Environment International 116 (2018) 43–51

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

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

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ARTICLE INFO

Keywords:
Heavy metals
E-waste
Rare earth elements
Birth weight
Bismuth

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

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https://doi.org/10.1016/j.envint.2018.03.048
Received 6 December 2017; Received in revised form 30 March 2018; Accepted 30 March 2018
Available online 09 April 2018
0160-4120/

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

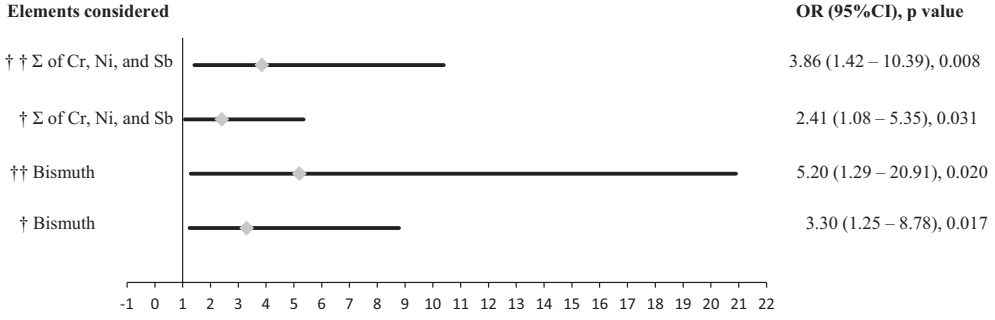

Fig. 1. Forrest plot of odds ratios (OR) with 95% confidence interval (CI) for inorganic elements and birth weight in univariate (†) and multivariate (††) analysis. Each diamond represents the OR and the horizontal line indicates the 95% CI. For multivariate analysis, gestational age, sex, nulliparity,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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.03.048.

Competing financial interests declaration

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

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