lo que nos rodea: cosméticos, productos de higiene, prendas de ropa, productos para el hogar, teléfonos y otros dispositivos móviles, ordenadores... La sociedad del siglo XXI depende de ellos.

Los seres humanos podemos estar expuestos a estos contaminantes ambientales a través de diversas vías (aire, agua y alimentos, cosméticos

etc.). En el caso de los niños, al igual que los adultos, esta contaminación se produce mediante vías de exposición simultáneas, por lo que es imprescindible priorizar los mensajes de salud en la práctica clínica (*Galvez and Balk 2017*).

Según la Organización Mundial de la Salud (OMS) 9 de cada 10 personas en el mundo respiran aire contaminado y más de una cuarta parte de las defunciones de niños menores de cinco años son consecuencia de la contaminación ambiental. La contaminación del aire es mayor en las ciudades, en los hogares cercanos a autopistas con alta densidad de circulación y en las proximidades de los aeropuertos. Cada año, se estima que la contaminación del aire provoca 570.000 muertes de niños menores de cinco años. Dicha contaminación se ha asociado a cambios estructurales en el cerebro infantil (Beckwith, Cecil et al. 2020). También es de especial importancia la exposición de los niños al humo del tabaco tanto dentro como fuera del hogar. Esta exposición se asocia con mayor frecuencia a síntomas respiratorios, así como empeoramiento de la salud general *(Lletjos, Continente et al. 2018)*.

En la construcción de los hogares, pueden existir múltiples productos químicos como el plomo utilizado en la pintura antes de los años 50, el asbesto utilizado como aislante o el formaldehido para conservar la madera. De tal forma, especialmente en los hogares antiguos, puede existir una carga química tóxica importante.

Los pesticidas pueden llegar al hogar por diferentes vías, desde los campos de cultivo próximos al hogar, así como por su aplicación directa en el mismo para controlar diferentes insectos.

El agua de consumo puede estar contaminada por plomo (utilizado en las tuberías de las instalaciones antiguas) o por nitratos procedentes de la agricultura. También puede estar contaminada por pesticidas infiltrados en el agua de pozos y galerías.

La alimentación, fuente imprescindible de nutrientes para el organismo, también es una de las fuentes más importantes de tóxicos. En 2010, la organización francesa *Generation Futures* en su estudio *Menus Toxiques,* buscó productos químicos presentes en un "menú tipo" francés encontrando hasta 128 resíduos químicos, 36 pesticidas diferentes, 47 sustancias con poder cancerígeno y 37 disruptores endocrinos.

Los cosméticos también se encuentran en el punto de mira ya que mucho de sus componentes están en estudio por sus posibles efectos adversos

sobre la salud como son el aluminio, los parabenos y los ftalatos. Por otro lado, los protectores solares presentan sustancias como el dióxido de titanio, las benzofenonas y el metoxicinamato de octilo, que aparte de ejercer efecto directo sobre la salud de los consumidores, producen la contaminación del agua de mares y océanos, y el consecuente alcance de la cadena alimentaria *(Grande and Tucci 2016)*.

En la fabricación de ropa, se está sustituyendo las materias primas naturales como el algodón, la seda o la lana por múltiples polímeros sintéticos. Asimismo, los tintes utilizados en esta industria contienen elementos como el plomo, el níquel o el cromo. Un estudio reciente realizado en la Universidad de Estocolmo ha encontrado cientos de productos químicos en las marcas de ropa utilizadas habitualmente en Europa *(Luongo 2015)*.

1.2. La contaminación química en la isla de La Palma

La isla de La Palma, es una isla del archipiélago canario, localizada en el Océano Atlántico, frente a las costas africanas. Tiene una superficie de 70.620,75 hectáreas y una población de 82.671 habitantes.

No hay constancia de la existencia de industrias importantes en la misma que pudieran ocasionar focos de contaminación química mayores a la contaminación química ambiental general. Sin embargo, el sector agrícola siempre ha tenido un peso importante en la economía insular, a través de diferentes monocultivos que han variado a lo largo del tiempo (caña de azúcar, vid, cochinilla, plátano y tomate, aguacate). En este último siglo, ha tenido especial importancia el cultivo intensivo del plátano. Asimismo, las zonas de cultivo dedicadas a la platanera coinciden con los principales núcleos de población de la isla, debido principalmente a los requerimientos climáticos de este cultivo.

Diferentes estudios de biomonitorización realizados a nivel autonómico han demostrado un elevado grado de contaminación por pesticidas de la población canaria *(Zumbado, Goethals et al. 2005, Luzardo, Goethals et al. 2006, AAP 2011, Risnes, Vatten et al. 2011, Burillo-Putze, Luzardo et al. 2014)*, poniéndose de manifiesto incluso, en la etapa prenatal *(Luzardo, Mahtani et al. 2009)*; Sin embargo, no tenemos constancia de ningún estudio realizado centrado únicamente en la isla de La Palma.

La isla ha tenido un desarrollo tecnológico similar al resto del territorio canario. Aunque no existen industrias de producción tecnológica, el Instituto de Astrofísica de Canarias tiene parte de sus observatorios

emplazados en la cumbre de la isla (Observatorio del Roque de los Muchachos). Siempre ha existido cierto temor a una posible contaminación de los acuíferos de la isla, por metales pesados, especialmente por aluminio, al estar situados a menor altitud que los observatorios. Los espejos primarios de los observatorios están formados por un baño de sales de aluminio que tiene que aplicarse periódicamente para su correcto funcionamiento. Estos productos químicos utilizados para la limpieza, así como los derivados de aluminio, son recogidos, almacenados y retirados fuera de la Isla por gestores de residuos especializados autorizados.

1.3. La contaminación química en la infancia

En los últimos cincuenta años ha habido una preocupación progresiva por la salud medioambiental en general, pero especialmente la que rodea a los niños, lo que ha llevado a los organismos internacionales a crear comités pediátricos de salud medioambiental, que examinan continuamente las amenazas medioambientales para la salud y elaboran recomendaciones para minimizar el impacto de las mismas. Fruto de este trabajo, la salud medioambiental se considera una nueva disciplina dentro de la pediatría y se ha potenciado la creación de Unidades Especiales de Salud Medioambiental. Sin duda, el organismo de referencia en esta disciplina es la ***Academia Americana de Pediatría*** *(American Academy of Pediatrics, AAP)* a través de su Comité en Salud Medioambiental *(Council on Environmental Health)* siendo el libro publicado por éste, la obra más completa en la materia *(AAP 2018)*.

Llama la atención el diferente ritmo de crecimiento de esta disciplina entre Europa y Estados Unidos. Mientras en el continente americano se ha producido un desarrollo progresivo existiendo múltiples unidades de salud medioambiental, en Europa casi no se ha desarrollado la misma. En España, en 2018, se creó el ***Comité de Salud Medioambiental dentro de la Asociación Española de Pediatría***, teniendo poca repercusión en la actualidad en las sociedades regionales de pediatría, así como en la práctica clínica pediátrica.

Dentro de la contaminación ambiental es necesario distinguir los contaminantes físicos (radiaciones ionizantes, campos eléctricos y magnéticos, el ruido, la radiación ultravioleta, etc.) y los contaminantes químicos (polución ambiental, metales pesados, contaminantes orgánicos persistentes, plásticos, pesticidas, nitratos, humo del tabaco, etc.). El objeto de esta tesis solo contemplará los grupos más importantes de los contaminantes químicos.

Los niños presentan vulnerabilidades únicas frente a los peligros ambientales. En cada estadío del desarrollo presentan susceptibilidades diferentes. Se han descrito diferentes ventanas críticas de exposición, en las cuales, el contacto con un tóxico ambiental puede ocasionar mayores repercusiones *(Selevan, Kimmel et al. 2000)*. Existen evidencias epidemiológicas amplias que apoyan la relación causal entre exposición prenatal y en la primera infancia a tóxicos ambientales y diferentes problemas de salud en el feto y en el niño *(Wigle, Arbuckle et al. 2008)*.

La población pediátrica y las mujeres embarazadas son especialmente vulnerables a la acción de los contaminantes químicos y diferentes estudios de biomonitorización han demostrado la exposición pediátrica a un gran rango de contaminantes químicos.

Es importante no considerar a los niños como "adultos en pequeño". Los niños tienen características fisiológicas, de comportamiento y de desarrollo, que les hacen especialmente susceptibles a la exposición tóxica ambiental. Los niños tienen mayor superficie corporal, ingieren mayor cantidad de alimentos y de agua por unidad de peso que los adultos y tienen mayor frecuencia respiratoria, lo que les hace más susceptibles a la intoxicación por sustancias vehiculizadas a través del agua, de los alimentos o inhaladas. Asimismo, la diversidad de alimentos que ingieren es mucho menor que en la alimentación adulta, teniendo gran relevancia en los primeros años la leche materna y las fórmulas lácteas infantiles. Los niños pasan más cantidad de tiempo en contacto con el suelo, alfombras o con la hierba, por lo que están más expuestos a posibles contaminantes presentes en la superficie de estos elementos, tales como los pesticidas *(AAP 2011)*. Además, en la fase de exploración oral, es frecuente que los más pequeños se lleven todo tipo de objetos a la boca, exponiéndose a los contaminantes que pueda haber en la superficie.

Una etapa especialmente crítica es el periodo intrauterino ya que el embrión es especialmente sensible a los tóxicos ambientales. Por este motivo, múltiples cohortes han estudiado la exposición a diferentes tipos de contaminantes ambientales y han intentado establecer la relación entre éstos y posibles alteraciones en el desarrollo fetal *(Kim, Ha et al. 2009, Vrijheid, Casas et al. 2012, Gehring, Casas et al. 2013)*.

Claros ejemplos de alteraciones fetales atribuidas a tóxicos durante la gestación son la alteración en la formación de las extremidades

debidas a la talidomida (un fármaco utilizado para los vómitos durante el embarazo), las alteraciones en el desarrollo cerebral producidas por la ingesta de alcohol por la madre (síndrome del alcohol fetal) y los problemas en la formación de los órganos genitales producidas por la ingesta materna del estrógeno dietiletilbestrol.

La exposición comienza desde el momento preconcepcional porque tanto el óvulo como el espermatozoide están expuestos a los tóxicos ambientales. Durante la gestación, la madre puede estar expuesta a tóxicos relacionados con su trabajo y a tóxicos ambientales no laborales.

Asimismo, se ha establecido que el desarrollo de muchas enfermedades crónicas en la edad adulta está condicionado por las condiciones de vida intrauterina. Se ha asociado el aumento del riesgo cardiovascular, la obesidad y el cáncer con algunos parámetros fetales *(Risnes, Vatten et al. 2011)*.

1.4. Contaminantes orgánicos persistentes

Los contaminantes orgánicos persistentes (COPs) son un grupo de sustancias químicas basadas en estructuras de carbono que poseen átomos de cloro en su molécula. Todos los COPs tienen en común una serie de características que determinan su persistencia en el medio ambiente:

- Debido a su enorme estabilidad físico-química, estas sustancias permanecen intactas por largos periodos de tiempo (persistencia).
- Se distribuyen por el medio ambiente mediante procesos naturales, encontrándose en el suelo, el agua y sobre todo en el aire (movilidad).
- Debido a su alta liposolubilidad, se acumulan en los tejidos grasos de seres vivos, incluido los seres humanos (bioacumulación) y se encuentran en concentraciones más altas en los niveles más altos de la cadena alimentaria (biomagnificación) *(Gray 2002)*.
- Son tóxicas para los seres humanos y para la vida silvestre.

El grupo de sustancias incluidas dentro de los COPs son principalmente plaguicidas organoclorados (POCs) y retardantes de la llama. Estos últimos fueron utilizados para la fabricación de diferentes productos como vehículos, textiles, transformadores eléctricos, circuitos de

impresión, piezas electrónicas, condensadores, espumas de poliestireno expandido y extruido, espumas flexibles de poliuretano, espuma contra incendios, imagen fotográfica, fluidos hidráulicos, etc. Sin embargo, algunos COPs también pueden producirse de forma no intencionada en procesos de combustión como incendios forestales o la quema de basura con mezcla de residuos, como es el caso de las dioxinas.

En las décadas pasadas se liberaron gran cantidad de estos COPs al medio ambiente fruto de la actividad agrícola e industrial, distribuyéndose por todo el planeta, incluso en las regiones donde nunca se usaron. Por tal motivo, varias generaciones se han expuesto a los mismos de forma aguda y de forma crónica. Los COPs pueden encontrarse en personas y animales que viven en el Polo Ártico, a miles de kilómetros de donde dichas sustancias fueron producidas *(Dietz, Riget et al. 2000, Sonne, Letcher et al. 2017)*.

Debido al peligro que presentan estas sustancias para la salud humana y el medio ambiente, en mayo de 1995, el Programa de las Naciones Unidas para el Medio Ambiente (PNUMA) inició un proceso internacional para evaluar la lista inicial de COPs.

En mayo de 2001 fue adoptado el ***Convenio de Estocolmo sobre contaminantes orgánicos persistentes*** y entró en vigor en mayo de 2004. Este acuerdo fue impulsado por la Organización de las Naciones Unidas (ONU) y actualmente cerca de 200 países forman parte de él. España firmó este convenio el 23 de Mayo de 2001, junto con otros 90 países. El objetivo del Convenio de Estocolmo sobre los COPs puede resumirse de la siguiente forma: *"Proteger la salud humana y el medio ambiente de contaminantes orgánicos persistentes, reduciendo o eliminando sus emisiones en el medio ambiente"*

Estas sustancias han sido catalogadas en la Convención de Estocolmo, bajo el auspicio del Programa de las Naciones Unidas para el Medio Ambiente *(UNEP 2008)* incluyéndose en tres grupos. Inicialmente se reconocieron 12 sustancias conocida como "La docena sucia". Estas sustancias estaban agrupadas en tres categorías:

- **Pesticidas:** aldrin, clordano, DDT, dieldrin, endrin, heptacloro, hexaclorobenceno, mirex, toxapheno.

- **Químicos industriales:** hexaclorobenceno, bifenilos policlorados.

- **Subproductos:** hexaclorobenceno, dibenzoparadioxinas policloradas, dibenzofuranospoliclorados, bifenilos policlorados.

Asimismo, continuamente se han ido incorporando varias moléculas químicas y se sigue valorando sustancias que pueden formar parte de estos anexos en el futuro. La composición actual de dicha lista es la siguiente:

- **Anexo A. Sustancias que deben ser eliminadas.** (Las partes deben tomar medidas para eliminar la producción y el uso de las sustancias listadas en el anexo).
  Se incluyen *plaguicidas organoclorados* (aldrina, clordano, clordecona, dieldrina, endrina, heptacloro, hexaclorobenceno, alfa hexaclorociclohexano, betahexaclorociclohexano, lindano, mirex, pentaclorobenceno, pentaclorofenol con sus sales y sus éteres, endosulfán y sus isómeros, toxafeno) y *productos químicos industriales* (decabromodifenileter, hexabromobifenilo, hexabromociclododecano, hexabromodifenileter y heptabromodifenileter, hexaclorobutidiona, bifenilos policlorados, naftalenos policlorados, parafinas cloradas de cadena corta, tetrabromodifenileter y pentabromodifenileter).

- **Anexo B. Sustancias de uso restringido** (las partes deben tomar medidas urgentes para restringir la producción y el uso de las sustancias incluidas en la lista).

  Se incluyen plaguicidas (DDT) y productos químicos industriales (sulfonatos de perfluorooctano, ácido perfluorooctanoico, sulfonado de perfluoroctano).

- **Anexo C. Disminución de las emisiones de sustancias de producción no intencionada** (las partes deben tomar medidas para reducir la liberación de productos químicos enumerados con el objetivo de minimizar la continuación de los mismos, y, cuando sea factible, la eliminación de dicha liberación).
  En el Anexo C, se incluyen productos industriales: Hexaclorobenceno, hexaclorobutadieno, pentaclocobenceno, bifenilos policlorados, dibenzoparadioxinas policloradas, dibenzofuranos policlorados, naftalenos policlorados.

A pesar de haber pasado décadas desde la prohibición y restricción de algunas sustancias, los COPs son detectados y cuantificados en el suero de los seres humanos y de otras especies *(Sonne, Letcher et al. 2017)*, incluso en poblaciones alejadas de las fuentes de emisión *(Dietz, Riget et al. 2000)*.

La alimentación es la principal fuente de exposición a los COPs. Los alimentos que más cantidad de COPs presentan son los que tienen mayor contenido graso, como la carne, el pescado y los lácteos. Aunque los niveles ambientales son progresivamente menores, los niveles residuales presentes en el suelo entran en la cadena alimentaria y se biomagnifican.

La exposición a COPs es un problema de especial importancia para los niños y familias que viven en las zonas polares, que se alimentan prioritariamente de la grasa de mamíferos marinos como focas y ballenas. La migración de los COPs a esas latitudes así como la bioconcentración de estos componentes en los depredadores superiores, provocan una alta concentración de COPs en estas especies *(Nuijten, Hendriks et al. 2016)*. En general, el nivel de COPs aumenta con la edad del individuo y es mayor en mujeres que en hombres *(Vallack, Bakker et al. 1998)*.

En el cuerpo humano, pueden atravesar la placenta *(Luzardo, Mahtani et al. 2009)* y se excretan en la leche humana, siendo ésta una fuente de exposición importante para los lactantes *(Muller, Polder et al. 2019)*.

Los COPs como grupo, ejercen diversos efectos adversos sobre la salud:

- Son *disruptores endocrinos*. La exposición a bajas concentraciones en momentos críticos del desarrollo (tanto en el periodo embrionario, como en el del recién nacido o en la infancia) puede producir alteraciones complejas en el funcionamiento del sistema endocrino. Las manifestaciones de estas alteraciones, pueden ponerse de manifiesto, en ocasiones, en un momento muy distante a la exposición *(Damstra 2002)*.

- Pueden causar alteraciones en el sistema reproductivo. La exposición a bajas dosis de COPs puede alterar la calidad y cantidad de espermatozoides, modificar el comienzo de la pubertad o aumentar la incidencia de endometriosis *(Damstra 2002)*.

- Pueden alterar la antropometría de los recién nacidos (peso, talla, perímetro craneal), observándose que la exposición prenatal es un momento crítico *(Dewan, Jain et al. 2013)*.

- Pueden propiciar el desarrollo de enfermedades cardiovasculares como la obesidad, hipertensión y diabetes tipo 2 *(Henriquez-Hernandez, Luzardo et al. 2014, Henriquez-Hernandez, Luzardo et al. 2017, Lee, Jacobs et al. 2018)*.

- Algunos pueden ser carcinogénicos *(Boada, Zumbado et al. 2012, Rivero, Henriquez-Hernandez et al. 2016)*.

Asimismo, debe dejarse constancia que todos estos tóxicos tienen un efecto aditivo y aunque en muchos estudios se busca la relación de un subgrupo con determinados efectos sobre la salud, en realidad, todos están modificando la homeostasis corporal al mismo tiempo, siendo difícil cuantificar el efecto sumatorio sobre la salud.

En este trabajo de Tesis doctoral, hemos analizado tres subtipos de COPs: los plaguicidas organoclorados (POCs), los bifenilos policlorados (PCBs) y los bifenilos polibromados (PBDEs).

1.4.1. Plaguicidas organoclorados

Bajo el nombre de plaguicidas organoclorados (POCs) se agrupa un número importante de compuestos sintéticos cuya estructura química, en general, corresponde a la de hidrocarburos clorados, aunque, además del cloro, algunos de ellos poseen oxígeno, azufre o ambos elementos en su estructura. Estos plaguicidas, fueron los primeros utilizados a gran escala. Entre sus propiedades destaca su reducida volatilidad, alta estabilidad química y solubilidad en lípidos, lenta biotransformación y degradación en el medio ambiente. Estas propiedades son la base de los problemas que plantean en el medio ambiente: persistencia, bioacumulación, biomagnificación en seres vivos, transporte de largo alcance y toxicidad, características propias y comunes de todos los COPs que les llevaron a la inclusión de la mayoría de estos plaguicidas en el Convenio de Estocolmo.

El DDT fue el primer POC prohibido en Estados Unidos gracias a los trabajos de la bióloga norteamericana Rachel Carson. Entre 1954 y 1961, en Sheldon (Estados Unidos), se pulverizaron las tierras con DDT para acabar con una invasión de escarabajo japonés, y con ello se inició un proceso afectación progresiva de las cadenas tróficas. A medida que el DDT iba escalando niveles tróficos, aumentaba su concentración en los tejidos animales. En 1962 la bióloga norteamericana Rachel Carson publicó el libro La Primavera Silenciosa que fundó las bases del ecologismo moderno *(Carson, Darling et al. 1962)*. Por primera vez se habló del peligro de usar DDT y otros productos químicos usados como plaguicidas. Lo más alarmante no era únicamente su toxicidad, sino también su capacidad para persistir en los organismos por medio de la acumulación en los tejidos grasos. Con la publicación de sus trabajos se inició un amplio debate que

condujo finalmente a la prohibición del uso del DDT y muchos otros insecticidas organoclorados en muchos países.

Las restricciones impuestas en el uso de estos compuestos organoclorados se han traducido en un marcado descenso en la concentración media de estos plaguicidas en tejidos humanos. Sin embargo, estudios recientes en nuestro país, demuestran que 35 años después de su prohibición, aún es posible medir su principal metabolito, el DDE, en la práctica totalidad de los individuos sanos, y el DDT está presente en cerca del 30% de la población *(Zumbado, Goethals et al. 2005, Luzardo, Goethals et al. 2006, Jakszyn, Goni et al. 2009)*, e incluso en el líquido amniótico *(Luzardo, Mahtani et al. 2009)*. A pesar de la prohibición de su uso en los países que han firmado el Convenio de Estocolmo, su uso continúa en países en vías de desarrollo, donde desempeñan un importante papel como agente para el control del vector de la malaria en algunos países de África y Sudamérica e incluso como insecticida de uso agrícola.

Los POCs más ampliamente utilizados fueron el DDT y el Lindano. En el medio ambiente e incluso en seres humanos, podemos encontrar todavía restos de DDT o sus metabolitos DDE, DDD.

La alimentación diaria se considera la principal fuente de exposición a POCs, siendo especialmente importante en los alimentos ricos en materia grasa.

Asimismo, la exposición prenatal está bien documentada por la presencia de éstos en la placenta *(Lopez-Espinosa, Granada et al. 2007)*, líquido amniótico *(Luzardo et al., 2009)* y sangre del cordón umbilical *(Luzardo, Mahtani et al. 2009, Zhang, Wu et al. 2018)*.

La alta concentración de grasa en la leche materna ocasiona que los contaminantes liposolubles alcancen una mayor concentración en la misma. Se han descrito múltiples contaminantes orgánicos en la leche materna, incluidos el DDT y el DDE, a pesar de lo cual, los beneficios que aporta ésta, superan los posibles riesgos. La Academia Americana de Pediatría continua recomendando la lactancia materna salvo en aquellos casos en los que se haya producido una liberación accidental de tóxicos al medioambiente *(Dorea 2012)*.

La exposición profesional en la actualidad es muy rara, pero, no debe olvidarse que el DDT se utiliza para el control de la malaria en algunos países del África Subsahariana, por lo que los aplicadores así como los habitantes locales pueden estar expuestos a altas concentraciones.

Diferentes estudios han correlacionado los niveles de exposición intraútero de algunos pesticidas organoclorados y el crecimiento fetal así como el aumento de parto pretérmino *(Vrijheid, Casas et al. 2016, Lopez-Espinosa, Murcia et al. 2016)*. Algunos estudios de cohortes con niños muestran que la exposición intraútero a este tipo de sustancias tiene efectos deletéreos en el neurodesarrollo *(Rosas and Eskenazi 2008, Berghuis, Bos et al. 2015)*. Dicha exposición se ha relacionado con alteraciones en el desarrollo psicomotor y aumento de la incidencia del trastorno de déficit de atención e hiperactividad *(Berghuis et al., 2015)*.

La exposición prenatal a pesticidas organoclorados se asocia a síntomas respiratorios en la primera infancia *(Gascon, Morales et al. 2013)*.

La reciente hipótesis de los obesógenos ambientales se centra en la habilidad de ciertas sustancias químicas en interferir con los sistemas metabólicos y endocrinos, modificando los patrones de crecimiento e induciendo ganancia de peso y obesidad con el consiguiente aumento del riesgo de diabetes tipo 2 *(Taylor, Novak et al. 2013)*. Bajas dosis de POCs son un factor de riesgo para la diabetes tipo 2 por múltiples mecanismos como el aumento de la resistencia a la insulina, la alteración directa de la célula beta pancreática y el aumento del índice de masa corporal (Lee, Porta et al. 2014, Lee, Jacobs et al. 2018). Los niveles de algunos metabolitos del DDT se correlacionan directamente con las cifras de glucemia *(Henriquez-Hernandez, Luzardo et al. 2017)*. Nuevos estudios han comenzado a evaluar otros factores de riesgo cardiovascular como la concentración de lípidos y la resistencia insulínica y su relación con los POCs *(Vrijheid, Casas et al. 2016)*.

Asimismo, los pesticidas organoclorados se han relacionado con el aumento de la tensión arterial *(Henriquez-Hernandez, Luzardo et al. 2014, Arrebola, Fernandez et al. 2015)*.

1.4.2. Bifenilos policlorados

Los bifenilos policlorados (PCBs) son un amplio grupo de compuestos químicos orgánicos formados por átomos de carbono, hidrógeno y cloro. El número de átomos de cloro y su localización en la molécula del PCB determinan sus propiedades químicas y físicas. Estas sustancias no presentan un sabor ni un olor definido y su consistencia varía desde el aceite a una cera sólida. Son una mezcla de hasta 209 compuestos clorados denominados congéneres. No hay fuentes naturales conocidas de los PCBs *(EPA 2019)*.

Estas moléculas fueron producidas desde 1929 hasta 1979. Debido a sus propiedades físicas como un elevado punto de ebullición, ser no inflamables y aislantes eléctricos se incluyeron en aparatos electrónicos, equipamiento hidráulico, pinturas de aceite, plásticos, productos de caucho, pigmentos, tintes y papel de copiar sin carbón. Estos productos químicos pueden encontrarse en transformadores eléctricos, reguladores de voltaje eléctrico, interruptores, barras fluorescentes, aislante de cables eléctricos, aceite lubricante de motores y sistemas hidráulicos, aislantes térmicos incluido fibra de vidrio, espumas y corcho, cintas adhesivas y un sinfín de productos industriales y domésticos que facilitó la rápida dispersión de estos productos por todo el planeta.

El descubrimiento progresivo de su toxicidad hizo que se prohibiera su uso en Estados Unidos en 1979 y por los países firmantes del Convenio de Estocolmo en 2001. En la actualidad todavía pueden liberarse al medio ambiente PCBs desde depósitos de basura industrial con un mal mantenimiento (ilegales o legales mal conservados), fugas desde transformadores eléctricos antiguos que contengan PCBs o en la incineración de productos industriales. Se produjeron más de 1,3 millones de toneladas de PCBs especialmente en Estados Unidos y Europa *(Breivik, Sweetman et al. 2002)*, lo que hace que los PCBs sean uno de los contaminantes ambientales más ampliamente distribuidos.

Al igual que el resto de los COPs, los PCBs pueden permanecer en el medio ambiente largos periodos de tiempo y desplazarse a gran distancia desde el punto donde se produjeron y utilizaron. Asimismo, se introducen en la cadena alimentaria en las plantas y en los organismos inferiores, produciéndose el fenómeno de biomagnificación en los organismos superiores, ya explicado con anterioridad.

En la actualidad, la principal fuente de exposición a PCBs es la alimentación habitual, especialmente pescados de gran tamaño, carne y productos lácteos. El contenido en estos contaminantes depende de las especies y del lugar de su captura *(Domingo and Bocio 2007)*. Asimismo, la relación carbono-proteica del alimento y el método culinario de preparación interfiere en la biodisponibilidad de los mismos *(Shen, Starr et al. 2016)*.

La lactancia materna es una fuente importante de exposición a PCBs para los recién nacidos, pero en la mayoría de los casos, los beneficios de la lactancia materna supera los riesgos *(van den Berg, Kypke et al. 2017)*.

Al igual que otros COPs, se ha descrito la transferencia de los PCBs a través de la placenta *(Jeong, Lee et al. 2018)* acentuando la importancia de la exposición prenatal.

También es posible la exposición directa desde aparatos industriales eléctricos de más de cuarenta años de antigüedad o la exposición ambiental directa en lugares cercanos a vertederos de productos industriales *(Davies and Delistraty 2016)*.

Se han descrito múltiples efectos sobre la salud de los PCBs *(ATSDR 2000)*. En los trabajadores directamente expuestos a los mismos, se han descrito lesiones cutáneas y alteraciones hepáticas.

Los PCBs han sido clasificados como carcinogénicos por Agencia Internacional para el Estudio del Cáncer (IARC 2016), especialmente aquellas sustancias que tienen un efecto *"Dioxin-like"* de acuerdo con la OMS (PCB-77,PCB-81, PCB-105, PCB-114, PCB-118, PCB-123,PCB-126, PCB-169, PCB-156, PCB-157, PCB-167,PCB-189). Los tipos de PCBs que tienden a bioacumularse en el pescado y en otros animales, son las mezclas con más potencial carcinogénico. En los estudios hechos en trabajadores expuestos se ha observado un aumento del riesgo de cáncer de hígado y de melanoma, existiendo gran variedad de estudios sin significación estadística o con factores de confusión.

La exposición prenatal durante periodos vulnerables en las etapas iniciales del desarrollo puede ocasionar daños cerebrales y alteraciones en el neurodesarrollo. La neurotoxicidad comenzó a estudiarse tras la exposición accidental ocurrida en Japón en 1960 al contaminarse el aceite de arroz utilizado para cocinar con PCBs, produciéndose la Enfermedad de Yushõ, afectando a más de 1800 niños. En esta cohorte se ha descrito progresivamente el aumento de incidencia múltiples patologías neurológicas, cutáneas, afectación de los órganos de los sentidos, afectación hematológica y aumento de la prevalencia de las enfermedades típicas de la edad avanzada *(Akahane, Matsumoto et al. 2018)*. La exposición prenatal a bajos niveles de PCBs se asocia a alteraciones en el desarrollo psicomotor y en la puntuación de los test de inteligencia *(Stewart, Lonky et al. 2008, Berghuis, Van Braeckel et al. 2018)*.

Se han observado alteraciones en el sistema inmune del mono que tiene un sistema inmune muy parecido al humano *(IARC 2016)* con una disminución del tamaño del timo y alteración de diferentes respuestas inmunes. La supresión del sistema inmune puede ser un mecanismo que favorezca la presentación de linfomas no Hodgkin tras la infección por el virus de Ebstein-Barr.

Los PCBs se consideran disruptores endocrinos al interferir en el correcto funcionamiento de las hormonas tiroideas tanto de las madres expuestas como de los recién nacidos *(Zheng, He et al. 2017, Baba, Ito et al. 2018)*.

1.4.3. Éteres de polibromodifenilos

Los éteres de polibromodifenilos (PBDEs) son compuestos orgánicos que contienen bromo en una estructura caracterizada por dos anillos aromáticos halogenados. Son una familia de más de 200 sustancias llamadas congéneres. Se clasifican en función del número de átomos de bromo en su molécula y comparten las características comunes a todos los contaminantes orgánicos persistentes. Pueden agruparse en dos grandes grupos:

- **PBDEs inferiores:** presentan de uno a cuatro átomos de bromo. Son considerados más peligrosos porque tienen mayor capacidad de bioacumularse. Además, tienen mayor capacidad de actuar como disruptores endocrinos a nivel de las hormonas tiroideas y del sistema reproductor.

- **PBDEs superiores:** presentan más de cuatro átomos de bromo por molécula.

Los PBDEs son sustancias que se agregaron a los plásticos y a los productos de espuma para hacer más difícil que ardieran. Los PBDEs han sido usados en una gran variedad de productos incluyendo materiales de la construcción, electrónica, mobiliario, motores de vehículos y de aviones, plásticos, espumas y textiles. Estructuralmente son parecidos a los PCBs y otros componentes halogenados. Los compuestos comerciales usados son una mezcla de varios tipos de congéneres. Existen tres congéneres que se usaron ampliamente:

- El **decaBDE** se usó principalmente en cubiertas de artículos electrónicos, por ejemplo, televisores.

- El **octaBDE** se usó principalmente en plásticos de artículos de oficina, por ejemplo, computadores.

- El **pentaBDE** se usó en espumas para relleno de tapices de muebles.

Estos productos se dejaron de producir a partir del año 2004, estando actualmente incluidos en el Anexo A del Convenio de Estocolmo.

La principal ruta de exposición a PBDEs para la población general es la inhalación de polvo contaminado en el hogar, en el lugar de trabajo o en el coche, representando entre el 80 y el 90% de la exposición total a

PBDEs de la población general. En los hogares persisten materiales que contienen PBDEs que liberan pequeñas cantidades de los mismos como televisores, aparatos eléctricos, sofás y armarios antiguos *(ATSDR 2017)*.

El personal que manipula los productos que contienen PBDEs tiene un elevado nivel de exposición. Es especialmente preocupante la posible exposición que puede tener el personal que trabaja en plantas de reciclado. Las vías de exposición difieren de unos países a otros en función de la normativa de prevención de incendios *(Bramwell, Harrad et al. 2017)*. Así, en Europa la principal vía de exposición es la alimentación mientras que en Estados Unidos sería la inhalación directa de estas sustancias *(Linares, Belles et al. 2015)*.

Al igual que otros COPs, los alimentos que tienen un mayor contenido graso pueden tener una mayor concentración de PBDEs. Así, están presentes en pescados y otros organismos acuáticos *(Babalola and Adeyi 2018)*, quesos y otros lácteos *(Poma, Malysheva et al. 2018)* ó carnes *(Pietron, Pajurek et al. 2019)*. En general el contenido de estos elementos es muy bajo y no supone un riesgo para la salud humana.

Los PBDES están presentes en la leche materna de forma universal, siendo especialmente elevados los niveles en las muestras obtenidas en Norte América *(Zhang, Chen et al. 2017)*.

La exposición a PBDEs comienza en el periodo prenatal como lo demuestra la existencia de estos productos químicos en muestras de sangre de cordón umbilical *(Cowell, Sjodin et al. 2018)* o en el líquido amniótico *(Miller, Chernyak et al. 2012)*.

Los estudios de biomonitorización han demostrado que la concentración de PBDEs ha aumentado rápidamente tanto en los animales como el ser humano. Con frecuencia se han descrito niveles superiores en Norte América con respecto a Europa o Asia, siendo especialmente preocupante la presencia de estos contaminantes en niños.

Los isómeros más frecuentemente encontrados en humanos son el tetra, penta y hexa-PBDE *(Linares, Belles et al. 2015)*.

Estas sustancias han demostrado ser disruptores endocrinos, al interferir especialmente con la homeostasis de las hormonas tiroideas *(Linares, Belles et al. 2015)*.

Existe una preocupación creciente en relación a la posible neurotoxicidad de los PBDEs, especialmente por la exposición prenatal y en los primeros años de la vida y su posible repercusión en el desarrollo psicomotor *(Gibson, Siegel et al. 2018)*. Revisiones bibliográficas recientes concluyen que existe suficiente evidencia para relacionar la exposición a PBDEs y la alteración del coeficiente intelectual *(Lam, Lanphear et al. 2017)*.

A pesar de ser moléculas similares a los PCBs, se han realizado menos estudios que evalúen la posible carcinogenicidad de los PBDEs. La IARC los clasifica en el grupo 2A (probablemente carcinogénicos) *(IARC 2016)*.

Diferentes estudios relacionan la exposición a PBDEs y alteraciones en el embarazo como alteraciones en la antropometría, aumento de la parto pretérmino o aumento del nacimiento de fetos muertos *(Linares, Belles et al. 2015)*. Los niveles maternos de determinados congéneres de PBDEs se asocian a un aumento de las pérdidas fetales *(Choi, Wang et al. 2019)*.

1.5. Hidrocarburos aromáticos policíclicos

Los hidrocarburos aromáticos policíclicos (PAHs) son un grupo de más de cien sustancias que se forman durante la combustión incompleta del carbón, petróleo, gasolina, basura y otras sustancias orgánicas como el tabaco y la carne asada con carbón. En general se encuentran como una mezcla de dos o más de estos compuestos como el hollín *(ATSDR 1995)*. Su estructura química está formada por múltiples anillos aromáticos. El más sencillo es el naftaleno con dos anillos y el antraceno y el fenantreno con tres anillos aromáticos.

Los procesos de combustión a bajas temperaturas como la quema de madera o el humo del tabaco generan moléculas de bajo peso molecular mientras que los procesos industriales a altas temperaturas generan moléculas con alto peso molecular.

Algunos hidrocarburos se encuentran en productos industriales como el petróleo crudo, la creosona y el alquitrán. Asimismo, algunos se usan para la fabricación de pinturas y pesticidas *(ATSDR 1995)*.

Los PAHs pasan al aire desde las emisiones volcánicas, los incendios forestales, la combustión del carbón, las emisiones de las industrias y de los automóviles. Pueden degradarse con la luz solar o con otras sustancias en el aire. Asimismo, algunos microorganismos del suelo los

pueden degradar. Los PAHs no degradados pueden contaminar el aire, el agua y el suelo, ocasionando que la cantidad presente en las plantas y en los animales sea mayor que el suelo o el agua donde viven.

La principal fuente de exposición en el ser humano es la inhalación de aire contaminado. El nivel de contaminación es mayor sobre todo en países en vías de desarrollo, donde hay un menor control de la calidad del aire junto con un expansivo proceso industrial.

Los PAHs pueden ingerirse con la alimentación. Prácticamente cualquier alimento crudo o procesado, puede contener PAHs. La mayor cantidad está presente en los alimentos ahumados o asados. La mayor producción de PAHs se produce al calentar alimentos con alto contenido graso y proteico. Como los ahumados y asados, son en general poco frecuentes en la dieta, la contribución global es mayor en alimentos como los cereales que absorben las partículas de la atmósfera ó los aceites vegetales *(Phillips 1999)*.

Al fumar, se forman PAHs, por tal motivo es preocupante la exposición de los niños como fumadores pasivos *(Shahsavani, Dehghani et al. 2017)*.

Los PAHs se eliminan en la leche materna relacionándose el contenido de ésta con el nivel de contaminación de la zona *(Pulkrabova, Stupak et al. 2016)*.

De forma general, estos productos producen efectos irritantes en la piel y en las mucosas y afectación del sistema respiratorio cuando se inhalan.

Estos compuestos están clasificados por la IARC como agentes carcinogénicos para humanos (Grupo 1), probables (Grupo 2A) o posibles (Grupo 2B) en función del tipo de molécula.

Los PAHs se han correlacionado con cáncer de piel, cáncer de pulmón, cáncer de laringe, cáncer renal, cáncer de vejiga y cáncer digestivo entre otros *(IARC 2010)*.

Los PAHs pueden aumentar los procesos alérgicos y el asma en niños a través de procesos oxidativos *(Wang, Karmaus et al. 2017)*. Asimismo, pueden aumentar el riesgo cardiovascular alterando el volumen plaquetario y diferentes proteínas que intervienen en la agregación plaquetaria (Hu, Hou et al. 2018).

Los PAHs pueden atravesar la placenta y producir toxicidad en el feto ocasionando crecimiento intrauterino retardado *(Perera, Rauh et al. 2003)*. Diferentes estudios han sugerido disminución del crecimiento fetal por la exposición a PAHs *(Dejmek, Solansky et al. 2000)* así como la disminución del perímetro cefálico *(Choi, Wang et al. 2012)*.

1.6. Contaminantes químicos inorgánicos

1.6.1. Metales y metaloides

Los metales y metaloides son contaminantes ubicuos que han acompañado al hombre desde la más remota antigüedad. Así los envenenamientos por arsénico, plomo y mercurio están presentes en diferentes episodios a lo largo de la historia.

A diferencia de otros contaminantes ambientales, los metales son elementos que el hombre no crea ni destruye. El hombre introduce en el medio ambiente estos elementos como consecuencia de distintas actividades humanas y, por otro lado, altera la forma química o bioquímica en la que se encuentran. Los metales están sujetos de forma natural a ciclos biogeoquímicos que determinan su presencia y concentración en los compartimentos ambientales: el suelo, aguas subterráneas, el aire y los seres vivos. La intervención humana puede modificar considerablemente la concentración de los metales en estos compartimentos y facilitar su distribución a partir de las reservas minerales en las que se encuentran naturalmente confinados.

Muchos de estos elementos son considerados micronutrientes esenciales para el hombre, siendo necesaria una alimentación equilibrada para asegurar una correcta ingesta de estos elementos. Estos requerimientos son aún más sensibles en el periodo fetal *(Kontic-Vucinic, Sulovic et al. 2006)*.

La trascendencia toxicológica de los metales es enorme, teniendo en cuenta su ubicuidad, la extensión de sus usos y su persistencia medioambiental.

Prácticamente para todos los metales, podríamos describir efectos tóxicos para la salud humana en función de la dosis recibida, mencionando a continuación algunos ejemplos.

La Agencia Internacional para la Investigación del Cáncer (IARC) clasifica a alguno de ellos como cancerígenos para los humanos (Grupo 1): cadmio, arsénico, berilio, cromo y níquel *(IARC 2012)*. Asimismo, el

plomo lo clasifica como posible carcinogénico (Grupo 2A) *(IARC 2009)*. Muchos de ellos tienen en común el presentar toxicidad neurológica.

La exposición al mercurio se asocia a infertilidad y otros problemas reproductivos *(Henriques, Loureiro et al. 2019)*. Asimismo, el mercurio se asocia a gran variedad de alteraciones neurológicas *(Puty, Leao et al. 2019)*, siendo especialmente preocupante la exposición de las mujeres embarazadas porque el cerebro fetal es más vulnerable que el del adulto. Existe correlación entre la exposición fetal al mercurio y la disminución del coeficiente intelectual de esos niños, años después. La exposición de las mujeres embarazadas al mercurio se asocia también a un aumento de malformaciones y pérdidas fetales *(Solan and Lindow 2014)*.

La exposición al plomo en la edad pediátrica, se asocia a alteraciones neurológicas en la edad adulta, alteraciones renales y cardiovasculares *(Bellinger 2017)*. Asimismo, debe incluirse la toxicidad por plomo en el diagnóstico diferencial del síndrome anémico *(Hsieh, Chung et al. 2017)*.

La exposición a cadmio durante el embarazo se asocia a diminución del coeficiente intelectual y otros problemas neurológicos posteriores *(Hsieh, Chung et al. 2017)*. Asimismo, se ha observado alteraciones placentarias que pueden influir en el crecimiento fetal *(Geng and Wang 2019)*. La toxicidad por cadmio se ha relacionado a múltiples enfermedades neurológicas como Enfermedad de Alzheimer, Enfermedad de Parkinson, esclerosis lateral amiotrófica y esclerosis múltiple *(Branca, Morucci et al. 2018)*. La exposición a cadmio puede aumentar el riesgo cardiovascular al aumentar la presión arterial *(Wei, Ye et al. 2017)*.

El arsénico actúa como un inmunosupresor, aumentado las enfermedades alérgicas y autoinmunes *(Ferrario, Gribaldo et al. 2016)*.

Se ha relacionado la exposición a cromo durante el embarazo con la disminución del peso al nacimiento *(Berry and Bove 1997, Xia, Hu et al. 2016)*; el bajo peso al nacimiento también se ha relacionado con la exposición a níquel *(Bell, Belanger et al. 2010)*, siendo el aire de la zonas industrializadas y el humo del tabaco las principales fuentes de exposición al mismo *(Cempel and Nikel 2006)*.

Las fuentes de exposición a muchos de estos metales son comunes, por lo que el efecto final en la salud humana es el sumatorio de múltiples de estos metales.

La Agencia para las sustancias tóxicas y el registro de las enfermedades de Estados Unidos (ATSDR), junto con la Agencia para la protección del medio ambiente (EPA) elaboran una ***lista de contaminantes prioritarios*** que se actualiza cada dos años combinando criterios de frecuencia, toxicidad de la sustancia y exposición humana potencial. En su edición de 2017 se incluye un total de 18 elementos inorgánicos: Plata (Ag), Arsénico (As), Bario (Ba), Berilio (Be), Cadmio (Cd), Cromo (Cr), Cobre (Cu), Mercurio (Hg), Níquel (Ni), Plomo (Pb), Antimonio (Sb), Selenio (Se), Estroncio (Sr), Torio (Th), Talio (Tl), Uranio (U), Vanadio (V) y Zinc (Zn) *(CDC 2017)*.

1.6.2. Elementos raros y otros elementos usados en la fabricación de dispositivos electrónicos

Los contaminantes emergentes son un grupo de elementos relacionados con la producción de aparatos electrónicos y el desarrollo de las nuevas tecnologías de la información. Son elementos, en general, escasos en la corteza terrestre y están habitualmente citados en la literatura científica como *elementos terrestres raros (REE) o elementos traza (TE)* en función de su disponibilidad *(Tansel 2017)*. En la naturaleza están formando parte de minerales complejos como la bastnasita, la xenotima o la monacita, siendo necesario sofisticados métodos de extracción y purificación para su disponibilidad.

Los REE son un grupo de 17 elementos naturales que incluyen 15 lantánidos y lantanoides, el escandio y el ytrio. A continuación se enumeran los RRE y los TE: Lantanio (La), Cerio (Ce), Praseodimio (Pr), Neodimio (Nd), Prometio (Pm), Europio (Eu), Gadolinio (Gd), Terbio (Tb), Disprosio (Dy), Holmio (Ho), Erbio (Er), Tulio (Tm) Yterbio (Yb), Lutecio (Yb), Escandio (Sc) e Ytrio (Y) *(USEPA 2012)*.

La contaminación natural por estos elementos prácticamente no existe por estar en concentraciones muy bajas en la corteza terrestre o, estar en el interior de la misma. Sin embargo, estos elementos se han extraído intensamente mediante actividad minera en los últimos cincuenta años para la fabricación de instrumentos electrónicos *(Hussain and Mumtaz 2014, Tansel 2017)*. Actualmente los principales productores de estos elementos son China y Estados Unidos.

En la fabricación de los productos tecnológicos se utiliza gran diversidad de materiales como metales, plásticos, cristal, elementos raros y elementos traza. En un teléfono móvil pueden encontrarse más de 60 de estos elementos.

La alta producción de elementos tecnológicos de una vida media muy corta ha llevado a una producción masiva de basura tecnológica *"e-waste"* siendo ésta una fuente de contaminación ambiental en los procesos de recolección, transporte y almacenamiento. Se calcula que la producción anual de basura tecnológica es de 20 a 50 millones de toneladas *(Hussain and Mumtaz 2014)*.

China produce más del 95% de los REE, existiendo por tanto un monopolio que ha incrementado progresivamente el precio de las materias primas. Este aumento, ha obligado al reciclado de los productos tecnológicos para rescatar estos preciados elementos y volverlos a utilizar en la fabricación de nuevos dispositivos. El reciclado de estos productos se produce sobre todo en países en vías de desarrollo. El pequeño tamaño y la fragilidad de los componentes requieren un importante trabajo manual de separación de los preciados elementos, pudiendo ocasionar una alta exposición laboral a los mismos si no se toman medidas de protección individual, no estando siempre garantizadas en estos países subdesarrollados.

Los RREs se emplean con fines médicos (por ejemplo, el gadolinio en la resonancia magnética nuclear), en fertilizantes para la agricultura y como parte de alimento para animales *(Du and Graedel 2011)*.

La progresiva contaminación del suelo y del agua permiten que estos elementos se introduzcan en la cadena alimentaria *(Turra 2018)*. Así, los vegetales producidos cerca de zonas mineras de estos elementos tienen concentraciones superiores de RRE y TE a los producidos en zonas alejadas a estas extracciones *(Zhuang, Zhao et al. 2017)*.

Hay una preocupación creciente en la comunidad científica en los posibles efectos sobre la salud que pueden tener estos contaminantes. Se carece de estudios amplios que evalúen la exposición ambiental y la exposición profesional. La exposición ambiental es mayor cuanto mayor sea la actividad minera, la actividad industrial, y el almacenamiento y reciclaje de la basura tecnológica *(Henriquez-Hernandez, Luzardo et al. 2017)*.

Existe un número creciente de publicaciones que comunican posibles efectos deletéreos de estos elementos, especialmente del cerio, lantanio y gadolinio en la salud humana. Estos daños se producen por alteración de los mecanismos que regulan el estrés oxidativo, formándose radicales de oxígeno, peroxidación de lípidos y modulación de la actividad antioxidante *(Pagano, Aliberti et al. 2015)*.

El gadolinio utilizado con fines de diagnóstico médico se ha observado que puede acumularse en diferentes órganos periféricos y en el cerebro, incluso en pacientes con una función renal normal. Se han descrito diferentes manifestaciones tras la administración del mismo como dolor de cabeza y dolor neuropático periférico. También se ha descrito una reacción grave pero muy infrecuente denominada fibrosis sistémica nefrogénica *(Ramalho, Ramalho et al. 2017)*.

Existen casos aislados de fibrosis pulmonar asociada a lantanio y a cerio, siendo necesario estudios amplios de exposición profesional *(Pagano, Aliberti et al. 2015)*.

En niños se ha descrito la disminución del coeficiente intelectual asociado al lantanio *(Gwenzi, Mangori et al. 2018)*.

La mezcla de varios de estos elementos se asocia inversamente con el nivel de hemoglobina y el hierro sérico *(Henriquez-Hernandez, Boada et al. 2017)*.

En definitiva, se carece de estudios amplios que valoren el efecto de la exposición simultánea a múltiples de estos elementos sobre la salud humana, y en el periodo neonatal son aún más escasos.

Justificación
de la Unidad Temática

En la Introducción de esta Tesis Doctoral, describimos como vivimos rodeados de múltiples contaminantes químicos con capacidad de interaccionar con el hombre y ocasionar problemas en su salud.

Diferentes organismos internacionales como la Organización de las Naciones Unidas han trabajado en los últimos 25 años para alcanzar acuerdos que minimicen y eliminen los riesgos de la contaminación química. Muchos de estos acuerdos identifican como objetivo prioritario los contaminantes orgánicos persistentes (COPs) siendo el Convenio de Estocolmo el instrumento internacional que regula el tratamiento de estas sustancias tóxicas. Este Convenio, recoge la necesidad de realizar acciones tendentes a verificar la efectividad de las medidas propuestas para la reducción/eliminación de los COPs. Por tal motivo, está justificada la determinación y cuantificación (monitorización) de estos COPs en alimentos, muestras ambientales y seres vivos incluyendo los seres humanos.

El desarrollo fetal es muy sensible a los factores ambientales como la presencia de elementos inorgánicos, por una parte, algunos de ellos son micronutrientes esenciales y, por otro parte está bien documentada la afectación fetal por elevadas concentraciones de los mismos.

La gran revolución tecnológica de los últimos cincuenta años ha propiciado la explotación y utilización de múltiples elementos raros que hasta ahora no habían estado en contacto con la salud humana, siendo por lo tanto necesarios estudios que evalúen la presencia de los mismos en el ser humano.

En la actualidad no nos consta ningún trabajo que evalué simultáneamente esta gran diversidad de tóxicos en neonatos en una muestra que abarca casi la totalidad de los recién nacidos del área a estudio.

Objetivos

1. Determinar la exposición de los recién nacidos a contaminantes orgánicos persistentes a través del análisis de sangre del cordón umbilical.

2. Evaluar la presencia de hidrocarburos aromáticos policíclicos en la sangre de cordón umbilical.

3. Valorar el nivel de elementos inorgánicos, incluyendo elementos esenciales, metales pesados, elementos raros y otros elementos usados en la fabricación de dispositivos electrónicos, en muestras de sangre umbilical.

4. Evaluar la simultaneidad de contaminantes orgánicos e inorgánicos en recién nacidos.

5. Valorar la influencia de la exposición a contaminantes orgánicos persistentes y elementos inorgánicos sobre variables antropométricas del recién nacido.

6. Aportar nuevos datos a la base del conocimiento toxicológico en relación a los contaminantes tóxicos presentes durante el embarazo.

Publicaciones

4

Artículo 1

4.1.

Association between prenatal exposure to multiple persistent organic pollutants (POPs) and growth indicators in newborns.

Asociación entre la exposición prenatal a múltiples contaminantes orgánicos persistentes (COPs) y variables antropométricas en recién nacidos.

Se analiza la presencia de contaminantes orgánicos persistentes en la sangre de cordón umbilical de 447 neonatos de la isla de La Palma nacidos entre marzo de 2015 y abril de 2016 y las alteraciones antropométricas observadas en los mismos.

Objetivos: 1, 2, 4, 5 y 6

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Association between prenatal exposure to multiple persistent organic pollutants (POPs) and growth indicators in newborns

Raúl Cabrera-Rodríguez[a], Octavio P. Luzardo[a,b,*], Maira Almeida-González[a], Luis D. Boada[a,b], Manuel Zumbado[a,b], Andrea Acosta-Dacal[a], Cristian Rial-Berriel[a], Luis Alberto Henríquez-Hernández[a,b]

[a] Toxicology Unit, Research Institute of Biomedical and Health Sciences (IUIBS), Universidad de Las Palmas de Gran Canaria, Paseo Blas Cabrera s/n, 35016 Las Palmas de Gran Canaria, Spain
[b] Spanish Biomedical Research Center in Physiopathology of Obesity and Nutrition (CIBERObn), Spain

A B S T R A C T

Despite the fact that many of persistent organic pollutants (POPs) have been banned for decades, they still constitute a group of harmful substances to human health. Prenatal exposure can have adverse effects on one's health as well as on their newborns. The present cross-sectional study, which includes 87% of the births registered in La Palma Island (Canary Islands, Spain) during 2016 (n = 447), aims to evaluate the potential adverse health effects exerted by a wide range of POPs on newborns. We quantified blood cord levels of twenty organochlorine pesticides, eighteen polychlorinated biphenyls (PCBs), eight bromodiphenyl ethers (BDEs), and sixteen polycyclic aromatic hydrocarbons (PAHs) using the method of gas chromatography-mass spectrometry. By groups, p,p′-DDE, PCB-28, BDE-47, and phenanthrene were the most frequently detected compounds (median values = 0.148, 0.107, 0.065, and 0.380 ng/mL, respectively). p,p′-DDE was found to be significantly associated with an increase in neonatal birth weight, with a special emphasis on girls. An inverse association between PCB-28 and PCB-52 with birth weight was observed, and these associations were determined by the gender. A similar trend was obtained for BDE-47 but not for any of the PAHs. When assessing the effect of mixtures, boys exhibiting ≥ 3 OCPs were at lower risk of having higher birth weight (OR = 0.25; 95% CI = 0.07 – 0.89; P = 0.032). The effect of these pollutants on birth weight does not go in the same direction, a fact that is conditioned by several factors, including the chemical nature of the substance or the gender of the newborn. Additional research is needed to understand the role of POPs on fetal development.

1. Introduction

Persistent organochlorine pollutants (POPs) are a group of chemical substances that are characterized by their lipophilicity and resistance to degradation in the environment (Ritter et al., 1996). POPs are often halogenated and trend to their bioaccumulation in fatty tissues (Ritter et al., 1996). Thus, they were banned several decades ago and were included in the Stockholm Convention for elimination (annex A), restriction (annex B) or reduction of their unintentional releases (annex C) (UNEP, 2008). Despite this, POPs are often encountered in abiotic and biotic media; they can be transported in the environment and can accumulate in nature. However, despite decades of restricted use and prohibition, POPs are detected and quantified in serum of human beings and other species (Sonne et al., 2017), even in populations located far away from the sources of emission of these substances (Dietz et al., 2000).

In addition to their persistence, POPs exert adverse effects on wildlife and human health. Their presence in the environment affects lives of birds (Malik et al., 2018), reptiles (Semenza et al., 1997), and mammals (Peterson et al., 1993), contributing to the erosion of the planet's capability to absorb wastes generated by human beings (Steffen et al., 2011). The molecular mechanisms behind the effects of POPs on health are difficult to elucidate because both the molecular mechanism of the disease and the mode of action of the contaminants are complex. For decades, great associations between diseases and POPs have been established. Such is the case of frequent chronic diseases such as diabetes mellitus (Henriquez-Hernandez et al., 2017b; Lee et al., 2006; Taylor et al., 2013), cancer (Boada et al., 2012), dyslipidemia (Aminov et al., 2013), obesity (Henriquez-Hernandez et al., 2017b; Lee et al., 2012; Zong et al., 2015), or cardiovascular diseases (Arrebola et al., 2015; Henriquez-Hernandez et al., 2014, 2017c; Zeliger, 2013). Recently, a novel model of approach has evaluated the effect of environmental contaminants on human interactome and diseases, and come up with a molecular explanation to the previous found associations (Iida and Takemoto, 2018), thus establishing a connection between both the events.

* Corresponding author at: Toxicology Unit, Research Institute of Biomedical and Health Sciences (IUIBS), Universidad de Las Palmas de Gran Canaria, Paseo Blas Cabrera s/n, 35016 Las Palmas de Gran Canaria, Spain.
E-mail address: octavio.perez@ulpgc.es (O.P. Luzardo).

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Intrauterine life is extremely vulnerable and sensitive to external changes. Exposure to chemicals during this life period has been associated with alterations of fetal development (Gehring et al., 2013; Vrijheid et al., 2012).

Birth weight is considered to be the main indicator of fetal growth and development and depends mainly on genetics, maternal nutrition, and placental circulation (Kontic-Vucinic et al., 2006). It is associated with the health outcome of the newborn, including short-term survival and development of future diseases (Wilcox, 2001). Moreover, it has been related to the development of chronic diseases in adulthood, such as cardiovascular disease or cancer (Risnes et al., 2011).

POPs are frequently measured in maternal serum, umbilical cord serum and amniotic fluid (Luzardo et al., 2009; Zhang et al., 2018) to indicate such chemical substances cross the placental barrier and exert an effect during the intrauterine period of life (Zhang et al., 2018). Polychlorinated biphenyls (PCBs) have been associated with the reduction in fetal growth parameters as abdominal circumference or femur length (Lopez-Espinosa et al., 2016). Newborns who are highly exposed to OCPs develop health complications, including low birth weight, congenital malformations, infections, or stillbirths (Toichuev et al., 2017). But this scenario becomes more complex when studying substances in particular. p,p′-DDE is associated with increased infant growth (Iszatt et al., 2015), and other authors have reported that exposure to PCBs, bromodiphenyl ethers (BDEs), or organochlorines pesticides (OCPs) have no or small associations with birth weight (Woods et al., 2017).

The population of Canary Islands —a Spanish archipelago located near the west coast of the African continent, 1600 km far away from mainland Spain— has been well studied as far as environmental pollutants are concerned. Serum levels of POPs are well known in our population for decades (Henriquez-Hernandez et al., 2011; Luzardo et al., 2006; Zumbado et al., 2005). Moreover, they have also been detected in the amniotic fluid of pregnant women from our region (Luzardo et al., 2009). Recently, we reported the occurrence of 44 elements in the human cord blood and amniotic fluid, showing that the exposure to certain inorganic compounds may affect fetal development in terms of low birth weight (Cabrera-Rodriguez et al., 2018; Henriquez-Hernandez et al., 2018).

Since the effects of POPs in fetal development is a controversial field of research and taking into account that exposure of newborns to POPs may have an impact in gestational development (Vizcaino et al., 2014), we have designed this study aimed (1) to determine the intrauterine exposure to a wide panel of POPs (OCPs, PCBs, BDEs and polycyclic aromatic hydrocarbons (PAHs), and (2) explore the association of intrauterine exposure to these substances with the clinical parameters recorded in newborns to try and shed light on the possible adverse effects of such compounds on fetal health. The sampling was conducted in a relatively isolated geographic region, which is essentially rural in nature.

2. Material and methods

2.1. Study population

The series was initially formed by 471 umbilical cord blood samples which were used for the determination of inorganic elements (Cabrera-Rodriguez et al., 2018). After that, a total of 447 umbilical cord blood samples were available for POP analyses. All samples were recruited in the island of La Palma (Canary Islands), a low industrialized area mainly dedicated to the agricultural sector. According to official statistics, La Palma has a total of 81,486 inhabitants, and during this study's sample collection period, a total of 516 births were registered on the island (General Hospital of La Palma). Thus, the present series represents the 86.6% of the total births during the recruited period (March 1, 2015, to April 30, 2016). In addition to the losses due to exhaustion of the sample, around 8% of the births were lost because some mothers refused to participate; no sample was initially available, or the collection of data at birth was incomplete. Thus, this research provides a real representation of the study population.

Birth parameters, including weight, length, cranial perimeter, Apgar score and congenital malformations, were recorded at the delivery room, as previously reported (Cabrera-Rodriguez et al., 2018). Data referred to mothers —harmful habits, chronic diseases, and anthropometric/demographic characteristics— were also recorded.

Three groups of newborns were created based on the growth curve database of Alexander et al. (Alexander et al., 1996): small for gestational age (SGA; lower than the tenth percentile, corresponding to 2593 g for boys and 2716 g for girls), appropriate for gestational age (AGA; birth weight between the tenth and ninetieth percentiles in both genders), and large for gestational age (LGA; higher than the ninetieth percentile, corresponding to 3970 g for boys and 3764 g for girls).

Both parents were required to sign an informed consent in order to participate in the study. This study was approved by the Ethics Committees of the Hospital of La Palma and the University of Las Palmas de Gran Canaria in accordance with the Declaration of Helsinki. The samples were stored according to the regulations dictated by the Spanish Law of Biomedical Investigation of 2007 (Law 14/2007) and the data were saved according to the Data Protection Act (Ley Orgánica 15/1999).

2.2. Sample preparation and instrumentation

Half-millilitre aliquots of serum samples were mixed with 1 mL of water/n-propanol (prepared in a proportion 85:15, v/v) and applied to 200 mg (3 mL) Chromabond® C18ec columns (Macherey-Nagel, Germany) mounted in a vacuum manifold (Waters Corporation, USA) as previously reported (Ruiz-Suarez et al., 2015).

We measured the serum levels of twenty OCPs, eighteen PCB congeners, eight BDEs, and the sixteen most environmentally relevant PAHs listed by the United States Environmental Protection Agency (n = 62 compounds; Additional file 1). These chemicals were determined as stated earlier (Henriquez-Hernandez et al., 2017a, 2016, 2011; Zumbado et al., 2005). We employed a Gas Chromatography (GC) system that was equipped with an automated sampler (Models 7890B and 7693, respectively; Agilent Technologies, Palo Alto, CA, USA) for gas chromatographic separations. Two fused silica ultra-inert capillary columns Agilent J&WHP-5MS (Crosslinked 5% phenyl-methylpolysiloxane, Agilent Technologies), each with a length of 15 m, 0.25 mm i.d., and a film thickness of 0.25 µm, were connected in series and used as the stationary phase. Both columns were connected by a Purged Ultimate Union (PUU; Agilent Technologies). Helium (99.999%), at a constant flow rate of 1.0 mL/min for column 1, was used as the carrier gas. We employed the back-flushing technique during the chromatographic separations. The oven temperature program was programmed as follows: (a) 60 °C held for 1 min; (b) increased to 170 °C at a rate of 40 °C/min; (c) increased to 310 °C at a rate of 10 °C/min to 310 °C; (d) a 3 min hold time at 310 °C; and (e) cooled down to 60 °C. The injector and the transfer line were set at 280 °C. The standards and samples were injected (1 µL) in the splitless mode using a 4-mm ultra-inert liner with glass wool (Agilent Technologies).

The detection of the analytes was performed using a Triple Quad 7010 mass spectrometer (Agilent Technologies, Palo Alto, CA, USA). The quantification was conducted using ten-point calibration curves, which were constructed using a least-squares linear regression from the injection of standard solutions that ranges from 0.025 to 0.25 µg/L.

The analytical limit of quantification (LOQ) was set at 0.05 µg/L for PCBs and p,p′-DDE, 0.1 µg/L for the rest of the organochlorine pesticides and BDEs, and 0.2 µg/L for the PAHs. All the data were presented in µg/L. The details of the sample extraction, the validated chromatographic method, and the quality control have been reported previously (Henriquez-Hernandez et al., 2016, 2017d).

2.3. Quality assurance and quality control (QA/QC)

All of the measurements were performed as triplicate measurements, and the means were used for the calculations. Three controls were included every eighteen vials: a reagent blank consisting of a vial containing only cyclohexane; a vial containing 2 ng/mL of each pollutant in cyclohexane; and an internal laboratory quality control sample (QC) consisting of commercial fetal bovine serum spiked at 10 ng/mL of each analyte, which was processed using the same method of extraction. The results were considered to be acceptable when the concentration of the analytes determined in the QC sample was within 15% of the deviation of the theoretical value.

2.4. Statistical analysis

We used PASW Statistics version 19.0 (SPSS Inc., Chicago, IL, USA) to manage the study database and perform statistical analysis. Normality was examined using the Kolmogorov-Smirnov test. We used the Mann-Whitney and Kruskal-Wallis tests to analyze the non-normally distributed variables. Bivariate correlations were assessed using Pearson's or Spearman's correlation tests, as appropriate. As the distributions of POPs lacked normality and homoscedasticity, non-parametric tests were employed. We used the chi-square test to examine the relationships between categorical variables and the bivariate correlation to examine the relationships between continuous variables. Logistic regression was used for the univariate and multivariate analyses. Confounding factors considered in multivariate analyses showed significance in univariate analysis. Probability levels of < 0.05 (two-tailed) were considered statistically significant.

3. Results and discussion

3.1. Clinical characteristics of mothers and newborns

Demographic, anthropometric and clinical characteristics of the series are shown in Table 1. The mean age of mothers at delivery was 31 years (range 16 – 42). A majority of them who gave birth via vaginal delivery (75.6%), were multiparous (62.0%), did not suffer previous miscarriages (72.3%), were free of diseases associated to pregnancy —diabetes, hypertension, or hypothyroidism— (72.0%) and did not smoke (88.8%). The average duration of lactation in previous pregnancies was 5.2 months and 23.1% of participants who had previously given birth did not breastfeed (Data not shown). This means that approximately 3 out of 4 children were breastfed during a mean period of 5 months, a higher proportion than that reported in Spain and other European countries (Victora et al., 2016). This can be explained by the rural origin of the study population, although we lack data regarding breastfeeding, such as its exclusion in order to properly interpret this observation.

With regard to the newborns, the mean gestational age was found to be 39.7 weeks. We recorded 4% of preterm births (gestational age < 37 weeks). Fetuses with < 35 weeks of gestation were referred to a primary hospital on a different island, indicating the loss of the participant's follow-up. Although the percentage of premature babies is lower than that reported worldwide, 12% (Blencowe et al., 2013), this result may be biased by the loss of data of preterm babies. The mean birth weight was found to be 3284 g, a majority of the newborns were girls (52.6%) with an Apgar score ≥ 9 (90.8%) and devoid of any malformation (Table 1). The SGA for boys and girls was found to be 2593 and 2716 g, respectively while the LGA for boy and girls as 3970 and 3764 g, respectively. Newborns showing a birth weight between the tenth and the ninetieth percentile of the distribution were considered as AGA. As expected, the preterm newborns showed SGA (16 out of 18 births, 88.8%) at a higher proportion compared to non-preterm babies (29 out of 429 births, 6.7%; $X^2 < 0.0001$). According to data reported by the World Health Organization (WHO), low birth weight is defined as the weight at birth that is lower than 2500 g (WHO, 2014). In our series, a total of 20 newborns weighted < 2500 g (4.5%) at birth, a proportion similar to the 7% reported in Spain (Fuster et al., 2015).

Given the very close relationship between specific variables, the gestation age, birth length, and cranial perimeter were assumed to be lower in the lesser weighing newborns (Table 1). In that sense, the Spearman Rho coefficient between birth weight and these infant characteristics was found to be 0.393, 0.774, and 0.611, respectively, showing a significant positive association ($P < 0.0001$; Data not shown). A total of 29 out of 212 boys had LGA (13.7%), whereas 16 out of 235 (6.8%) of girls had LGA, a significant difference ($P = 0.029$) that was previously reported by other authors who showed that birth weight is often higher among boys (Alexander et al., 1999).

We observed that the women who had not previously given birth

Table 1
Anthropometric and clinical characteristics of mothers and newborns grouped by standardized birth weight.

	Total (n = 447)	SGA (n = 45)	AGA (n = 357)	LGA (n = 45)	*P*
Maternal characteristics					
Age (years)[a]	31.0 (16 – 42)	31.2 (17 – 42)	30.8 (17 – 42)	32.5 (21 – 41)	n.s.
Vaginal delivery[b]	338 (75.6)	29 (64.4)	275 (77.0)	34 (75.6)	n.s.
Nulliparity[b]	170 (38.0)	21 (46.7)	139 (38.9)	10 (22.2)	0.042
Lactation (months)[*]	5.2 (0 – 72)	3.0 (0 – 36)	4.9 (0 – 78)	9.2 (0 – 78)	0.004
Miscarriages[*] (yes)[b]	124 (27.7)	12 (26.7)	95 (26.7)	17 (37.8)	n.s.
Disease[**] (yes)[b]	125 (28.0)	13 (28.9)	98 (27.5)	14 (31.1)	n.s.
Smoking (yes)[b]	50 (11.2)	10 (22.2)	33 (9.2)	7 (15.6)	0.021
Infant characteristics					
Gestational age (weeks)[a]	39.6 (35 – 42)	37.5 (35 – 42)	39.8 (36 – 42)	40.4 (37 – 42)	< 0.0001
Sex (% male)[b]	212 (47.4)	24 (53.3)	159 (44.5)	29 (64.4)	0.029
Birth weight (g)[a]	3284 (1680 – 5050)	2400 (1680 – 2670)	3293 (2680 – 3870)	4094 (3880 – 5050)	< 0.0001
Length (cm)[a]	49 (41 – 55)	46 (41 – 49)	49 (43 – 55)	52 (50 – 55)	< 0.0001
Head circumference (cm)[a]	34 (28 – 39)	32 (28 – 36)	34 (30 – 38)	36 (34 – 39)	< 0.0001
Malformations[***] (yes)[b]	43 (9.6)	3 (6.7)	33 (9.2)	7 (15.6)	n.s.
Apgar score 7 – 8[b]	41 (9.2)	8 (17.8)	30 (8.4)	3 (6.7)	n.s.

Abbreviations: SGA, small for gestational age (< 10th percentile); AGA, appropriate for gestational age; LGA, large for gestational age (> 90th percentile); n.s., non-significant.

* Data referred to previous pregnancies.

** Include diabetes, arterial hypertension and hypothyroidism.

*** Include cardiac, oral, urogenital, skin, orthopaedic and other malformations.

[a] Kruskal-Wallis tests; mean and range were reported.

[b] Chi squared test; absolutely frequency and percentage were reported.

had children of lower birth weight (12.3 vs 8.7%, respectively; P = 0.042), a finding that coincides with what was previously published by other authors (Shah, 2010). Smoking during pregnancy is associated with low birth weight (Krol et al., 2012; McCowan et al., 2009). A similar trend was observed in our series, despite the fact that only 11.2% of women were smokers. Thus, SGA newborns among smokers and non-smokers were found to be 20% and 8.8%, respectively (P = 0.021).

3.2. Organochlorine pesticides in cord blood and association with birth weight

A total of 20 different OCPs were analyzed in 447 samples of cord blood, and p,p′-DDE and hexachlorobenzene (HCB) were the OCPs that were detected more frequently (98.7% and 79.9%, respectively). Compounds detected in < 33% of the series were not taken into account for subsequent analyses in an attempt to avoid the lack of statistical power. The compound p,p′-DDE was detected at the highest concentration (0.148 ng/mL) followed by lindane (0.111 ng/mL; frequency of detection = 2.7%). We did not observe significant differences regarding the cord blood concentration of OCPs between genders (Additional file 1).

The frequency of detection of p,p′-DDE worldwide is close to 100% (Choi et al., 2018; Govarts et al., 2018; Xu et al., 2017), despite the fact that the parental compound was banned 40 years ago. However, its concentrations may vary depending on the geographical area of the planet - higher in developing countries (Choi et al., 2018; Govarts et al., 2018). The median value reported in the present series was similar to that reported in other European cohorts (Govarts et al., 2018), such as FLEHS II (median = 0.153 ng/mL), INMA mat (median = 0.131 ng/mL), or PELAGIE (median = 0.180 ng/mL) (Govarts et al., 2018). A similar trend was observed for HCB (Govarts et al., 2018).

We observed a positive association between the cord blood concentration of p.p′-DDE and the birth weight (Additional file 2). Thus, higher levels of this compound were associated with a higher birth weight (Spearman r = 0.103, P = 0.030). Interestingly, when the series was segmented according to gender, such an association was observed only among girls (Spearman r = 0.130, P = 0.049; Additional file 2). A similar trend was obtained between the cord blood levels of HCB and the birth weight: a positive association in the whole series, which was lost among boys when the series was segmented according to the gender of the newborns (Additional file 2). Other bivariate correlations between OCPs and variables of mothers and newborns are contained in Additional file 2. Additionally, when the birth weight was segmented, the cord blood concentration of p,p′-DDE was found to be significantly higher among female newborns with appropriate/large weight (0.11 vs. 0.15 and 0.19 for SGA, AGA and LGA respectively; P = 0.041). This result was not observed among boys or for HCB (Table 2). This positive association has been published by other authors. DDT isomers and their metabolites —DDD and DDE— are associated with an increase in neonatal birth weight (Coker et al., 2018; Xu et al., 2017), a finding that suggests that these OCPs may be a risk factor for obesity. In that case, newborn girls with higher levels of p,p′-DDT and p,p′-DDE have shown a higher body mass index at the age of 2 years old (Coker et al., 2018). We have also published similar results in a series of 429 subjects from our region, showing that p,p′-DDE is a risk factor for the development of overweight (Henriquez-Hernandez et al., 2017b), a finding recently proved in an wide meta-analysis, including in vivo and in vitro data (Cano-Sancho et al., 2017).

We analyzed the role of mixtures in relation to birth weight (Table 3) and observed that the proportion of newborns with ≥ 3 different OCPs was significantly higher among boys with SGA (61.9% vs. 44.5% and 15.0% for SGA, AGA, and LGA respectively; $P = 0.008$). This trend was not observed among girls, suggesting that the effect of mixtures had different consequences in the birth weight. Because humans are contaminated by POP mixtures, epidemiological and in vitro/ex vivo studies are needed to disclose the impact of the combined effect of POP on the gene transcription and activity of receptors as a risk factor for human health (Rivero et al., 2016). This premise is especially relevant when complex health variables such as birth weight or diseases of multiple etiology are taken into account, where a more than probable environmental interaction has been established (Lee et al., 2014). The combined effect of these substances on weight at birth has been previously reported by other authors (Toichuev et al., 2018), highlighting the complexity of this analysis to examine the health effects of chemical mixtures (Coker et al., 2018). As an example of this complexity, we observed in our series that the number of OCPs (< 3 vs. ≥ 3 different compounds) appeared as a protective factor for LGA in multivariate analysis only among boys (OR = 0.25, CI 95% 0.07 – 0.89, $P = 0.032$), but was not a risk factor for SGA in neither in boys nor girls (Data not shown). To explain these observations, the potential role of other OCPs —HCB or HCH isomers— in birth weight (Guo et al., 2014) according to gender (Callan et al., 2016) has been considered, which may not have significance due to lower detection rates in the population.

Taken together, OCPs seem to have different effects on birth weight, depending on the compound or their mixture, and this effect varies according to the gender of the newborn.

3.3. Polychlorinated biphenyls and brominated diphenyl ethers in cord blood and association with birth weight

A total of 18 different PCBs were analyzed in 447 samples of cord blood. As expected, marker-PCBs (M-PCBs) were the congeners that showed the highest frequencies of detection and highest concentrations (IUPAC numbers 28, 52, 101, 138, 153, and 180). Thus, congeners 28 and 153 were found to be the PCBs detected more frequently (65.3% and 62.6%, respectively; Additional file 1). The congener PCB-28 was detected at the highest concentration (0.107 ng/mL) followed by PCB-189 and PCB-52 (0.080 and 0.055 ng/mL, frequency of detection = 0.4% and 49.7%, respectively). Compounds detected in < 33% of the series were not taken into account for subsequent analysis in an attempt to avoid the lack of statistical power. We did not observe significant differences regarding the cord blood concentration of PCBs between genders (Additional file 1).

Our results are comparable to other studies with a similar design. M-PCBs are often more present in high concentrations. Tang et al. reported median values for PCB-52 and PCB-153 as 0.29 and 0.22 ng/mL, respectively (frequency of detection = 91.5 and 81.1) in a series of Chinese newborns recruited in 2011–2012 (Tang et al., 2018). Recent studies in European population have shown a frequency of detection for PCB-138, 153 and 180 as 18.8, 43.5, and 61.8, respectively (Dufour et al., 2018) and median values of 0.11, 0.94, and 0.37 ng/mL, respectively in South Portugal (Lopes et al., 2014); median values of 0.46 and 0.68 ng/mL for PCB-153 were found in newborns from Norway and Sweden, respectively (Lauritzen et al., 2017). These values are almost ten times higher than those reported in our series, a fact that can be explained by the rural origin of our study population and the close relationship between the level of industrialization and the concentration of PCBs (Henriquez-Hernandez et al., 2011).

We did not observe a significant association between cord blood concentration of any PCB and birth weight (Additional file 2). But when the series was segmented according to gender, we observed an inverse association between PCB-28 and birth weight among boys (Spearman r = -0.172, $P = 0.039$; Additional file 2). A similar trend was detected between the cord blood levels of PCB-52 and the birth weight among girls (Spearman r = -0.184, $P = 0.040$), suggesting a possible influence of M-PCBs in fetus development, which depends of the gender of the newborn. Other bivariate correlations between PCBs and variables of mothers and newborns are contained in Additional file 2. These significant associations were not reproduced when birth weight was segmented (Table 2). In the same line, the influence of mixtures did not show any statistically significant associations (Table 3).

Table 2
Quantitative levels of POPs in umbilical cord blood according to birth weight among boys and girls. Only substances detected in > 33% of the series were included in the analysis. The results are expressed as median and presented in ng/mL.

	Boys				Girls			
	SGA (n = 21)	AGA (n = 171)	LGA (n = 20)	P#	SGA (n = 23)	AGA (n = 189)	LGA (n = 23)	P#
p,p′-DDE	0.13	0.16	0.20	0.667	0.11	0.15	0.19	0.041
HCB	0.03	0.04	0.04	0.066	0.04	0.04	0.04	0.355
PCB-28	0.15	0.10	0.05	0.143	0.08	0.12	0.09	0.525
PCB-52	0.07	0.06	0.04	0.710	0.08	0.05	0.04	0.072
PCB-101	0.04	0.06	0.05	0.384	0.02	0.03	0.03	0.615
PCB-138	0.06	0.04	0.08	0.344	0.03	0.04	0.05	0.071
PCB-153	0.05	0.04	0.05	0.395	0.03	0.05	0.05	0.286
PCB-180	0.03	0.03	0.03	0.871	0.03	0.03	0.04	0.449
Fluoranthene	0.19	0.18	0.11	0.970	0.09	0.18	0.11	0.225
Fluorene	0.13	0.12	0.12	0.738	0.18	0.12	0.12	0.739
Phenanthrene	0.78	0.45	0.18	0.336	0.24	0.39	0.42	0.084
Pyrene	0.14	0.16	0.09	0.440	0.06	0.16	0.12	0.079

Abbreviations: SGA, small for gestational age (< 10th percentile; ≤2593 g for boys and ≤2716 g for girls); AGA, appropriate for gestational age; LGA, large for gestational age (> 90th percentile; ≥3970 g for boys and ≥3764 g for girls).
Kruskal-Wallis test.

This lack of association has been reported previously by other authors who have published no or small associations of PCBs and birth weight (Woods et al., 2017). However, while some studies have reported higher odds for SGA birth with increasing serum levels of PCB-153 (Govarts et al., 2018; Lauritzen et al., 2017; Lignell et al., 2013), others have reported of the opposite scenario (Patel et al., 2018). The complexity of the matter is such that some authors have even reported that PCB congeners with different molecular weight — low-chlorinated vs. high chlorinated PCBs— have different associations with hormones and birth outcomes (Tang et al., 2018). Thus, to understand the role of such compounds on the health of newborns, the identity of the compound, the chemical nature itself, or their interaction with other compounds must be considered apart from the gender of the individual and other demographic parameters, which will condition the final effect on the subject.

A total of eight BDEs were analyzed, and only BDE-47 showed a frequency of detection > 10% (10.1% and median value = 0.065 ng/mL). Although BDE concentrations differ with regions of the World, BDE-47, BDE-153 and BDE-209 are the major components since the peak of concentration in 2006 (Tang and Zhai, 2017). It has to be highlighted that BDE-209 was not determined in the present series. However, a recent study published in Spain reported a frequency of detection in the umbilical cord serum for BDE-47 as 59.0% and a median value = 0.43 ng/mL (Lopez-Espinosa et al., 2015). Our series showed lower compared to other European cohorts (Lignell et al., 2013), possibly due to similar reasons to those exposed for PCBs: the rural origin of our study population and the close relationship between the level of industrialization and the concentration of BDEs, compounds applied as additives to numerous polymers and present in various consumer products, including furniture, electronic devices and automobile parts.

We observed a significant association between the cord blood concentration of BDE-47 and the birth weight only among girls (Spearman r = -0.643, P = 0.001; Fig. 1A). This result was also observed when birth weight was considered as a dichotomized variable segmented according to the 90th percentile (SGA; Fig. 1B). On the other hand, no significant associations was observed among boys or in the whole series.

It has been reported that certain BDE congeners influence maternal thyroid hormone status in early pregnancy (Lignell et al., 2016), and it is well known that thyroid hormones are crucial in fetal development. Thus, the maternal body burden of BDE-153 is inversely associated with the first trimester total T3, a fact that would affect normal fetal growth (Forhead and Fowden, 2014). Other authors have published an inverse association between BDEs (sum of BDE-47, BDE-99, BDE-100 and BDE-153) and birth weight, although this association was stronger among male newborns (Lignell et al., 2013). Similar results support the hypothesis of a deleterious role of BDEs on fetal development (Lopez-

Table 3
Association between the number of POPs in umbilical cord blood according to birth weight among boys and girls. The cut-off was established according to the median of the distribution.

	Boys				Girls			
	SGA (n = 21)	AGA (n = 171)	LGA (n = 20)	P#	SGA (n = 23)	AGA (n = 189)	LGA (n = 23)	P#
N OCPs				0.008				0.600
0	0	0	0		0	2 (1.0)	0	
1–2	8 (38.1)	95 (55.5)	17 (85.0)		16 (69.5)	110 (58.2)	11 (47.8)	
≥ 3	13 (61.9)	76 (44.5)	3 (15.0)		7 (30.5)	77 (40.2)	12 (52.2)	
N PCBs				0.372				0.440
0	3 (14.4)	18 (10.5)	1 (0.05)		0	0	0	
1–4	9 (42.8)	108 (63.1)	14 (70.0)		11 (47.8)	109 (57.7)	9 (39.1)	
≥ 5	9 (42.8)	45 (26.4)	5 (25.0)		6 (52.2)	67 (42.3)	10 (60.9)	
N PAHs				0.784				0.612
0	6 (28.6)	40 (23.4)	7 (35.0)		5 (21.7)	43 (22.7)	4 (17.4)	
1–2	6 (28.6)	59 (34.5)	5 (25.0)		10 (43.5)	56 (29.6)	9 (39.1)	
≥ 3	9 (42.8)	72 (42.1)	8 (40.0)		8 (34.8)	90 (47.7)	10 (43.5)	

Abbreviations: SGA, small for gestational age (< 10th percentile; ≤2593 g for boys and ≤2716 g for girls); AGA, appropriate for gestational age; LGA, large for gestational age (> 90th percentile; ≥3970 g for boys and ≥3764 g for girls).
Chi square test.

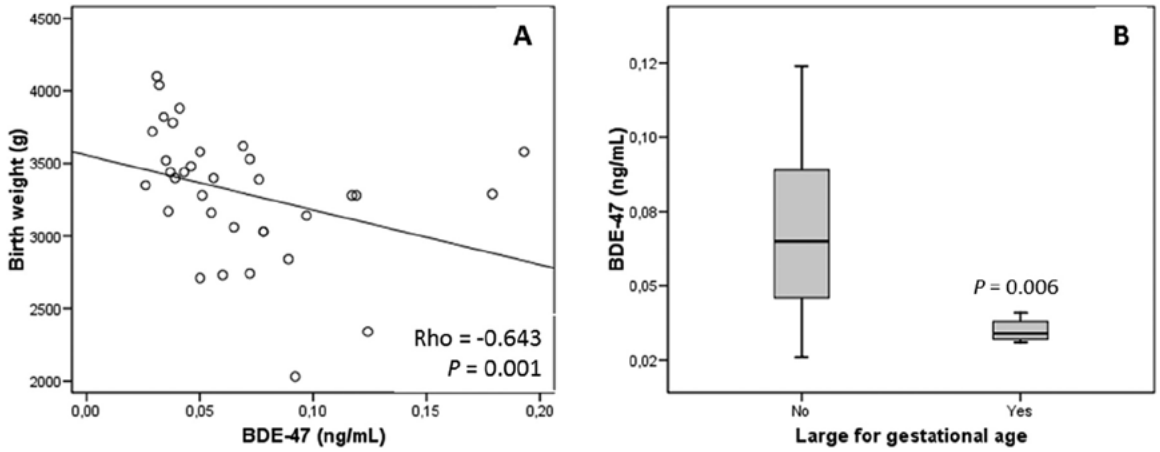

Fig. 1. Significant associations among girls between the blood concentration of BDE-47 and the birth weight were considered as a continuous variables (A) and dichotomized according to the 90th percentile (large for gestational age) (B). Bivariate correlation was assessed using Spearman's correlation test (panel A). The lines in the box plots show the medians, covering percentiles ranging from 25 to 75, and the minimal and maximal values are shown by the ends of the bars. The *P* value for panel B was calculated using the Mann-Whitney *U* test.

Espinosa et al., 2015) although this association was not always reproduced by other authors (Serme-Gbedo et al., 2016).

Taken together, some PCB and BDE congeners seem to have an impact on birth weight, but this phenomenon depends on the compound, the chemical nature of the chemical component, or their interaction with other compounds. The gender and other demographic parameters will condition the final effect on the newborn.

3.4. Polycyclic aromatic hydrocarbons in cord blood and association with birth weight

A total of 16 different PAHs were analyzed in 447 samples of cord blood. Phenanthrene and pyrene were more frequently detected (57.7% and 55.7%, respectively; Additional file 1). Naphthalene was detected at the highest concentration (1.19 ng/mL, frequency of detection = 28.0%) followed by phenanthrene (0.383 ng/mL). The compounds detected in < 33% (12 out of 16) of the series were not taken into account for subsequent analyses in an attempt to avoid the lack of statistical power. We did not observe significant differences regarding the cord blood concentration of PAHs between genders (Additional file 1).

Low molecular weight PAHs, including phenanthrene, pyrene, and naphthalene, have showed higher levels of cord blood than high molecular weight in PAHs (Zajda et al., 2017). In regard to that, we agree with the literature, although the cord blood level of PAHs reported in our series was lower than those reported by other authors. Thus, the cord blood concentration of naphthalene, phenanthrene, and pyrene among Polish samples were 50.0, 45.0, and 12.35 ng/mL, respectively (1.19, 0.38, and 0.14 ng/mL in the present series, respectively) (Zajda et al., 2017). This difference is attributable to the level of contamination of the local environment together with some toxic habits such as smoking (Ma and Harrad, 2015), and as stated previously, the population of La Palma island is rural and located far from primary sources of industrial pollution (Table 4).

PAHs can cross the placental barrier, and the exposure of the fetus to these pollutants can lead to toxicity effects, such as intrauterine growth retardation (Perera et al., 2003). Different studies suggest fetal growth reduction associated with transplacental PAHs have been exposed in humans (Dejmek et al., 2000; Perera et al., 2003). Even more, an increased risk of fetal growth ratio reduction and cephalization index elevation has been associated with fetal exposure to PAHs (Choi et al., 2012). Despite this, we have not observed any association between the cord blood concentration of PAHs and the birth weight, possibly due to lower levels detected in the present series. We also did not observe any association when the population was segmented by gender.

Table 4
Multivariate linear regression model analyzing the role of the number of detected OCPs among boys and girls in birth weight.

	BOYS		GIRLS	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Gestational age (week)	1.56 (1.01 – 2.42)	0.045	1.83 (1.17 – 2.86)	0.008
Maternal smoking[a]	0.51 (0.60 – 4.23)	0.529	1.78 (0.52 – 6.13)	0.361
Nulliparity[b]	2.71 (0.93 – 7.90)	0.068	1.69 (0.61 – 4.69)	0.311
Number of OCPs[c]	0.25 (0.07 – 0.89)	0.032	1.45 (0.60 – 3.52)	0.410

Abbreviations: OR, odds ratio; CI, confidence interval; OCP, organochlorine pesticide.
Dependent variable: birth weight introduced in the model as a dichotomous variable (0, ≤ percentile 90th; 1, > percentile 90th).
Independent variables: gestational age (introduced in the model as a continuous variable), maternal smoking, nulliparity, and number of detected OCPs.
[a] Dichotomous variable (0 = not, 1 = yes). Reference category = 1.
[b] Dichotomous variable (0 = not, 1 = yes). Reference category = 1.
[c] Dichotomous variable (0, < 3 OCPs; 1, ≥ 3 OCPs). Reference category = 0.

These results suggest that the series was exposed to very low concentrations of these contaminants and that these levels of exposure did not seem to have an impact on the birth weight of newborns.

4. Conclusions

The present results demonstrate that birth weight —considered as an important clinical endpoint of a series of biological insults in the newborns— is influenced by the presence of different persistent organochlorine pollutants (mainly p,p′-DDE, M-PCBs, and BDE-47). The effect of these pollutants on birth weight does not go in the same direction, a fact that is conditioned by several factors, including the chemical nature of the substance or the sex of the newborn. Although the body of knowledge is broad, it is a complex matter requiring further investigation.

Competing financial interest's declaration

There are no actual or potential conflict of interest to declare for any author.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2018.12.064.

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Artículo 2

4.2.

Database of persistent organic pollutants in umbilical cord blood: concentration of organochlorine pesticides, PCBS, PBDEs and polycyclic aromatic hydrocarbons.

Base de datos de contaminantes orgánicos persistentes en sangre de cordón umbilical: concentración de pesticidas organoclorados, PCBS, PBDEs e hidrocarburos aromáticos policíclicos.

Se analiza la presencia de contaminantes orgánicos persistentes en la sangre de cordón umbilical de 447 neonatos de la isla de La Palma nacidos entre marzo de 2015 y abril de 2016. Asimismo se aporta información de los parámetros antropométricos, el test de Apgar, la presencia de malformaciones congénitas e información referida a sus madres (hábitos, enfermedades crónicas, características demográficas) como base para futuros estudios multicéntricos.

Objetivos: 1, 2, 4 ,5 y 6

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Data Article

Database of persistent organic pollutants in umbilical cord blood: Concentration of organochlorine pesticides, PCBs, BDEs and polycyclic aromatic hydrocarbons

Raúl Cabrera-Rodríguez [a], Octavio P. Luzardo [a, b], Maira Almeida-González [a], Luis D. Boada [a, b], Manuel Zumbado [a, b], Luis Alberto Henríquez-Hernández [a, b, *]

[a] Toxicology Unit, Research Institute of Biomedical and Health Sciences (IUIBS), Universidad de Las Palmas de Gran Canaria, Paseo Blas Cabrera s/n, 35016, Las Palmas de Gran Canaria, Spain
[b] Spanish Biomedical Research Center in Physiopathology of Obesity and Nutrition (CIBERObn), Spain

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ABSTRACT

Persistent organic pollutants (POPs) have been banned over the last decades for being damaged to the environment and to the health of humans and animals. However, due to their lipophilic nature and resistance to degradation, they are frequently detected in biological samples. Its presence has been associated with the increased risk of suffering from different diseases in human series, being newborns and children especially sensitive. The present data reports umbilical cord blood levels of twenty organochlorine pesticides (aldrin, dieldrin, endrin, o,p'-DDD, p,p'-DDD, o,p'-DDE, p,p'-DDE, o,p'-DDT, p,p'-DDT, endosulfan alfa, endosulfan beta, endosulfan sulphate, heptachlor, HCB, αHCH, βHCH, δHCH, lindane, methoxychlor and mirex), eighteen polychlorinated biphenyls (congeners 28, 52, 77, 81, 101, 105, 114, 118, 123, 126, 138, 153, 156, 157, 167, 169, 180 and 189), eight bromodiphenyl ethers (congeners 28, 47, 85, 99, 100, 153, 154 and 183), and sixteen polycyclic aromatic hydrocarbons (acenaphthalene, acenaphthene, anthracene, benzo(a)anthracene, benzo(a)pyrene, benzo(b)fluoranthene, benzo(g,h,i)perylene, benzo(k)fluoranthene, chrysene, dibenzo(a,h)anthracene, fluoranthene, fluorine, indene(1,2,3-cd)pyrene, naphthalene, phenanthrene and pyrene). A

* Corresponding author. Toxicology Unit, Research Institute of Biomedical and Health Sciences (IUIBS), Universidad de Las Palmas de Gran Canaria, Paseo Blas Cabrera s/n, 35016, Las Palmas de Gran Canaria, Spain.
E-mail address: luis.henriquez@ulpgc.es (L.A. Henríquez-Hernández).

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total of 447 samples, representing 86.6% of the total births during the recruited period (March 1, 2015, to April 30, 2016), were available for POP analyses. POPs were determined in a Gas Chromatography (GC) system equipped with an automated sampler (Models 7890B and 7693; Agilent Technologies, Palo Alto, CA, USA) for gas chromatographic separations. The detection of the analytes was performed using a Triple Quad 7010 mass spectrometer (Agilent Technologies). All of the measurements were performed as triplicate measurements, and the means were used for the calculations. Data are reported in ng/mL. The present data also includes birth parameters, including weight, length, cranial perimeter, Apgar score and congenital malformations, and data referred to mothers (harmful habits, chronic diseases, and anthropometric/demographic characteristics).

Specifications Table

Subject	Toxicology
Specific subject area	Detection and quantification of persistent organic pollutants in umbilical cord blood from 447 newborns from La Palma (Canary Islands, Spain)
Type of data	Table
How data were acquired	Gas chromatography - mass spectrometry Instruments: GC model 7890B and Triple Quad 7010, respectively. Agilent Technologies, Palo Alto, CA, USA.
Data format	Raw
Parameters for data collection	Birth weight, length, and cranial perimeter of newborns were recorded at delivery. Data on congenital malformations were detected at birth, identified and recorded. Gestational age was calculated based on the last menstrual period. Other anthropometric and biological characteristics of the mother included age, parity, type of delivery, and previous miscarriages.
Description of data collection	Cord blood samples were collected in EDTA tubes after collection by venipuncture of the umbilical cords obtained immediately after delivery. Samples were stored at −80 °C until the moment of their processing for analysis. Recruited period: March 1, 2015 to April 30, 2016. All samples were recruited in La Palma (Canary Islands)
Data source location	Institution: Toxicology Unit, Clinical Sciences Department, Universidad de Las Palmas de Gran Canaria City/Town/Region: Las Palmas de Gran Canaria (Gran Canaria, Canary Islands) Country: Spain
Data accessibility	With the article
Related research article	Cabrera-Rodríguez R, Luzardo OP, Almeida-González M, Boada LD, Zumbado M, Acosta-Dacal A, Rial-Berriel C, Henríquez-Hernández LA. Association between prenatal exposure to multiple persistent organic pollutants (POPs) and growth indicators in newborns. Environmental Research 2019 Apr; 171:285–292. https://doi.org/10.1016/j.envres.2018.12.064.

Value of the Data

- The present data is useful because reports levels of 62 POPs in a series of 447 umbilical cord blood samples, together with the demographic and clinical parameters recorded for the series. The present data help interpreting effects caused by the inadvertent exposure to these hazardous compounds.
- These data will benefit everyone conducting biomonitoring studies in human populations, especially those who conduct

1. Data description

The data contains umbilical cord blood concentration of organochlorine pesticides, PCBs, BDEs and polycyclic aromatic hydrocarbons. Data are provided in excel format containing the following data (Table in Supplementary data):

- Demographical and clinical data referred to the mothers: age at birth (years), type of delivery (vaginal/caesarean), nulliparity (yes/no), lactation (months), miscarriages (yes/no), diseases — including diabetes, arterial hypertension and hypothyroidism (yes/no), smoking habit (yes/no)
- Clinical data referred to the newborn: gestational age (weeks), sex (male/female), birth weight (g), length (cm), head circumference (cm), malformations at birth (yes/not), Apgar score
- Concentration of pollutants in ng/mL: organochlorine pesticides (aldrin, dieldrin, endrin, o,p'-DDD, p,p'-DDD, o,p'-DDE, p,p'-DDE, o,p'-DDT, p,p'-DDT, endosulfan alfa, endosulfan beta, endosulfan sulphate, heptachlor, HCB, αHCH, βHCH, δHCH, lindane, methoxychlor and mirex), eighteen polychlorinated biphenyls (congeners 28, 52, 77, 81, 101, 105, 114, 118, 123, 126, 138, 153, 156, 157, 167, 169, 180 and 189), eight bromodiphenyl ethers (congeners 28, 47, 85, 99, 100, 153, 154 and 183), and sixteen polycyclic aromatic hydrocarbons (acenaphthalene, acenaphthene, anthracene, benzo(a)anthracene, benzo(a)pyrene, benzo(b)fluoranthene, benzo(g,h,i)perylene, benzo(k)fluoranthene, chrysene, dibenzo(a,h)anthracene, fluoranthene, fluorine, indene(1,2,3-cd)pyrene, naphthalene, phenanthrene and pyrene). A summary table reporting the ranges of concentration of the pollutants is showed in Table 1.

2. Experimental design, materials, and methods

All samples were recruited in the island of La Palma (Canary Islands, Spain). The present series represents the 86.6% of the total births during the recruited period (March 1, 2015, to April 30, 2016). Birth parameters were recorded at the delivery room, as previously reported [1]. Data referred to mothers were recorded and included anonymously in the database. Both parents were required to

Table 1
Ranges of concentration of the POPs (ng/mL).

OCPs	Range	PAHs	Range	PCBs	Range	BDEs	Range
Aldrin	0.002–0.161	Acenaphthalene	0.001–0.231	PCB 101	0.002–0.269	BDE 100	0.046–0.051
o,p'-DDD	ND	Acenaphthene	0.007–0.306	PCB 105	0.007–0.062	BDE 153	0.026–0.067
p,p'-DDD	0.011–0.095	Anthracene	0.181–0.181	PCB 114	0.024–0.037	BDE 154	0.006–0.072
o,p'-DDE	0.068–0.068	Benzo(a)anthracene	0.193–0.229	PCB 118	0.001–0.151	BDE 183	0.072–0.078
p,p'-DDE	0.001–3.762	Benzo(a)pyrene	0.160–0.164	PCB 123	0.002–0.189	BDE 28	0.050–0.075
o,p'-DDT	0.010–0.040	Benzo(b)fluoranthene	0.053–0.162	PCB 126	0.001–0.084	BDE 47	0.014–0.137
p,p'-DDT	0.095–1.027	Benzo(g,h,i)perylene	0.052–0.475	PCB 138	0.001–0.220	BDE 85	ND
Dieldrin	0.001–0.723	Benzo(k)fluoranthene	0.001–0.232	PCB 153	0.002–0.234	BDE 99	0.039–0.056
Endosulfan alfa	0.066–0.069	Chrysene	0.093–0.122	PCB 156	0.025–0.025		
Endosulfan beta	0.035–0.097	Dibenzo(a,h)anthracene	0.019–0.338	PCB 157	ND		
Endosulfan sulphate	0.003–0.055	Fluoranthene	0.001–1.382	PCB 167	0.002–0.029		
Endrin	ND	Fluorene	0.001–1.828	PCB 169	0.017–0.023		
Heptachlor	0.023–0.026	Indene(1,2,3-c,d)pyrene	0.081–0.088	PCB 180	0.005–0.143		
HCB	0.001–0.350	Naphthalene	0.023–22.196	PCB 189	0.079–0.081		
α-HCH	ND	Phenanthrene	0.005–8.417	PCB 28	0.001–2.129		
β-HCH	0.010–1.340	Pyrene	0.004–1.187	PCB 52	0.002–0.354		

sign an informed consent. This study was approved by the Ethics Committees of the Hospital of La Palma and the University of Las Palmas de Gran Canaria in accordance with the Declaration of Helsinki. The samples were stored according to the regulations dictated by the Spanish Law of Biomedical Investigation of 2007 (Law 14/2007) and the data were saved according to the Data Protection Act (Ley Orgánica 15/1999).

Sample preparation, instrumentation, and quality assurance/quality control are extensively exposed in a previous publication [2,3]. We used PASW Statistics version 19.0 (SPSS Inc., Chicago, IL, USA) to manage the database and perform statistics [2].

Conflict of Interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dib.2019.104918.

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[2] R. Cabrera-Rodríguez, O.P. Luzardo, M. Almeida-González, L.D. Boada, M. Zumbado, A.C. Acosta-Dacal, C. Rial-Berriel, L.A. Henríquez-Hernández, Association between prenatal exposure to multiple persistent organic pollutants (POPs) and growth indicators in newborns, Environ. Res. 171 (2019) 285–292. https://doi:10.1016/j.envres.2018.12.064.

[3] O.P. Luzardo, M. Badea, M. Zumbado, L. Rogozea, L. Floroian, A. Ilea, M. Moga, G. Sechel, L.D. Boada, L.A. Henríquez-Hernández, Body burden of organohalogenated pollutants and polycyclic aromatic hydrocarbons in Romanian population: influence of age, gender, body mass index, and habitat, Sci. Total Environ. 656 (2019) 709–716. https://doi:10.1016/j.scitotenv.2018.

4.3. Artículo 3

Occurrence of 44 elements in human cord blood and their association with growth indicators in newborns.

Presencia de 44 elementos en sangre de cordón umbilical y su asociación con parámetros antropométricos en recién nacidos.

Se analiza la presencia de 44 elementos inorgánicos en la sangre de cordón umbilical de 471 neonatos de la isla de La Palma nacidos entre marzo de 2015 y abril de 2016 incluyendo metales, metaloides y elementos raros usados en la fabricación de dispositivos electrónicos. Asimismo se estudia la relación de estos elementos con los parámetros antropométricos.

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Occurrence of 44 elements in human cord blood and their association with growth indicators in newborns

Raúl Cabrera-Rodríguez[a,1], Octavio P. Luzardo[a,b,*,1], Ana González-Antuña[a], Luis D. Boada[a,b], Maira Almeida-González[a], María Camacho[a], Manuel Zumbado[a], Andrea Carolina Acosta-Dacal[a], Cristian Rial-Berriel[a], Luis Alberto Henríquez-Hernández[a]

[a] Toxicology Unit, Research Institute of Biomedical and Health Sciences (IUIBS), Universidad de Las Palmas de Gran Canaria, Paseo Blas Cabrera s/n, 35016 Las Palmas de Gran Canaria, Spain
[b] Spanish Biomedical Research Center in Physiopathology of Obesity and Nutrition (CIBERObn), Spain

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ABSTRACT

There is growing concern about environmental pollution produced by elements, including "emerging" contaminants, such as rare earth elements (REE) and other trace elements (TE), which are extensively and increasingly employed in the manufacture of consumer electronics. Previous research has shown that prenatal exposure to some elements (mainly heavy metals) may be associated with decreased fetal growth and other adverse birth outcomes. Recent studies have also shown that environmental exposure to REE and TE may be related to adverse effects on human health. This cross-sectional study, which included nearly 92% of the births in 2016 in La Palma (Canary Islands, Spain; n = 471), aimed to evaluate the potential adverse health effects exerted by a wide range of elements on newborns. We quantified the levels of 44 elements (including 26 REE and TE) in their umbilical cord blood. Our results showed low or very low levels of most elements. We found an inverse association between antimony (Sb) and birth weight (Spearman's r = −0.106, p = 0.021). A similar trend was observed between nickel (Ni) and birth weight and between chromium (Cr) and birth length, although in this case the significance was borderline. Bismuth appeared as a risk factor for having a birth weight below the tenth percentile in the univariate (OR = 3.30; 95% CI = 1.25–8.78; p = 0.017) and multivariate analyses (OR = 5.20; 95% CI = 1.29–20.91; p = 0.020). When assessing the effect of element mixtures, the sum of Cr, Ni, and Sb appeared as a risk factor for having a birth weight below the tenth percentile in the univariate (OR = 2.41; 95% CI = 1.08–5.35; p = 0.031) and multivariate analyses (OR = 3.84; 95% CI = 1.42–10.39; p = 0.008). Our findings suggest that some inorganic elements—isolated or in mixture—are associated to a lower fetal growth. Additional research is needed to understand the role of inorganic pollutants on fetal development.

1. Introduction

It is clearly established that the period of intrauterine life is extremely vulnerable and sensitive to external changes. For this reason, the study of exposure to environmental pollutants during this time is extremely important, which is why numerous birth cohorts worldwide have studied exposure to different types of chemical contaminants during this period. In addition, many have tried to establish epidemiological relationships between these exposures and alterations in fetal development (Gehring et al., 2013; Kim et al., 2009; Townsend et al., 2016; Vrijheid et al., 2012). Furthermore, it has also been established that the development of many chronic diseases in adulthood may be conditioned by intrauterine life, so that proper fetal development is a determinant of health not only in newborns but also in future adults. Thus, increased risks for cardiovascular disease (CVD), obesity, and cancer have been associated with fetal parameters (Risnes et al., 2011). Birth weight is an indicator of fetal growth and development and depends mainly on genetics, maternal nutrition, and placental circulation (Kontic-Vucinic et al., 2006). It is one of the parameters that have been most related to health outcomes, especially the short-term survival of the newborn, but also the development of future diseases (Wilcox, 2001). The 2020 Healthy People program established a reduction in low birth weight (LBW) rates as one of its priority objectives. According to recent data, the current low birth weight (LBW) rate in developed

* Corresponding author at: Toxicology Unit, Clinical Sciences Department, Universidad de Las Palmas de Gran Canaria, Paseo Blas Cabrera Felipe s/n, 35016 Las Palmas, Spain.
E-mail address: octavio.perez@ulpgc.es (O.P. Luzardo).
[1] Both authors contributed equally to this work and should be considered first authors.

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countries stands at 8.2% of births (CDC, 2000; Creel et al., 2017). According to recent data, the low birth weight (LBW) rate in Spain was 8.1% (Ayerza-Casas and Herraiz-Esteban, 2015). No data about birth weight are available through the Canary Institute of Statistics (information at http://www.gobiernodecanarias.org/istac).

Among the environmental factors to which the fetus may be more sensitive is exposure to inorganic elements. On the one hand, adequate exposure to elemental micronutrients is essential, and a balanced diet is required to ensure the correct intake of these elements (Kontic-Vucinic et al., 2006). Marginal or severe trace element imbalances are considered risk factors for several important public health diseases, especially when multiple micronutrient deficiencies, rather than single deficiencies, are encountered (Mertz, 1981). On the other hand, as important as the deficiency of elements—which is rare in developed countries where supplementation is commonly prescribed—is overexposure to some of them. Thus, exposure during gestation to environmental pollutants (such as toxic elements) can lead to serious health problems at birth, and possibly also in adult life, and even in future generations (Gillman et al., 2007; Wigle et al., 2007). Early exposure to elements on pregnancy outcomes and child health were previously investigated (McDermott et al., 2015; Pletz et al., 2016; Wigle et al., 2007). Most of the available studies focused on excess or deficiencies of micronutrients or on a few elements for which evidence of exposure exists (As, Cd, Cr, Hg, Ni, and Pb, among others). However, according to the latest edition of the list of priority pollutants produced by the Agency for Toxic Substances and Disease Registry (ATSDR), there are up to 18 elements whose effects on human and environmental health must be monitored (Camacho et al., 2013; CDC, 2017) based on a combination of their frequency, toxicity, and potential for human exposure at National Priority List (NPL) sites (CDC, 2017). It is noteworthy that this list includes several essential elements, indicating that although these are homeostatically regulated, overexposure to some may represent a threat to human health.

In addition, there are a number of other elements that have not been classified as toxic or priority pollutants and to which human exposure has been irrelevant in the past because their occurrence in the earth's crust is limited to extremely unlikely. They are the rare earth elements (REE) and other trace elements (TE), to which only those who live near places with the highest concentration of these elements would be exposed in natural conditions. However, this group of elements has begun to be extracted intensively from mines since they are extensively and increasingly used because their properties have made them highly valuable for technological industry (Hussain and Mumtaz, 2014; Tansel, 2017). The mobilization and universal use of these high-tech-related elements has caused people to currently be exposed to them on a daily basis (Henriquez-Hernandez et al., 2017b), mainly due to e-waste dispersed into the environment. In addition, REE and TE are employed in medical (such as gadolinium in magnetic resonance imaging), agricultural (as fertilizers), and zootechnical (such as REE-supplemented diets for rabbits, ruminants, and broiler chickens) applications (Du and Du and Graedel, 2011; Pagano et al., 2015a; Pang et al., 2002; USEPA, 2012). Therefore, the potential health effects of human exposure to these “emerging” pollutants began to worry the scientific community (Henriquez-Hernandez et al., 2017a; Henriquez-Hernandez et al., 2017b; Pagano et al., 2015a; Pagano et al., 2015b). Moreover, animal studies and data from human occupational exposure suggest that some REE/TE-induced tissue-specific bioaccumulation may damage the lungs, liver, and brain (Pagano et al., 2015b). To date, adverse health effects of human environmental exposure to low levels of many of these high-tech-related elements are unknown. However, due to increasing environmental contamination, the potential health risks associated with single or multiple exposures to low levels of chemicals need to be investigate further, especially since the combined action of pollutants varies from the effects of individual exposure (Rivero et al., 2017; Rivero et al., 2016). Moreover, studies on the adverse effects of exposure to these mixtures of elements during intrauterine life for the neonate are even scarcer.

Taking into account all of the above, we have designed this study, in which we: (1) determined the intrauterine exposure to a wide panel of elements (n = 44), including both those elements that are considered as priority in biomonitoring studies and others that we have termed “emerging pollutants” (REE and other high-tech-related TE); and (2) explored the association of intrauterine exposure to these elements with the clinical parameters recorded in newborns, trying to shed light on the possible adverse effects of such compounds on fetal health. In addition, a very important point of this study is that the sampling was conducted in a relatively isolated geographic region, essentially rural in nature. This, in addition to allowing presenting for the first time the values of exposure of many of these elements during intrauterine life, provide a first reference for the background levels of these elements related to natural environmental contamination.

2. Materials and methods

2.1. Study population

This study analyzed a total of 471 umbilical cord blood samples. These samples represented 91.4% of the total number of births recorded during 1 year (March 1, 2015, to April 30, 2016) on the island of La Palma (Canary Islands, Spain). La Palma is considered a rural area with very low level of industrialization. According to official statistics, La Palma has a total of 81,486 inhabitants, and during this study's sample collection period, a total of 516 births were registered on the island (General Hospital of La Palma), which corresponds with the officially recorded birth rate (6.5/1000 inhabitants) (ISTAC, 2015, 2016), so we assume that these 516 represent 100% of births on the island. Overall, 8.6% of births were lost to this study because the mothers refused to participate, no sample was available, or the collection of data at birth was incomplete. Thus, this study provides the rare opportunity to include almost all of the births that occur in a territory in a cohort, thus obtaining a real representation of the study population.

At birth, delivery room staff measured the birth weight, length, and cranial perimeter following standard anthropometric procedures. The score was collected using the Apgar test according to usual practice in neonatology (Apgar, 1966). Data on congenital malformations—mainly cardiac, oral, urogenital, skin, and orthopedic—were detected at birth and identified and recorded. Gestational age was calculated based on the last menstrual period. We collected data regarding the other variables from the mother (such as harmful habits, chronic diseases, food consumption, occupation, socioeconomic status, etc.) using a structured questionnaire. Other anthropometric and biological characteristics of the mother included age, parity, type of delivery, and previous miscarriages.

Three groups of newborns were created based on the growth curve database of Alexander et al. (Alexander et al., 1996): small for gestational age (lower than the tenth percentile, corresponding to 2662 g for newborn baby boys and 2583 g for newborn baby girls; SGA), appropriate for gestational age (birth weight between the tenth and ninetieth percentiles in both genders; AGA), and large for gestational age (higher than the ninetieth percentile, corresponding to 3878 g for newborn baby boys and 3760 g for newborn baby girls; LGA). Fetal size was stratified due to the importance of the prognosis and clinical management of newborns.

Both parents were required to sign informed consent in order to participate in the study. This study was approved by the Ethics Committees of the Hospital of La Palma and the University of Las Palmas de Gran Canaria in accordance with the Declaration of Helsinki. The samples were stored according to the regulations dictated by the Spanish Law of Biomedical Investigation of 2007 (Law 14/2007) and the data were saved according to the Data Protection Act (Ley Orgánica 15/1999).

2.2. Trace element measurements

Cord blood samples were collected in metal-free EDTA tubes after collection by venipuncture of the umbilical cords obtained immediately after delivery. The samples were immediately sent via urgent courier to the Toxicology Laboratory at the Research Institute of Biomedical and Health Sciences (IUIBS) of the University of Las Palmas de Gran Canaria, where they were stored at −80 °C until the moment of their processing for analysis. All the samples were received in perfect condition and correctly identified.

We determined the whole blood concentration levels of 44 elements, which were selected according to their biological importance, as is the case for some essential elements, their toxicity, or their frequent use in the manufacture of electronic consumer products (Hussain and Mumtaz, 2014; Tansel, 2017): Ag (silver); As (arsenic); Au (gold); Ba (barium); Be (beryllium), Bi (bismuth), Cd (cadmium), Ce (cerium), Cr (chromium), Cu (copper), Dy (dysprosium), Eu (europium), Er (erbium), Ga (gallium), Gd (gadolinium), Hg (mercury), Ho (holmium), In (indium), La (lanthanum), Lu (lutetium), Nb (niobium), Nd (neodymium), Ni (nickel), Os (osmium), Pb (lead), Pd (palladium), Pr (praseodymium), Pt (platinum), Ru (ruthenium), Sb (antimony), Se (selenium), Sm (samarium), Sn (tin), Sr (strontium), Ta (tantalum), Tb (terbium), Th (thorium), Tl (tallium), Tm (thulium), U (uranium), V (vanadium), Y (yttrium), Yb (ytterbium), and Zn (zinc).

For the elemental analyses, we employed an Agilent 7900 ICP-MS (Agilent Technologies, Tokyo, Japan) equipped with standard nickel cones, Ultra High Matrix Introduction (UHMI) system, and a Cross-Flow Nebulizer with a make-up gas port (X400 Nebulizer, Savillex Corporation, Eden Prairie, MN, USA). We followed a procedure for human blood, which had been previously validated in our laboratory, using certified reference materials (González Antuña et al., 2017). Briefly, 130 µL of cord blood were diluted using 1120 µL of ammonia solution (0.05% of EDTA, 0.05% of Triton X-100, and 1% of NH_4OH), and 50 µL of internal standards (ISTD) were added (final volume = 1.3 mL). The ISTD solution was composed of Sc (scandium), Ge (germanium), Rh (rhodium), and Ir (iridium) at a stock concentration of 20 mg/mL each. Pure standards of elements in acid solution (5% HNO_3, 100 mg/L) were purchased from CPAchem (Stara Zagora, Bulgaria). Two standard curves (10 points, 20 ng/mL–0.005 ng/mL) were produced to avoid interference between elements: (1) one using a commercial multi-element mixture (CPAchem, 100 mg/L, 5% HNO_3) containing all of the essential elements and main heavy metals and (2) another multi-element mixture tailor-made in our laboratory from individual elements (CPAchem) that contained REE and TE. To avoid the memory effect associated with Hg, a cleaning solution consisting of 2.0% HNO_3 and 0.5% HCl was introduced between samples. A blank sample was also introduced each 5–10 samples to ensure that there was no memory effect for any element. Limits of quantification (LOQs) were calculated as the signal that was six times higher than the signal of the blanks (n = 24), and limits of detection (LOD) were established as the signal that were three times higher than the signal of the blanks. The LOQs ranged between 0.02 and 1.0 ng/mL (Additional File 1), and the accuracy of measurements was at the range of 79–128%, with relative standard deviations (RSD) below 6% in all cases as previously described (González Antuña et al., 2017). A value of 1/2 LOQ was assigned to the elements whose concentrations were below its LOQ value but higher than its LOD. The concentrations of elements below the LOD were assigned a zero (0) value.

2.3. Statistical analysis

We used PASW Statistics version 19.0 (SPSS Inc., Chicago, IL, USA) to manage the study database and perform statistical analyses. Normality was examined using the Kolmogorov-Smirnov test. We used the Mann-Whitney and Kruskal-Wallis tests to analyze the non-normally distributed variables. Bivariate correlations were assessed using Pearson's or Spearman's correlation tests, as appropriate. The chemical distributions lacked normality and homoscedasticity (except for Zn); therefore, we used non-parametric tests. We used the chi-squared test to examine the relationships between the categorical variables and the bivariate correlation to examine the relationships between continuous variables. Logistic regression was used for the univariate and multivariate analyses. Birth weight (tenth percentile as cutoff) and the sum of Cr, Ni, and Sb (percentile 90th as cutoff), and Bi (percentile 95th as cutoff) were included as dichotomous variables in the model. Confounding factors considered in multivariate analyses were all the variables that showed significance in previous univariate analysis. The results were reported as means ± standard deviation, medians, and percentiles of distribution. Probability levels of < 0.05 (two-tailed) were considered statistically significant.

3. Results

3.1. Clinical characteristics of mothers and newborns

The mean age of the mothers participating in this study was 31.1 ± 5.5 years. A total of 75.5% of them gave birth via vaginal delivery, and the rest were delivered by caesarean section. Overall, 61.5% of the participants had given birth previously. A total of 127 mothers had previously undergone abortions, and 130 had some type of illness: 30 women had gestational diabetes (6.4%), 92 had hypothyroidism (19.5%), and 22 suffered gestational hypertension (4.7%). Daily tobacco use was recorded from the 11.3% of the women who reported being smokers. The mean gestational age was 39.6 ± 1.5 weeks, and only 4% of the women (n = 19) had preterm deliveries (gestational age < 37 weeks). No post-term deliveries (gestational age > 42 weeks) were recorded in our series.

With regard to the newborns, their mean birth weight was 3270 ± 486 g. Forty-seven of the newborns were classified as SGA (< 2662 g, corresponding to the tenth percentile of the weight distribution), 377 were classified as AGA, and 47 were classified as LGA (> 3878 g, corresponding to the ninetieth percentile of the weight distribution). None of the births was recorded with an Apgar score—measured at minute 5—lower than 7. As expected, the preterm newborns showed SGA (17 out of 19 births, 89.5%) at a higher proportion than the newborns born at 37–42 gestational weeks (30 out of 452, 6.6%; $X^2 < 0.0001$). The general characteristics of the mothers and their newborns in the whole series and in the three groups of birth weights are shown in Table 1.

According to our results, the proportion of the newborns classified as SGA was higher among the women who had not previously given birth (46.8%, p = 0.025). Thus, our results indicate that the primipara mothers in our series gave birth to smaller babies. As expected, the mean gestational age was lower among the SGA infants, and a significant difference between girls and boys was also observed (Table 1). Finally, maternal smoking in the SGA group was significantly higher than in the AGA and LGA groups (p = 0.021). Subsequently, all the comparisons among the newborn groups were adjusted by the above-mentioned variables. As expected, length and head circumference were strongly associated with birth weight (Pearson's r = 0.798 and 0.646, respectively; p < 0.0001), and these were subsequently considered variables dependent on birth weight.

3.2. ATSDR's priority elements in cord blood and association with birth weight

Although as indicated above, ATSDR's priority contaminant list includes not only clearly toxic elements but also some essential elements, these were not initially ruled out as potentially toxic in this study. This decision was based on our previous experience in populations in the neighboring geographical area of the Canary Islands (West African continental shelf), in which we found that a relatively high percentage

Table 1
Anthropometric and clinical characteristics of mothers and newborns grouped by standardized birth weight.

	Total (n = 471)	SGA (n = 47)	AGA (n = 377)	LGA (n = 47)	*P*
Maternal characteristics					
Age (years)[a]	31.1 (16–42)	31 (16–42)	31 (17–42)	32 (21–41)	n.s.
Vaginal delivery[b]	351 (74.5)	29 (61.7)	286 (75.9)	36 (76.6)	n.s.
Nulliparity[b]	180 (38.2)	22 (46.8)	148 (39.3)	10 (21.3)	0.025
Miscarriages[1] (yes)[b]	129 (27.4)	11 (23.4)	99 (26.3)	19 (40.4)	n.s.
Disease[2] (yes)[b]	130 (27.6)	12 (25.5)	104 (27.6)	14 (29.8)	n.s.
Smoking (yes)[b]	53 (11.3)	10 (21.3)	35 (9.3)	8 (17.0)	0.021
Infant characteristics					
Gestational age (weeks)[a]	39.6 (29–42)	37 (29–42)	39 (36–42)	40 (37–42)	< 0.0001
Sex (% male)[b]	222 (47.1)	25 (53.2)	167 (44.3)	30 (63.8)	0.028
Birth weight (g)[c]	3270 (1600–5500)	2372 (1600–2660)	3281 (2670–3870)	4087 (3880–5050)	< 0.0001
Length (cm)[a]	49 (41–55)	46 (41–49)	49 (43–55)	52 (50–55)	< 0.0001
Head circumference (cm)[a]	34 (28–39)	32 (28–36)	34 (30–38)	36 (34–39)	< 0.0001
Malformations[3] (yes)[b]	46 (9.8)	3 (6.4)	36 (9.5)	7 (14.9)	n.s.
Apgar score 7–8[b]	43 (9.1)	8 (17.0)	32 (8.5)	3 (6.4)	n.s.

Abbreviations: SGA, small for gestational age (< 10th percentile); AGA, appropriate for gestational age; LGA, large for gestational age (> 90th percentile); n.s., non-significant.

[1] Data referred to previous pregnancies.

[2] Include diabetes, arterial hypertension and hypothyroidism.

[3] Include cardiac, oral, urogenital, skin, orthopedic and other malformations.

[a] Kruskal-Wallis tests; mean and range were reported.

[b] Chi squared test; absolutely frequency and percentage were reported.

[c] Since birth weight showed a normal distribution, ANOVA test was used.

of the participants exhibited high (potentially toxic) levels of some of these elements, such as Cu, Cr, and Se (Henriquez-Hernandez et al., 2017a; Henriquez-Hernandez et al., 2017b) or Zn (unpublished data).

The results of the concentrations of this group of elements in cord blood samples are shown in Table 2 (n = 18 elements, 5 of them considered essential elements). Only Zn showed a normal distribution (Kolmogorov-Smirnov test, p = 0.591). As, Cu, Sb, Se, Sr, and Zn were detected in 100% of the samples. At the opposite end, the least frequently detected elements were Be (20%), Tl (56.1%), Th (57.1), and U (57.3%). The elements that were quantified at the highest concentrations were Cu, Se, Zn, and Sr (Table 2, Additional File 1). This is logical in the case of Cu, Se, and Zn because they are essential elements. Because the concentrations of these three elements were within the physiological range, they were not further considered in the statistical analyses. The median levels of As, Ba, Cr, Pb, and Sb were > 0.5 ng/mL for all of the elements.

An inverse correlation was observed between Sb concentration in cord blood and birth weight (Spearman's $r = -0.106$, $p = 0.021$). Regarding nickel, the correlation study almost reached statistical significance (Spearman's $r = -0.080$, $p = 0.084$), and due to its relevance as a heavy metal with potential effects on human health, it was considered for further analyses. We also found a similar trend between Cr and the length of newborns (Spearman's $r = -0.078$, $p = 0.082$). However, no differences were found in the concentrations of any of

Table 2
Quantitative levels of trace metals included in the ATSDR's priority pollutant list in umbilical cord blood, in the whole series and according to birth weight. The results were presented in ng/mL.

Element	Whole series (n = 471)			SGA (n = 47)	AGA (n = 377)	LGA (n = 47)	*P#*
	% of detection	Mean ± SD	Median	Median	Median	Median	
Ag (silver)	95.5	0.15 ± 0.48	0.05	0.04	0.05	0.05	n.s.
As (arsenic)	100	1.36 ± 3.02	0.59	0.58	0.62	0.49	n.s.
Ba (barium)	96.8	2.06 ± 2.79	1.60	1.64	1.60	1.54	n.s.
Be (berillium)	20.0	0.02 ± 0.05	< LOQ	< LOQ	< LOQ	< LOQ	n.s.
Cd (cadmium)	65.0	0.01 ± 0.02	0.01	0.01	0.01	0.01	n.s.
Cr (chromium)[a]	98.1	1.10 ± 0.66	0.99	1.03	1.01	0.93	n.s.
Cu (copper)[a]	100	402.04 ± 193.95	367.77	314.16	372.56	344.18	n.s.
Hg (mercury)	99.4	0.81 ± 0.56	0.67	0.66	0.67	0.58	n.s.
Ni (nickel)[a]	92.4	0.78 ± 0.86	0.61	0.73	0.62	0.53	n.s.
Pb (lead)	89.8	1.62 ± 2.26	0.81	0.43	0.82	0.8	n.s.
Sb (antimony)	100	13.82 ± 9.67	11.22	11.75	11.22	10.57	n.s.
Se (selenium)[a]	100	66.69 ± 24.31	62.09	54.68	63.40	61.75	0.070
Sr (strontium)	100	41.09 ± 20.00	37.07	33.21	37.41	38.72	n.s.
Th (thorium)	57.1	0.01 ± 0.01	0.01	0.01	0.01	< LOQ	n.s.
Tl (tallium)	56.1	0.01 ± 0.01	0.01	0.01	0.01	0.01	n.s.
U (uranium)	57.3	0.02 ± 0.05	0.01	0.01	0.01	< LOQ	n.s.
V (vanadium)	99.8	0.24 ± 0.25	0.17	0.15	0.17	0.17	n.s.
Zn (zinc)[a]	100	1179 ± 417	1162	1165	1165	1053	n.s.

Abbreviations: LOQ, limit of quantification; SD, standard deviation; SGA, small for gestational age (< 10th percentile); AGA, appropriate for gestational age; LGA, large for gestational age (> 90th percentile); n.s., non-significant.

#Kruskal-Wallis test.

Sum of 3 elements included Cr, Ni, and Sb.

[a] Elements considered as essentials.

Table 3
Multivariate linear regression model analyzing the role of Cr, Ni, and Sb.

	OR (95% Cl)	*P*
Gestational age (week)	3.60 (2.62–4.50)	< 0.0001
Maternal smoking[a]	1.77 (0.64–4.85)	0.269
Sex[b]	1.43 (0.64–3.21)	0.388
Nulliparity[c]	2.12 (0.94–4.77)	0.071
Σ of Cr, Ni, and Sb (ng/mL)[d]	3.84 (1.42–10.39)	0.008

Abbreviations: OR, odds ratio; CI, confidence interval.
Dependent variable: birth weight introduced in the model as a dichotomous variable (0, ≤percentile 10th; 1, > percentile 10th).
Independent variables: gestational age (introduced in the model as a continuous variable), maternal smoking, sex, primiparous, and sum of Cr, Ni, and Sb.
[a] Dichotomous variable (0 = not, 1 = yes). Reference category = 1.
[b] Reference category = male.
[c] Dichotomous variable (0 = not, 1 = yes). Reference category = 1.
[d] Dichotomous variable (0, ≤percentile 90th; 1, > percentile 90th). Reference category = 1.

these elements among the birth weight groups (Table 2). In an attempt to clarify the potential role of Cr, Ni, and Sb, we explored the possible relationships considering the sum of these three elements. We found that the median value of their summed concentrations was higher in the SGA group (18.17 ng/mL) than in the AGA (15.68 ng/mL) group and higher than in the LGA group (13.31 ng/mL). These differences did not reach statistical significance, but they were very close (p = 0.057) (Table 2). However, when the summation (which was clearly dominated by Sb concentrations) was dichotomized according to the ninetieth percentile of the distribution, we observed that sum of Cr, Ni, and Sb appeared as a risk factor for having a birth weight below the tenth percentile in univariate analysis; odds ratio (OR) = 2.41, 95% confidence interval (95% CI) = 1.08–5.35, and p = 0.031. Moreover, this trend was also observed in the multivariate analysis adjusting by the confounding factors (gestational age, smoking habit, sex, and nulliparity, Table 3). In addition to gestational age (OR = 3.60, 95% CI = 2.62–4.50, p < 0.0001), only the sum of Cr, Ni, and Sb appeared as a risk factor for low birth weight (OR = 3.84, 95% CI = 1.42–10.39, p = 0.008) (Fig. 1). No other associations were observed.

3.3. REE and TE in cord blood and association with birth weight

Within the REE and TE groups (26 elements), the most frequent elements found in cord blood were Ce (92.8%), Sn (82.6%), and La (76.0%) (Table 4). At the opposite end, the least frequently detected elements were Dy, Gd, Pd, and Yb (< 10% of the samples). In terms of concentrations, Sn was the element detected at the highest concentration within this series (median value = 0.210 ng/mL), followed by Ce and Ga (0.030 and 0.020 ng/mL, respectively) (Table 4, Additional File 1).

We observed a negative correlation between Bi and birth weight, but although close to statistical significance, this was not achieved (Spearman's r = −0.086, p = 0.063).

We explored the role of Bi in the clinical outcome of the newborns. We found that the concentration of Bi was higher in the SGA group (0.024 ng/mL) than in the AGA (0.014 ng/mL) and LGA (0.008 ng/mL) groups, although this difference did not reach statistical significance (p = 0.056, Table 4). The frequency of detection of Bi was similar in the three groups (X^2 test, p = 0.060). When the Bi concentration was dichotomized according to the ninetieth percentile of the distribution (> 0.04 ng/mL), we observed that Bi was a risk factor for having a birth weight below the tenth percentile in univariate analysis (OR = 3.30, 95% CI = 1.25–8.78, p = 0.017). Moreover, this trend was also observed in multivariate analysis (Table 5). In addition to gestational age (OR = 3.53, 95% CI = 2.57–4.84, p < 0.0001), and nulliparity (OR = 2.35, 95% CI = 1.04–5.29, p = 0.039), Bi appeared as a risk factor for low birth weight (OR = 5.20, 95% CI = 1.29–20.91, p = 0.020) (Fig. 1). No other associations were observed within this group of elements.

4. Discussion

The levels of 44 inorganic elements—18 elements included in the ATSDR list of priority pollutants (which includes also some essential elements) and 26 other hi-tech-related elements (mainly REE and other TE)—were analyzed in 471 umbilical cord blood samples from La Palma Island (Canary Islands, Spain). To the best of our knowledge, no previous study has analyzed such a substantial number of elements in such a large population of newborns. It is true that there are some international multicenter studies that include a large number of cord blood samples, but these have been limited to a finite number of elements (As, B, Cd, Co, Hg, Mb, Mn, Pb, and Se) (Vrijheid et al., 2012). The concentrations of these elements we found in this study were very similar or even lower than those published in other birth cohorts around the world (Barbieri et al., 2016; Rahbar et al., 2015; Vrijheid et al., 2012). However, the present study includes the determination of REE and other TE that had not been previously determined in newborns. We consider the main strength of this study is that for most of these elements, information documenting levels of in utero exposure is not available elsewhere. If we add to this the fact that the samples have been collected from a relatively geographically isolated rural area, it could be considered that the series of data that we present here provides a good basis for setting background levels of human exposure related to natural environmental contamination.

As expected, nulliparity, smoking, gestational age, and the sex of the newborn were related to birth weight, as previously published (Alexander et al., 1999; Krol et al., 2012; McCowan et al., 2009; Shah, 2010; Skjaerven et al., 2000): In our series, 53 mothers were smokers (11.3%), similar to the 12.3% reported by other authors (Tong et al., 2013), and univariate analysis found that smoking appeared as a risk factor for SGA (OR 2.39, 95% CI = 1.11–5.15, p = 0.026). A potential effect on birth weight of Pb and Cd through smoking has been suggested (Chelchowska et al., 2013; Sun et al., 2014), but we did not observe statistical differences in lead or Cd concentrations in relation to smoking, possibly due to the low number of smoking mothers (data not

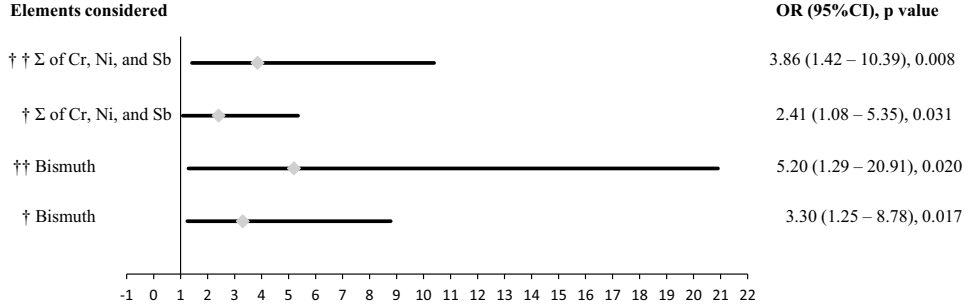

Fig. 1. Forrest plot of odds ratios (OR) with 95% confidence interval (CI) for inorganic elements and birth weight in univariate (†) and multivariate (††) analysis. Each diamond represents the OR and the horizontal line indicates the 95% CI. For multivariate analysis, gestational age, sex, nulliparity, and smoking variables were also included.

Table 4
Quantitative levels of trace metals not included in the priority pollutant list but related to e-waste in umbilical cord blood, in the whole series and according to birth weight. The results were presented in ng/mL.

Element	Whole series (n = 471)			SGA (n = 47)	AGA (n = 377)	LGA (n = 47)	*P#*
	< LOQ (n, %)	Mean ± SD	Median	Median	Median	Median	
Au (gold)	52.4	0.009 ± 0.01	0.010	0.010	0.010	< LOQ	n.s.
Bi (bismuth)	36.1	0.014 ± 0.03	< LOQ	< LOQ	< LOQ	< LOQ	0.056
Ce (cerium)	92.8	0.059 ± 0.11	0.030	0.030	0.030	0.030	n.s.
Dy (dysprosium)	5.9	0.002 ± 0.01	< LOQ	< LOQ	< LOQ	< LOQ	n.s.
Eu (europium)	57.3	0.017 ± 0.02	0.010	0.010	0.010	0.010	n.s.
Er (erbium)	24.8	0.004 ± 0.01	< LOQ	< LOQ	< LOQ	< LOQ	n.s.
Ga (gallium)	70.9	0.029 ± 0.03	0.020	0.020	0.020	0.010	n.s.
Gd (gadolinium)	7.2	0.002 ± 0.01	< LOQ	< LOQ	< LOQ	< LOQ	n.s.
Ho (holmium)	46.1	0.049 ± 0.10	< LOQ	< LOQ	< LOQ	< LOQ	n.s.
In (indium)	27.2	0.008 ± 0.02	< LOQ	< LOQ	< LOQ	< LOQ	n.s.
La (lanthanum)	76.0	0.041 ± 0.27	0.010	0.010	0.020	0.010	n.s.
Lu (lutetium)	18.3	0.008 ± 0.02	< LOQ	< LOQ	< LOQ	< LOQ	n.s.
Nb (niobium)	66.0	0.013 ± 0.02	0.010	0.010	0.010	0.010	n.s.
Nd (neodimium)	55.4	0.009 ± 0.01	0.010	< LOQ	0.010	0.010	n.s.
Os (osmium)	50.7	0.013 ± 0.02	0.010	0.010	0.010	< LOQ	n.s.
Pd (palladium)	6.4	0.001 ± 0.01	< LOQ	< LOQ	< LOQ	< LOQ	n.s.
Pr (praseodymium)	37.4	0.007 ± 0.01	< LOQ	< LOQ	< LOQ	< LOQ	n.s.
Pt (platinum)	57.1	0.021 ± 0.05	0.010	0.010	0.010	< LOQ	n.s.
Ru (ruthenium)	42.5	0.008 ± 0.06	< LOQ	< LOQ	< LOQ	< LOQ	n.s.
Sn (tin)	82.6	0.378 ± 0.76	0.210	0.160	0.220	0.160	n.s.
Sm (samarium)	29.9	0.009 ± 0.02	< LOQ	< LOQ	< LOQ	< LOQ	n.s.
Ta (tantalum)	22.1	0.005 ± 0.02	< LOQ	< LOQ	< LOQ	< LOQ	n.s.
Tb (terbium)	47.3	0.009 ± 0.01	< LOQ	< LOQ	< LOQ	< LOQ	n.s.
Tm (thulium)	43.5	0.010 ± 0.01	< LOQ	< LOQ	< LOQ	< LOQ	n.s.
Y (Ytrium)	60.9	0.012 ± 0.02	0.010	0.010	0.010	0.010	n.s.
Yb (ytterbium)	5.9	0.001 ± 0.01	< LOQ	< LOQ	< LOQ	< LOQ	n.s.

Abbreviations: LOQ, limit of quantification; SD, standard deviation; SGA, small for gestational age (< 10th percentile); AGA, appropriate for gestational age; LGA, large for gestational age (> 90th percentile); n.s., non-significant.
#Kruskal-Wallis test.

Table 5
Multivariate linear regression model analyzing the role of Bi.

	OR (95% Cl)	*P*
Gestational age (week)	3.53 (2.57–4.84)	< 0.0001
Maternal smoking[a]	1.77 (0.63–4.94)	0.276
Sex[b]	1.45 (0.65–3.26)	0.363
Nulliparity [c]	2.35 (1.04–5.29)	0.039
Bi (ng/mL)[d]	5.20 (1.29–20.91)	0.020

Abbreviations: OR, odds ratio; CI, confidence interval.
Dependent variable: birth weight introduced in the model as a dichotomous variable (0, ≤percentile 10th; 1, > percentile 10th).
Independent variables: gestational age (introduced in the model as a continuous variable), maternal smoking, sex, primiparous, and Bi.
[a] Dichotomous variable (0 = not, 1 = yes). Reference category = 1.
[b] Reference category = male.
[c] Dichotomous variable (0 = not, 1 = yes). Reference category = 1.
[d] Dichotomous variable (0, ≤percentile 95th; 1, > percentile 95th). Reference category = 1.

shown). However, the association of toxic chemicals and tobacco is dose-dependent (Rhainds and Levallois, 1997), and only one mother in our series was considered a heavy smoker (> 20 cigarettes per day). Finally, among the well-known variables that influence anthropometric measurements at birth, in our study gestational age was associated with birth weight and appeared as a risk factor for SGA in univariate analysis (OR 3.39; 95% CI = 2.53–4.56; p < 0.0001). We recorded 4% of preterm births (gestational age < 37 weeks), which is lower than the 11–12% estimated preterm birth rate previously reported worldwide (Blencowe et al., 2013). It must be taken into account that fetuses with < 35 weeks of gestation are referred to a primary hospital on another island of our archipelago. Thus, in our study population, the influence of a very low gestational age would be considered as lower in relation to birth weight.

When the concentrations of Cr, Ni, and Sb were summed, the infants with the highest concentrations of these were at increased risk for SGA, which was demonstrated in both univariate and multivariate analyzes (Fig. 1). However, we should note that the sum approach is an "artificial" sum of the elements, which is calculated by the simple addition of concentrations, and the relative weights of each are very different. Therefore, these results should be taken with some caution. Nevertheless, when the concentrations of each of these 3 elements were considered separately, they were also separately related to birth weight.

In relation to Cr, exposure to this metal can be through the ingestion of contaminated water and food or directly by the inhalation of air containing it (Kotas and Stasicka, 2000). Once absorbed, Cr is able to easily cross the placental barrier, and different studies in animals have indicated that > 250 ppm in drinking water may exert embryotoxic effects and fetal toxicity in a dose-dependent manner (Trivedi et al., 1989). Although very few epidemiological studies have focused on prenatal exposure to Cr and its effects on newborns, a significantly increased risk of low birth weight (LBW) was found among infants born to residents living near Cr-contaminated areas (OR = 5.1; 95% CI = 2.1–12.3) (Berry and Bove, 1997). Similar results were observed in Hubei province (China), where the risk of LBW was associated with higher levels of chromium (> 3 ng/mL) in maternal urine (Xia et al., 2016). However, other studies indicate that there is no relationship between plasma Cr levels in mothers and low birth weight of their children (Bogden et al., 1978; Yurdakok et al., 1993). Our study did not find a statistical relationship between this metal and the weight of the newborns.

Regarding Ni, the second element in our study that was related to the anthropogenic factors measured at birth (weight), exposure to high levels of this metal (> 0.0031 μg/m^3 determined in $PM_{2.5}$ filters) was related to low birth weight, although in conjunction with exposure to other small particles (≤2.5 μm; $PM_{2.5}$), such as vanadium or zinc (Bell et al., 2010). In fact, it has been estimated that the risk of low birth

weight increases by 5.7 (95% CI = 2.7–8.8) due to the exposure of mothers to Ni and other $PM_{2.5}$ (Ebisu and Bell, 2012). It must be taken into account that Ni is a nutritionally essential trace metal for several animal species, micro-organisms, and plants, and is the 24th most abundant element in the earth's crust. Moreover, increased levels of Ni are encountered in highly industrialized areas, and smoking is considered a main source of Ni exposure in humans (Cempel and Nikel, 2006).

With respect to the third of the elements that were found to have a relationship with the anthropometric variables of the newborns—Sb—it is necessary to emphasize that available studies are very scarce. One study aimed at exploring low-level exposure to heavy metals during pregnancy—including Sb—reported non-significant association with the birth size of the newborns, finding a geometric mean concentration of urinary Sb of < 0.21 μg/g creatinine (Shirai et al., 2010). Emissions of Sb in the environment result from both natural events, such as rock weathering and soil erosion, and human activities, especially mining, smelting, and traffic emissions, and Sb compounds are present as fire retardants in commonly used materials (such as textiles, carpet backings, plastics, and synthetic fibers) and in the production of polyesters, ceramics, glass, and rubber. Environmental exposure to metals—including Sb—of newborns, infants, and young children must be further studied since it is a potential threat to health and quality of life (Patriarca et al., 2000).

Finally, in relation to Bi, this study found that blood levels of this metal seem to have an influence on birth weight, contributing to its decrease. Bi is a relatively scarce metal found in the earth's crust at about the same abundance as silver and almost never occurring in its native state. Up to the present time and to the best of our knowledge, the role of Bi on human fetal development has not been explored, although its toxicity on fetal development in experimental animals has been demonstrated (fetal malformations and intrauterine growth retardation) (Lee et al., 2013). This element has been used in pharmaceutical and cosmetic products and is frequently found at low concentrations in biological and environmental samples, such as blood, urine, food, and water (Dolara, 2014).One of the most popular over-the-counter drugs, bismuth subsalicylate, which is used for the treatment of dyspepsia and traveler's diarrhea (Giddings et al., 2016), is not recommended for chronic consumption, especially during pregnancy or lactation, precisely because of its probable adverse effects on fetal development (Lee et al., 2013; Mahadevan, 2007). In addition, in vitro studies found that Bi causes chromosomal aberrations in mammalian cells (Asakura et al., 2009). However, this study did not find any statistical association between Bi and fetal malformations. In this respect, it is necessary to bear in mind that although this series of births covers the majority of those registered on the island of La Palma for one year, the number of samples, and therefore of malformations, was likely too small to find this kind of association (9.8%). Nevertheless, in light of the published data and those found in this study, we believe that the role of Bi during pregnancy deserves more attention, especially in pregnant women suffering from gastrointestinal problems.

Taken as a group, many high-tech-related elements can be considered “emerging pollutants” to which the humans are increasingly exposed, given the parallel increase in their use in a variety of applications, mainly the consumer electronics industry (Henriquez-Hernandez et al., 2017a; Pagano et al., 2015a). However, toxicological investigations into the health effects that may be related to exposure to these new pollutants are still scarce (Henriquez-Hernandez et al., 2017a; Pagano et al., 2015b), and many questions remain to be resolved. Most of the data available refer to short exposures (of occupational type) to some of the elements within these groups (mainly Ce [CeO_2 NP] and La) and suggest that these can exert a toxic effect on some organs, such as the liver, lungs, and kidneys (Pagano et al., 2012). Regarding the exposure to environmental levels, in a recent study by our group, the results pointed to the possibility that the increasing exposure to REE and other high-tech-related TE can play a role in the development of anemia (Henriquez-Hernandez et al., 2017a). However, in-depth studies on the effects of long-term exposure to these elements are still lacking, and at least as far as we know, the role of these elements during intrauterine life is wholly unknown. To date, there is a single study in which the levels of some of these elements were described in the umbilical cord blood of Australian mother-children pairs (antimony, beryllium, bismuth, cesium, gallium, rubidium, silver, strontium, thallium, thorium, and vanadium) (Hinwood et al., 2015). Comparing the levels of these selected elements to those of the same in our study in mothers on the island of La Palma, we found that these were lower in our study in all of the cases (the mean values for Bi were < 0.05 ng/mL and < LOQ, respectively). One possible explanation is that the elements studied by Hinwood et al. are mostly linked to processes of mining and refining or combustion of coal and oil and are commonly used in the electronics, semiconductor, and defense industries. It is likely that all of these are minor sources of exposure on an island such as La Palma, whose population is mostly rural. Nonetheless, other factors must be taken into account. This is the case for diet (including alcohol consumption), which is considered the most important source of pollutant intake. Information about the diet of the mothers was not available in the present study and this could be considered a limitation on the interpretation of the differences observed between the groups.

The mechanism of action underlying the adverse effects of REEs is largely unknown in many cases. However, most of those studied to date (mainly Ce, La, Pr, Nd, Ho, and Tb) have been shown to have mitotic activity or produce cytogenetic abnormalities (Pagano et al., 2015b). Although the majority of studies published on this topic were carried out on plants, micronuclear and chromosomal aberrations have also been observed in cultures of mammalian cells treated with Pr and Nd (Jha and Singh, 1995). In animal models, the literature reporting REE toxicity shows that these elements induce a differential expression of the genes involved in immune response/inflammation, apoptosis, the cell cycle or oxidative stress (Cheng et al., 2014), liver weight decrease and increased activity of the liver enzyme (Nalabotu et al., 2011), histopathological changes in the kidneys, changes in lipid peroxidation levels, and increased activity of ROS and decreased superoxide dismutase (SOD) activity (Zhao et al., 2013), among other effects on the kidneys, liver, and lungs (Pagano et al., 2015a).

5. Conclusions

The present results demonstrate the importance of the blood levels of some elements—Bi, Cr, Ni, and Sb—on the weight at birth. The reported findings suggest that these elements could be additional factors that trigger the low birth weight condition, which is a clinical endpoint considered a marker of a series of biological insults both in the newborn and in adulthood. More research is needed to better understand the role of trace elements in fetal growth to reveal the molecular mechanisms of action behind this effect.

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Competing financial interests declaration

There are no actual or potential conflicts of interest to declare for any author.

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Conclusiones

- **1.** Nuestros estudios confirman la exposición prenatal simultánea a múltiples contaminantes orgánicos e inorgánicos.

- **2.** La serie está expuesta a un nivel muy bajo de contaminantes orgánicos persistentes y, estos no parecen que tengan un impacto importante en la antropometría de los recién nacidos. El peso de los recién nacidos se ve afectado por algunos contaminantes clorados (principalmente el p,p'-DDE, M-PCBs y BDE-47). El efecto de estos contaminantes depende del sexo del recién nacido así como de otros condicionantes tales como la naturaleza química de la sustancia.

- **3.** El nivel de pesticidas persistentes es similar al de otras series publicadas, mientras que el nivel de PCBs y PBDEs es inferior al de otras series, tal vez por carácter rural y la ausencia de actividad industrial en la isla de La Palma.

- **4.** Los hidrocarburos aromáticos policíclicos fueron los compuestos menos frecuentemente encontrados en la muestra, la mayoría de ellos presente en menos del 10%.

- **5.** Los contaminantes inorgánicos considerados esenciales (cobre, selenio, zinc) se encontraron dentro del rango fisiológico.

- **6.** Se observó una relación inversa entre las concentraciones de antimonio, cromo y níquel y el peso al nacimiento.

- **7.** Los elementos raros y otros elementos usados en la fabricación de dispositivos electrónicos se encontraron con poca frecuencia en la serie, estando presentes, en general, en menos de un tercio de las mismas. La concentración de bismuto se relacionó inversamente con el peso al nacimiento, aunque este elemento no es un REE.

- **8.** Los resultados de esta Tesis doctoral aportan datos relevantes en relación a la gran variedad de tóxicos ambientales a los que el feto está expuesto intraútero. Mientras que para muchas de estas sustancias químicas están bien documentados los efectos deletéreos a corto y largo plazo, para otros se requiere realizar estudios amplios de exposición.

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