Environmental Research 197 (2021) 111028

Contents lists available at ScienceDirect

Environmental Research

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

Review article

Toxic metals in toenails as biomarkers of exposure: A review

Inmaculada Salcedo-Bellido [a,b,c,1,*], Enrique Gutiérrez-González [c,d,e,1], Esther García-Esquinas [c,f], Nerea Fernández de Larrea-Baz [c,g], Ana Navas-Acien [h], María Téllez-Plaza [g], Roberto Pastor-Barriuso [c,g], Virginia Lope [c,g], José Luis Gómez-Ariza [i,j], Tamara García-Barrera [i,j], Marina Pollán [c,g], José Juan Jiménez Moleón [a,b,c,2], Beatriz Pérez-Gómez [c,d,g,**,2]

[a] Department of Preventive Medicine and Public Health, University of Granada, Av. de La Investigación, 11, 18016, Granada, Spain
[b] Instituto de Investigación Biosanitaria ibs. GRANADA, Spain
[c] Consortium for Biomedical Research in Epidemiology & Public Health (CIBER en Epidemiología y Salud Pública - CIBERESP), Monforte de Lemos 5, 28029, Madrid, Spain
[d] Public Health & Preventive Medicine Teaching Unit, National School of Public Health, Carlos III Institute of Health, Monforte de Lemos 5, 28029, Madrid, Spain
[e] Spanish Agency of Food Safety and Nutrition, Ministry of Consumer Affairs, Alcalá, 56, 28014, Madrid, Spain
[f] Department of Preventive Medicine and Public Health, Universidad Autónoma de Madrid, C/ Arzobispo Morcillo 4, 28029, Madrid, Spain
[g] Department of Epidemiology of Chronic Diseases, National Centre for Epidemiology, Carlos III Institute of Health, Monforte de Lemos 5, 28029, Madrid, Spain
[h] Department of Environmental Health Sciences, Columbia University Mailman School of Public Health, 722 W 168th St, New York, NY, 10032, USA
[i] Department of Chemistry, Faculty of Experimental Sciences, Campus El Carmen, University of Huelva, Fuerzas Armadas, Ave., 21007, Huelva, Spain
[j] Research Center for Natural Resources, Health and the Environment, University of Huelva, Spain

ARTICLE INFO

Keywords:
Toenail
Biomonitoring
Toxic metals
Exposure
Biomarker

ABSTRACT

Toenails have been used as biomarkers of exposure to toxic metals, but their validity for this purpose is not yet clear and might differ depending on the specific agent. To evaluate this issue, we reviewed the literature on: a) the time-window of exposure reflected by toenails; b) the reproducibility of toenail toxic-metal levels in repeated measures over time; c) their relationship with other biomarkers of exposure, and; d) their association with potential determinants (i.e. sociodemographic, anthropometric, or lifestyle characteristics) or with sources of exposure like diet or environmental pollution.

Thus, we performed a systematic review, searching for articles that provided original data for levels of any of the following toxic metals in toenails: aluminum, beryllium, cadmium, chromium, mercury, nickel, lead, thallium and uranium.

We identified 88 articles, reporting data from 67 different research projects, which were quite heterogeneous with regard to population profile, sample size and analytical technique. The most commonly studied metal was mercury. Concerning the time-window of exposure explored by toenails, some reports indicate that toenail cadmium, nickel and lead may reflect exposures that occurred 7–12 months before sampling. For repeated samples obtained 1–6 years apart, the range of intraindividual correlation coefficients of aluminum, chromium and mercury was 0.33–0.56. The correlation of toxic metal concentrations between toenails and other matrices was higher for hair and fingernails than for urine or blood. Mercury levels were consistently associated with fish intake, while other toxic metals were occasionally associated with specific sources (e.g. drinking water, place of residence, environmental pollution, and occupation). The most frequently evaluated health endpoints were cardiovascular diseases, cancer, and central nervous system diseases.

Available data suggest that toenail mercury levels reflected long-term exposures and showed positive associations with fish intake. The lack of standardization in sample collection, quality control, analytical techniques and procedures – along with the heterogeneity and conflicting results among studies – mean it is still difficult to

* Corresponding author. Department of Preventive Medicine and Public Health, University of Granada, Av. de La Investigación, 11, 18016, Granada, Spain.
** Corresponding author. Carlos III Institute of Health, Monforte de Lemos 5, 28029, Madrid, Spain.
E-mail addresses: isalcedo@ugr.es (I. Salcedo-Bellido), bperez@isciii.es (B. Pérez-Gómez).

[1] Joint first authors.
[2] Joint senior authors.

https://doi.org/10.1016/j.envres.2021.111028
Received 17 December 2020; Received in revised form 13 March 2021; Accepted 14 March 2021
Available online 19 March 2021

conclude that toenails are a good biomarker of exposure to toxic metals. Further studies are needed to draw solid conclusions about the suitability of toenails as biomarkers of exposure to toxic metals.

1. Introduction

Non-essential toxic metals are trace elements with no established biological functions in humans which can potentially exert long-term deleterious health effects (Nordberg et al., 2015). Some of these, for instance, nickel (Ni), hexavalent chromium (Cr), beryllium (Be), cadmium (Cd), and uranium (U) are known human carcinogens (IARC, 2012). Others, for instance, Cd, lead (Pb), and mercury (Hg) are possible cardiovascular disease risk factors (Nigra et al., 2016; Solenkova et al., 2014; Tellez-Plaza et al., 2018) or neurotoxicants (Pb, Hg, aluminum (Al) (Dórea, 2020; Lukiw et al., 2019; Yang, 2019), thallium (Tl) (Campanella et al., 2019; Lin et al., 2020; Osorio-Rico et al., 2017)).

The main sources of exposure to toxic metals for humans are air, food and water. After a metal has been incorporated into the organism, it is deposited onto the walls of the airways or the mucosa of the gastrointestinal tract and, then, a fraction is transferred to the systemic circulation. It has been reported that several factors can influence the amount deposited in the organism, one of which is the chemical form of the metal (Elder et al., 2015). Generally, toxic metals lack homeostatic controls (Ballatori, 2002); there are several routes for their excretion from the body with the most important being gastrointestinal and renal (Elder et al., 2015).

Compared to blood or urine, toenails may reflect longer-term exposure to toxic metals due to their relatively slow rate of growth (12–18 months to grow completely from the cuticle) (Adair et al., 2006; Yaemsiri et al., 2010), and due to these metals' independence from metabolic activities once they have been incorporated into the nails' keratin structure (Sukumar, 2006). In addition, toenails have indisputable logistical advantages over other matrices: they are easier to collect, transport and store (Carneiro et al., 2011), and have a lower probability of external contamination than either hair or fingernails (Adair et al., 2006). However, there are a number of uncertainties regarding the value of toenails as suitable biomarkers of toxic metal exposure. Indeed, as not all metals are incorporated equally into the keratin, it is possible that toenails might be useful biomarkers of exposure for some, but not all, metals. In this review, the main objective was to evaluate the validity of toenails as biomarkers of exposure to non-essential toxic metals based on: 1) the reproducibility of toenails' metal concentrations in repeated measures over time and the time-window of exposure; 2) their relationship with other biomarkers of exposure; 3) their association with potential determinants like sociodemographic, anthropometric or lifestyle characteristics, and with sources of exposure like diet or environmental pollution.

2. Material and methods

2.1. Search strategy

This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement criteria (Liberati et al., 2009). We searched three different databases: PubMed/Medline, Web of Science and Scopus. The initial search strategy comprised essential and toxic trace metals, although arsenic (Signes-Pastor et al., 2020) and essential metals in toenails (Gutiérrez-González et al., 2019) have now been covered by specific reports. Therefore, for the purposes of this review, we included those articles with information on other toxic non-essential metals (Al, Be, Cd, Hg, Ni, Pb, Tl and U) – as well as on Cr, an essential metal in its trivalent form and a carcinogen in its hexavalent form – which was not included in the already published review on essential metals in toenails. MeSH terms were: #1 nail OR toenail; #2 exposure OR biomonitoring OR biomarker; #3 metals OR trace elements OR beryllium OR vanadium OR chromium OR cobalt OR nickel OR copper OR zinc OR arsenic OR selenium OR cadmium OR platinum OR lead OR uranium OR mercury OR thallium OR aluminum OR molybdenum OR manganese OR iron OR silicon OR boron; and were combined as follows: #1 AND #2 AND #3. The initial search yielded 2632 articles; plus 52 additional articles identified by manually reviewing reference lists.

2.2. Study selection

This article is part of a large and comprehensive review of the available literature on toenails as biomarkers of exposure to trace elements carried out by our research group. We selected all the studies that reported original quantitative data on metals measured in human toenails, published in English or Spanish from inception (the first published study) to December 2017. Figure S1 (Supplementary Material) is a flow diagram representing the process . The initial search yielded 2632, plus 52 additional articles identified when manually reviewing reference lists. After duplicate reference removal, 953 records were selected for title and abstract screening, with 880 manuscripts identified for full-text assessment. We applied the following exclusion criteria: (1) no original research (i.e., reviews, editorials, non-research letters); (2) non-human toenails; (3) no quantitative metal levels reported; (4) sample matrix different from toenails or unknown nail origin, after having tried to contact the corresponding author; (5) only reporting on arsenic and/or essential metals, as these parts of the review have already been published (Gutiérrez-González et al., 2019; Signes-Pastor et al., 2020); (6) papers written in other languages or those that could not be located after an extensive search. Selected articles were reviewed by two investigators (ISB and EGG). Any discrepancies were resolved by consensus, and if necessary, a third reviewer was involved (BPG). Finally, 88 manuscripts with information about toxic-metal levels (Al, Be, Cr, Cd, Hg, Ni, Pb, Tl, U), from 67 different research projects, were included in this review; 39 of these articles explicitly evaluated the association of toenail metal concentrations with a specific health effect.

2.3. Data extraction

Using a previous purpose-designed protocol, we extracted the following information from each manuscript: a) Basic data (first author data; country & year of publication; project; list of studied metals; b) Study characteristics (epidemiological design; sample size; population sampling method and participant main features; ethical committee approval; informed consent); c) Sample and analytical information (toenail specification, i.e. big toe, other toes, all toes; sample pretreatment; analytic methodology; quality control procedures and limit of detection (LOD) and limit of quantification (LOQ) data; availability of metal levels measured in other biological matrices); d) Metal levels and their association with other biomarkers, personal characteristics, environmental data, or previous toenail measures; e) Association with health effects related with the observed concentrations.

The majority of studies reported toenails' metal concentrations in micrograms per gram (μg/g), although others used different concentration units such as nanograms per gram (ng/g), micromoles per kilogram (μmol/kg), nanomoles per gram (nmol/g), milligrams per kilogram (mg/kg), parts per million (ppm) and parts per billion (ppb). Thus, to allow comparison across studies, metal concentrations were transformed to micrograms per gram (μg/g). A quantitative pooling of abstracted estimates was not appropriate given the great heterogeneity of the populations and analytical techniques.

3. Results

3.1. General description of the included articles

A total of 88 unique articles were included in this systematic review, summarized in Fig. 1. The main characteristics of each study are described in the Supplementary Material, Table S1. Publication date ranged from 1976 to 2017, although most reports were published in the last 10 years of this period, which shows a growing interest in the use of toenails as biomarkers of exposure (Fig. 2). Study aims, participant characteristics and selection strategy (mostly convenience sampling) and sample sizes (usually between 100 and 1000) were heterogeneous. Almost half of the studies had a cross-sectional design ($n = 47$), while the remaining had a prospective cohort or case-control design ($n = 41$). Only 10 papers provided participation rates (range from 21.4% to 95.2%). In the case-control studies ($n = 3$) participation rates were higher among cases compared to controls. A total of 31 (35.2%) studies were based on North American populations, and only one (the EURAMIC study) included populations from more than one continent (Gualler et al, 2002, 2005) (Supplementary Material, Table S1).

3.2. Analytical methodology: sample collection, nail preparation, analysis and quality control

The methods for the sampling and preparation of toenails, described in most of the articles, varied widely (Supplementary Material, Table S1). Toenail type was detailed in 43 studies; in 37, they used a pool of nails from all toes.

Regarding the amount of biological matrix considered in the analysis, the majority of the studies ($n = 64$) did not provide quantitative information on toenail mass and, in those that did so, this ranged from 0.53 to 1000 mg. In two studies, toenail weight was considered as a confounding factor (Gutierrez-Bedmar et al., 2017; MacIntosh et al., 1997); in other cases, residuals from the regression of log-transformed toxic-metal values on toenail weight were used to predict mean toenail levels (Garland et al, 1993, 1996; Platz et al., 2002; Yoshizawa et al., 2002). It has been reported that toenail weight can limit toxic metal measurement and consequently bias the measured concentrations. Platz et al. and Yoshizawa et al. reported inverse correlations between toenail weight and Cd levels (Pearson $r = -0.22$, p-value < 0.0001 (Platz et al., 2002); and Pearson $r = -0.48$, p-value < 0.001 (Yoshizawa et al., 2002)). Seven studies also declared that the LOD differed depending on toenail weight (Bai et al., 2015; Guallar et al, 2002, 2005; Gutierrez-Bedmar et al., 2017; Schreier et al., 2015; Suzuki et al., 1989; Wilhelm et al., 1991), and one study defined a minimum weight (0.1g) needed for metal determination (Mordukhovich et al., 2012).

Most of the studies ($n = 78$) reported information on pretreatment of toenails after clipping and storage. If samples had nail polish, this was generally removed; in the case of visible dirt, it was manually taken off. Cleaning methods varied from washing with detergent and rinsing with

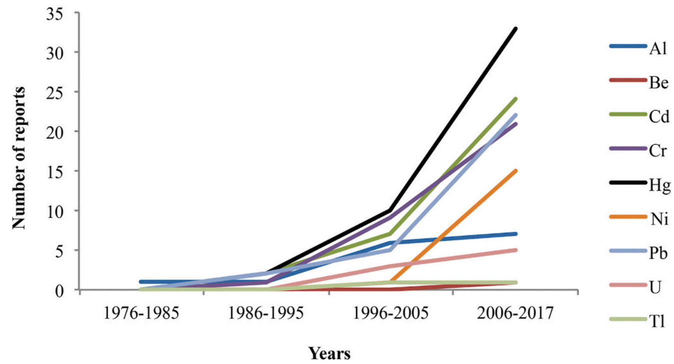


Fig. 2. Temporal evolution of number of published studies with data on toxic trace metals in toenails by metal studied (1976–2017).

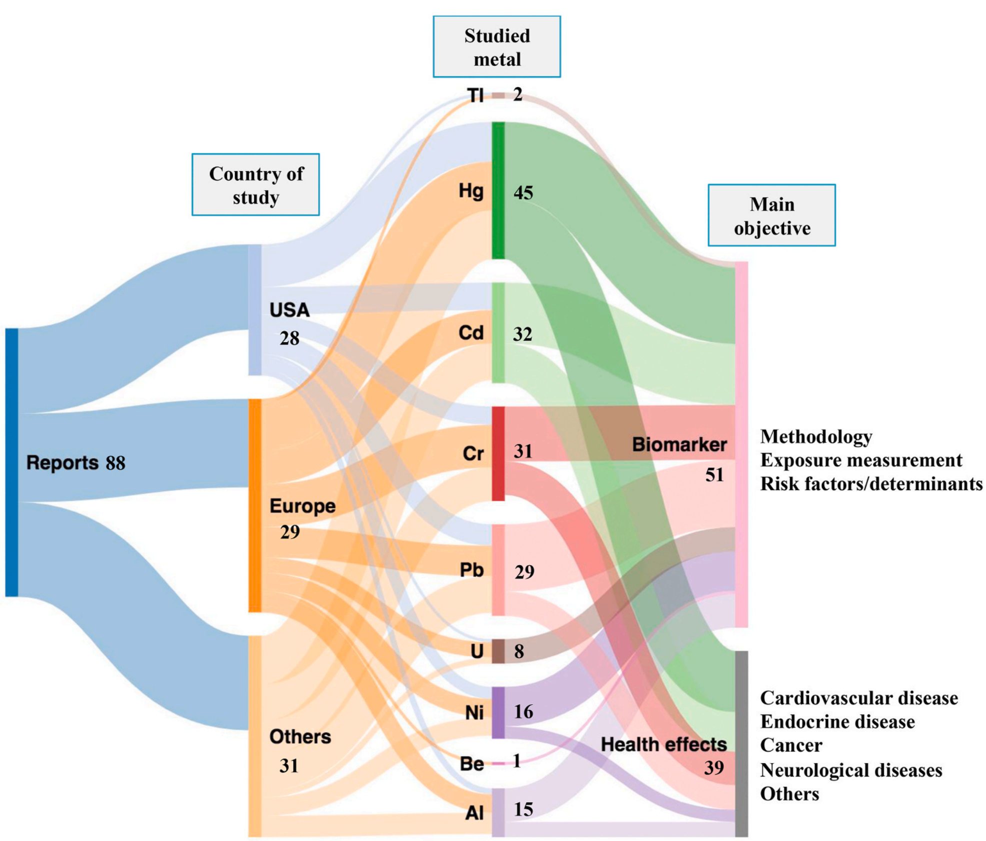
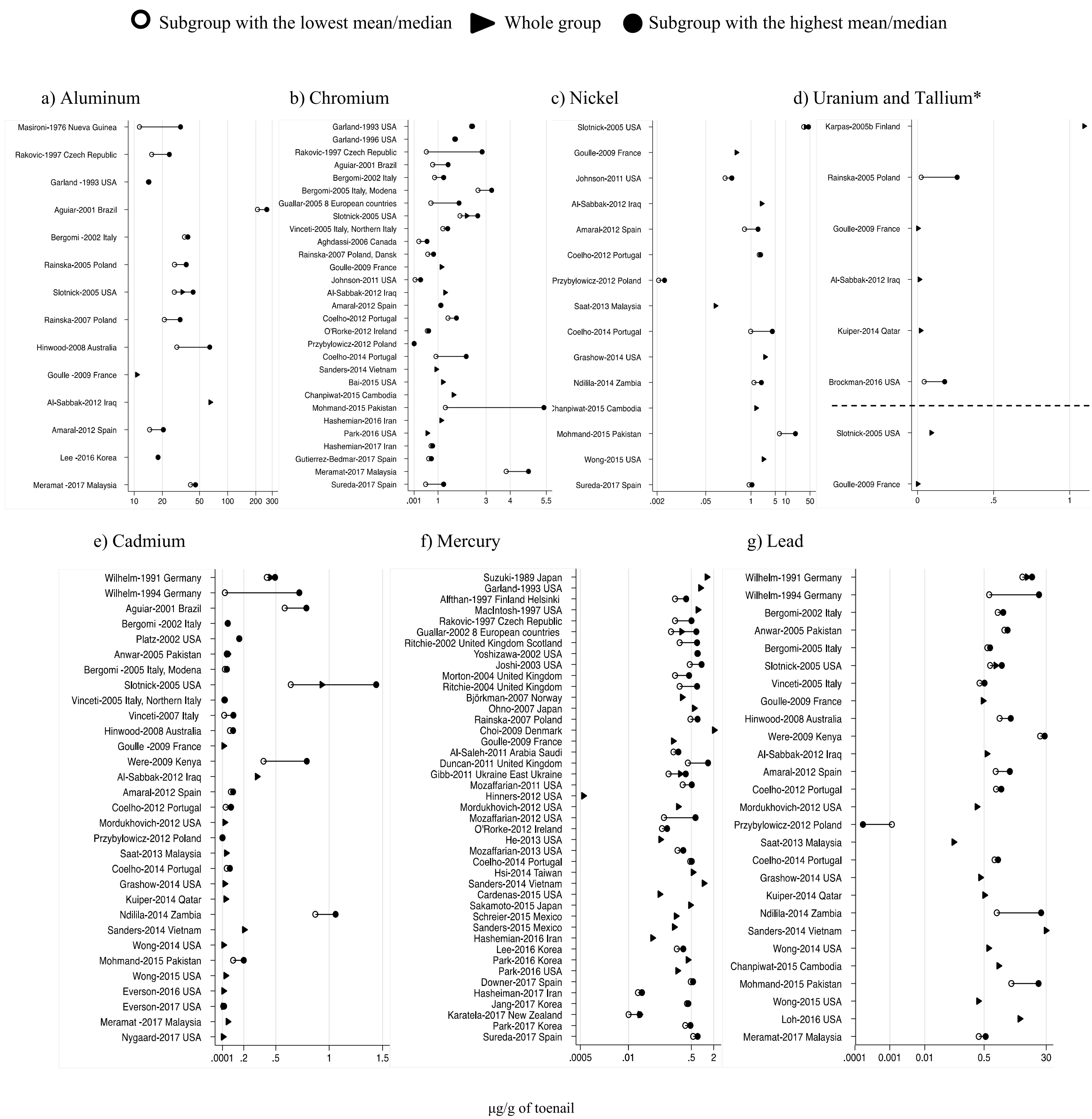


Fig. 1. Graphical summary of the systematic review results. Sankey diagram.
The total number of articles included in the review is represented in the first column. The place where studies were performed is shown in the second column. The number of articles that assessed each toxic metal is illustrated in the third column (many articles included more than one element). The main objective of articles is shown in the last column (studies may share both objectives).

deionized water to washing in other solutions (e.g. including bidistilled water, Triton solution, acetone, diethyl-ether, hexane, ethanol and methanol); the process was sometimes assisted by the use of a sonicator or an ultrasound bath. When needed, digestion of samples was done using nitric acid with or without hydrochloric acid, perchloric acid, sulphuric acid or hydrogen peroxide. Samples were then air-dried, dried in an oven or freeze-dried.

The most frequently used technique for determination of trace toxic metal levels in toenails was inductively coupled plasma mass spectrometry (including ICP-MS, multicollector-ICP-MS, ICP-optical spectrometry, ICP-quadrupole mass spectrometry, n = 39), followed by neutron activation analysis (NAA or instrumental NAA (INAA); n = 32) and atomic absorption spectrometry (AAS, CVAAS; n = 18). Other less used analytical techniques were cold vapor atomic fluorescence spectrometry (Björkman et al., 2007; Gibb et al., 2011), the Magos' method (Suzuki et al., 1989) and MERX methylmercury (MeHg) analysis method (Hsi et al., 2014). In the MELANOMA Case-Control Study and the study by Bergomi et al. (2002) the researchers employed different techniques depending on the metal studied. In addition, a study measured Hg using a different technique depending on the year when each analysis was



*The upper part of the figure represents uranium and the lower part represents thallium.
When the variability in toxic metals concentrations was high, the scale was logarithmic (aluminum, mercury, nickel and lead).

Fig. 3. Toxic metal levels [mean or median (µg/g dry weight)] in human toenails (1976–2017).

performed (Duncan et al., 2011). Another study carried out a comparative analysis between MC-ICP-MS and ICP-QMS showing a high correlation (r = 0.98) for U between both techniques (Karpas et al., 2006) (Supplementary Material, Table S1).

Sixty-four studies reported information on laboratory quality-control procedures. Some studies used certified reference materials for other matrices such as urine or hair, or performed calibrations with standard solutions, procedural blanks, duplicate samples or spike samples.

3.3. *Toxic metal concentrations in toenails across populations*

The main descriptive data for levels of each toxic metal in toenails per study included in this review are graphically represented in Fig. 3, and presented in more detail in Supplementary Material, Tables S4-S12. The toxic metal most frequently studied was Hg (n = 45) and the least studied was Be (n = 1); forty-two studies provided toenail measurements for two or more metals. All studied toxic metals except for Al reported values < 1 μg/g, and the elements with the lowest median reported were Be, Cd, Tl and U.

Table 1
Reproducibility over time of toxic metals levels in toenails and correlation with levels in other biological specimen.

Toenail metal	Author	Year	N	Whole blood	Occipital cortex	Urine	Hair	Fingernail	Cord blood	Infant toenails	Placenta	Toenails reproducibility over time[a]
Al	Garland [h]	1993	127									r = 0.39 (6-year)
Cd	Anwar	2005	160				r = 0.17					
	Grashow [h]	2014	48									
	Kuiper [i]	2014	239			NS						
	Punshon [h]	2016	750							NS	NS	
Cr	Garland [h]	1993	127									r = 0.33 (6-year)
	Chanpiwat [h]	2015	180			NS	NS					
Hg	Suzuki	1989	22				r = 0.88[b] r = 0.42[c]	r = 0.82–0.89[b]* r = 0.55–0.68[c]*				
	Garland [h]	1993	127									r = 0.56 (6-year)
	Alfthan	1997	111	r = 0.78[b]			r = 0.78[b]					
	Morton [i]	2004	335			r = 0.31		r = 0.71				
	Björkman	2007	29	r = 0.63[b]	r = 0.59[b]							
	Ohno [i]	2007	59			r = 0.79[b]	r = 0.86[b]					
	Choi	2009	42	r = 0.60			r = 0.70					
	Al-Saleh [i]	2011	162				r = 0.29					
	Hinners [i]	2012	43				r = 0.95					r = 0.92 (135 days) r = 0.87 (135 days) r = 0.75 (270 days)
	Coelho [h]	2014	122				r = 0.44	r = 0.52				
	Hsi	2014	83				r > 0.78[d]	r > 0.78[d]				
	Sakamoto [i]	2015	54				r = 0.74[e] r = 0.87[f]	r = 0.92[e] r = 0.89[f]	r = 0.79			
	Punshon [h]	2016	750							NS	NS	
Ni	Coelho [h]	2014	122					r = 0.32				
	Chanpiwat [h]	2015	180			NS	NS					
Pb	Wilhelm	1991	461				r = 0.19					
	Anwar	2005	160				r = 0.17					
	Coelho [i]	2012	102					r = 0.56				
	Coelho [h]	2014	122					r = 0.24				
	Grashow [h]	2014	48									
	Kuiper [i]	2014	239			NS						
	Sanders [h]	2014	20	r = 0.65								
	Chanpiwat [i]	2015	180				r = 0.28					
	Loh [h]	2016	60			NS						
	Punshon [h]	2016	750							NS	+	
U	Karpas	2005a	45				r = 0.98[g]					
	Rainska	2005	26				r = 0.53					

N, number of participants (samples) in the study; r, correlation coefficient; NS, Non-significant (p > 0.05) except in Chanpiwat (2015) (p > 0.01) or author only stated that correlation was not statistically significant; +, positive significant correlation with maternal toenails; *, samples were collected in three-point of the time.

[a] Between parenthesis is expressed the interval of time between both measurements.
[b] Total mercury.
[c] Inorganic mercury.
[d] Methylmercury.
[e] At 4th weeks of pregnancy.
[f] Parturition.
[g] U234/U238.
[h] Spearman correlation.
[i] Pearson correlation.

Only one study reported the LOQ and 22 studies specified the LOD. LODs ranged from 0.0003 μg/g (Goullé et al., 2009) to 0.20 μg/g (Nygaard et al., 2017) for Cd, from 0.0003 μg/g (Goullé et al., 2009) to 0.01 μg/g (Chanpiwat et al., 2015) for Pb, from 0.00001(Ohno et al., 2007; Sakamoto et al., 2015) to 0.11 μg/g (Guallar et al., 2002) for Hg, from 0.01 (Goullé et al., 2009) to 0.02 μg/g (Chanpiwat et al., 2015; Grashow et al., 2014) for Ni, from 0.01 μg/g (Bai et al., 2015) to 0.4 μg/g for Cr (Guallar et al., 2005), and from 3.2×10^{-10} μg/g (Brockman et al., 2016) to 0.00004 μg/g (Goullé et al., 2009) for U. Only one study reported the LOD for Al (0.02 μg/g), Be (0.002 μg/g) and Tl, (0.00005 μg/g) (Goullé et al., 2009). The proportion of samples under the LOD, when reported, varied by toxic metal (i.e. non-existent or low for Al and Hg). Usually, individuals with levels under LDO were assigned either a value equal to half of their LOD or the lowest observed value in the batch.

3.4. Toenail as a biomarker of long-term integrated exposure

To assess the suitability of toenails as biomarkers of exposure, it is necessary to study the time-window of exposure reflected by toenails and the stability of repeated measurements over time.

The time-window of exposure was evaluated only for toenail Cd, Ni and Pb, and in a single study performed in occupationally exposed workers (welders); their data indicated that levels of these metals reflected an exposure which took place 7–12 months before clipping collection and that levels were associated with the number of welding hours (Grashow et al., 2014).

To use this biomarker to explore long-term exposure it is also very valuable to know if point estimates of metals in toenail clippings (i.e. samples taken only at recruitment, which is the usual situation in large epidemiological studies) may be considered a good proxy for continuous exposure; that is to say, if a single measurement of toxic metals has a good correlation with subsequent determinations in the same individual. Thus, three studies (Alfthan, 1997; Garland et al., 1993; Hinners et al., 2012) analyzed the reproducibility of toenail metal concentrations over time (Table 1). Information on Hg-concentration reproducibility was reported in three publications, which consistently showed moderate-to-high reproducibility. Their time-frame was different; one author found an intra-individual variation for total Hg of 17% after a four week period (Alfthan, 1997); comparing visits, another study reported Pearson correlation coefficients of 0.92 for 1 vs. 2, 0.87 for 2 vs. 3, and 0.75 for 1 vs. 3, across three clinical visits separated an average of 135 (±18) days apart (Hinners et al., 2012); and a final study obtained a Spearman correlation coefficient of 0.56 in a subgroup of 127 participants the Nurse Health Study I (United States), which provided 2 samples of toenails collected 6 years apart (Garland et al., 1993); this last study also reported intra-individual correlation coefficients for Al and Cr of 0.39 and 0.33, respectively.

3.5. Correlations between toxic metals in toenails and other biological matrices

To better understand the information provided by toenail metal levels as a biomarker of exposure to these agents, it is necessary to contrast them with the levels measured in other commonly used matrices such as blood and urine. A total of twenty-three studies, with different numbers of participants (n = 20 to 750), assessed the correlation between toenail metal levels and the same metal in other matrices, with inconsistent results (Table 1). In general, we observed a strong to moderate correlation between both Hg and U levels in toenails and in hair or fingernails, and weak for Pb and hair, but information was scarce for other toxic metals studied.

Most studies (14 out of 23) evaluated the correlation between *toenails and hair,* probably due to their similar keratin-based compositions. Positive correlations across both matrices were strong for isotopic ratio U234/U238 (r = 0.98) (Karpas et al., 2005a) and Hg (r > 0.70) (Alfthan, 1997; Hinners et al., 2012; Hsi et al., 2014; Ohno et al., 2007; Sakamoto et al., 2015; Suzuki et al., 1989); however, some studies had small sample sizes (<60). Several studies focused on Hg specified the chemical species of the metal: two articles measured total Hg (Alfthan, 1997; Ohno et al., 2007), one MeHg (Hsi et al., 2014) and another total and inorganic Hg in toenails (Suzuki et al., 1989). For other metals, the correlation was moderate for U (r = 0.53) (Raińska et al., 2005) and weak for Cd (Anwar, 2005) and Pb (r < 0.30) (Anwar, 2005; Chanpiwat et al., 2015; Wilhelm et al., 1991).

For *fingernails*, the majority of the studies that evaluated the correlation between Hg in toenails and fingernails showed strong correlations (r > 0.70) (Hsi et al., 2014; Morton et al., 2004; Sakamoto et al., 2015; Suzuki et al., 1989). A study reported a strong correlation between toenail Hg levels and this metal in *hair or fingernails* in pregnant women at two different moments: at 4 weeks of pregnancy, with a Pearson correlation of 0.74 for toenail and *hair*, and 0.92 for toenail and *fingernail*; and at delivery, with r = 0.87 for toenail and *hair* and r = 0.89 for toenail and *fingernail* (Sakamoto et al., 2015).

Regarding the chemical forms of toxic metals, Suzuki et al. speciated Hg in hair, fingernails and toenails and reported stronger correlations with total Hg compared to inorganic Hg (Suzuki et al., 1989).

For *blood*, only one study reported data for Pb, with a moderate correlation (Spearman coefficient of 0.65) with toenails (Sanders et al., 2014). For Hg, one study found a strong correlation when assessing total Hg (r = 0.78) (Alfthan, 1997) and two others reported a moderate correlation, one of them without specifying the chemical form (Björkman et al., 2007; Choi et al., 2009).

The correlation between metals in *toenails* and *urine* was non-significant for Cd (Kuiper et al., 2014), Pb (Kuiper et al., 2014; Loh et al., 2016), Cr and Ni (Chanpiwat et al., 2015). Finally, regarding other matrices, maternal toenail Cd and Hg levels were neither correlated with placenta levels nor with infant toenail Cd levels, while for Pb there was a positive correlation between maternal toenail and placenta levels (Punshon et al., 2016).

3.6. Correlations of toxic metals with other toenail metals

The correlation between levels of each toxic metal and the levels of other essential or toxic metals, also measured in toenails, was assessed in 16 papers (Supplementary material, Table S2) and generally ranged from moderate (0.30–0.70) to strong (>0.70). The strongest correlations among toxic metals were found for Tl and Cd (Pearson correlation of 0.94), Tl and Cr (Pearson correlation of 0.81) (Slotnick et al., 2005), and for Al and Cr (Pearson correlation of 0.80) (Hashemian et al., 2016). Other toxic metals like Al and Cr have been strongly correlated with scandium (Sc) (Pearson correlation of 0.99 and 0.82 respectively) (Hashemian et al., 2016). Regarding essential metals, the strongest correlations were found for Al and Cr with iron (Fe) (Pearson correlation r = 0.98 and r = 0.84 respectively) (Hashemian et al., 2016). It is interesting to note that negative correlations were also reported, which were low for Cd and selenium (Se) (<-0.30) (Everson et al., 2017), and moderate for Hg with Al and Sc (Hashemian et al., 2016).

3.7. Determinants of toxic metals in toenails

The identification of the factors related to toxic metal levels measured in this matrix is essential in order to understand the information they provide. In spite of the high variability among studies in design, variables and populations studied, we have summarized, in Table 2, the possible relations between metal concentrations and the different factors reported in each paper, identified by the first author and publication date of each one. In general, none of the personal characteristics or exposures studied appeared to have a great influence on toenail toxic metal, perhaps with the exception of the association between toenail Hg and fish intake, which seemed to be quite consistent. Regarding environmental exposures, toenail levels for several metals

Table 2
Associations between toenail toxic trace metals and personal characteristics, diet and other exposures reported in the included studies (Author year).

	Personal characteristics			Lifestyle and social factors				Other environmental exposures			
Metal	Age	Sex	BMI	Physical Activity	Diet	Tobacco use	Socio-economic/ Educational level	Water	Residential exposure	Dust/air	Occupational exp →Time since exp.
Al	+ Bergomi (2002) – Masironi (1976) Rakovic (1997) Slotnick (2005)	♀ Rakovic (1997) Slotnick (2005) ♂ Hinwood (2008) Ø Masironi (1976) Lee et al. (2016)				+ Hinwood (2008)		+ Hinwood (2008)	Ø Rainska et al. (2007)		+ Rakovic (1997) Hinwood (2008) Menezes (2004) Ø Rainska (2005)
Cd	- Slotnick (2005) Abdulrahman (2012) Kuiper (2014) Ø Anwar (2005) Everson (2017)	♀ Bergomi (2002) Everson (2017) ♂ Abdulrahman (2012) Przybylowicz (2012) Ø Anwar (2005)			***Alcohol*** + Mordukhovich (2012) (♂) ***Fish*** Ø Anwar (2005)	Ø Anwar (2005) Mordukhovich (2012) Everson (2017)	– Mordukhovich (2012) (♂) Ø Anwar (2005) Everson (2017)		+ Wilhelm (1991) Were (2009) Mohmand (2015) Ø Anwar (2005) Coelho (2012), 2014 Sanders (2014)	+ Ndilila (2014) Wong (2014) Mohmand (2015)	+ Grashow et al. (2014) → 10–12m – Hinwood (2008) Kuiper (2014) Ø Coelho (2012), 2014
Cr	+ Abdulrahman (2012) – Garland (1996) Rakovic (1997) Guallar (2005) Slotnick (2005) Bai (2015) Gutierrez-Bedmar (2017) Ø Johnson (2011)	♀ Rakovic (1997) Coelho (2014) Bai (2015) Gutierrez-Bedmar (2017) ♂ Abdulrahman (2012) Przybylowicz (2012) Ø Johnson (2011) Sureda (2017)		+ Bai (2015) Sureda (2017) (♀)	***Alcohol*** + Garland (1996)		+ Bai (2015)	Ø Chanpiwat (2015)	+ Johnson (2011) ♀ Coelho (2014) Sanders (2014) Chanpiwat (2015) Mohmand (2015) Ø Rainska et al. (2007) Coelho (2012)	+ Mohnmand (2015)	+ Menezes et al. (2004) Ø Coelho (2012) - Coelho (2014)
Hg	+ Alfthan (1997) Park and Seo (2016) – Rakovic (1997) Park and Seo (2017)	♀ Rakovic (1997) ♂ Alfthan (1997) Duncan (2011) Ø Suzuki (1989) Sureda (2017)	+ Park and Seo (2016) – Mozaffarian (2011), 2012	+ Mozaffarian (2011), 2012 – Sureda (2017) (♀) Ø Park and Seo (2016)	***Alcohol*** + Mozaffarian (2011), 2012 Park and Seo (2016) ***Fish*** + Alfthan (1997)	+ Park and Seo (2016) Ø Suzuki (1989) Mozaffarian (2011)	+ Park and Seo (2016), 2017 – Hsi (2014)		+ Alfthan (1997) Gibb (2011) Sanders (2014) Ø Coelho (2014) Rainska 2007		+ Yoshizawa (2002) Joshi (2003) Duncan (2011) Ø Ritchie et al. (2002, 2004) Menezes (2004)

(*continued on next page*)

Table 2 (*continued*)

	Personal characteristics			Lifestyle and social factors				Other environmental exposures			
Metal	Age	Sex	BMI	Physical Activity	Diet	Tobacco use	Socio-economic/ Educational level	Water	Residential exposure	Dust/air	Occupational exp →Time since exp.
	Ø Mozaffarian (2011)				Suzuki (1989) Garland (1993) Yoshizawa (2002) Ohno (2007) Mozaffarian (2011), 2012 Hsi (2014) Joshi (2003) [a] MacIntosh (1997) [b] Mordukhovich (2012) (♂)[c] Park and Seo (2016), 2017 [d] ***Other foods*** + Mozaffarian (2012) Fruits, vegetables Processed meat and unprocessed red meat – MacIntosh (1997) *Skim milk, mashed potatoes, tomato sauce, pizza, pancakes* ***Dietary lipids*** + Mozaffarian (2012) (Omega 3) Mozaffarian (2011) [e] – Mozaffarian (2011) [f] ***Dietary protein*** + Mozaffarian (2011)						Coelho (2014)
Ni	+ Abdulrahman (2012) Ø Johnson (2011)	♀ Coelho (2014) Ø Johnson (2011) Przybylowicz (2012)		Ø Sureda (2017)				– Chanpiwat (2015) Ø Ndilila (2014)	+ Slotnick (2005) Johnson (2011) ♀ Coelho (2014) Chanpiwat (2015) Mohmand (2015) Ø Coelho (2012), 2014 Ndilila (2014)	Ø Ndilila (2014) Wong (2014)	Ø Coelho (2012), 2014 + Grashow 2014→ 7–9m
Pb	+ Abdulrahman (2012) – Anwar (2005) Slotnick (2005)	♀ Bergomi (2002) Przybylowicz (2012) ♂			***Alcohol*** + Mordukhovich (2012) ***Fish***	+ Anwar (2005)	– Mordukhovich (2012) Ø Anwar (2005)	+ Wilhelm (1991) *Hardness* Ø Chanpiwat (2015)	+ Wilhelm (1991) Were (2009)	+ Ndilila (2014) Mohnmand (2015) Ø	+ Wilhelm (1991) Hinwood (2008)

(*continued on next page*)

Table 2 (*continued*)

	Personal characteristics			Lifestyle and social factors				Other environmental exposures			
Metal	Age	Sex	BMI	Physical Activity	Diet	Tobacco use	Socio-economic/ Educational level	Water	Residential exposure	Dust/air	Occupational exp →Time since exp.
		Abdulrahman (2012) Ø Anwar (2005) Sanders (2014)			+ Anwar (2005)				Ndilila (2014) Chanpiwat (2015) Mohmand (2015) Ø Anwar (2005) Were (2009) Coelho (2012), 2014 Sanders (2014)	Wong (2014)	Grashow (2014) → 10–12m – Saat et al. (2013) Ø Coelho (2012), 2014
U	– Karpas (2005b)	Ø Karpas (2005b)						+ Karpas (2005a) Karpas (2005b)			+ Raińska et al. (2005) – Kuiper (2014) Ø Brockamn (2016)

+, Positive; Ø, No association; -, Negative; BMI, Body Mass Index; exp, exposure; ♀, women; ♂, men.
[a] Tuna, saltwater fish.
[b] Dark fish, tuna, other fish.
[c] Dark-meat fish, shellfish, tuna.
[d] Whale, shark meat.
[e] Eicosapentaenoic and docosahexaenoic acid, polyunsaturated fat.
[f] Saturated fat, monounsaturated fat, trans fat, dietary cholesterol.

showed variability associated with the place of residence or with occupational exposure.

3.7.1. Sociodemographic and anthropometric determinants

3.7.1.1. Age. Most studies found an inverse association between aging and toenail metal concentrations for a majority of the metals, such as Al (Masironi et al., 1976; Rakovic et al., 1997; Slotnick et al., 2005), Cd (Abdulrahman et al., 2012; Kuiper et al., 2014; Slotnick et al., 2005), Cr (Bai et al., 2015; Garland et al., 1996; Guallar et al., 2005; Gutierrez-Bedmar et al., 2017; Rakovic et al., 1997; Slotnick et al., 2005), Pb (Anwar 2005; Slotnick et al., 2005), or U (Karpas et al., 2005b). For Hg, results were inconsistent, with two studies reporting an inverse association (Park and Seo, 2017; Rakovic et al., 1997), while others showed a positive relationship (Alfthan, 1997; Park and Seo, 2016) and one final study, no association (Mozaffarian et al., 2011).

3.7.1.2. Sex. For most metals there was not a clear pattern of association with sex; this was the case even for Cr, in which most studies reported higher concentrations in women (Bai et al., 2015; Coelho et al., 2014; Gutierrez-Bedmar et al., 2017; Rakovic et al., 1997), other authors reported similar (Johnson et al., 2011; Sureda et al., 2017), or even lower levels in women than in men (Abdulrahman et al., 2012; Przybylowicz et al., 2012).

3.7.1.3. Socioeconomic status and educational level. Socioeconomic status-related variables were not associated with Cd concentrations (Anwar, 2005; Everson et al., 2017), but were positively related with Cr (Bai et al., 2015) and Hg levels (Park and Seo, 2016, 2017), and showed inconsistent results for Pb (Anwar, 2005; Mordukhovich et al., 2012).

3.7.1.4. Body Mass Index (BMI). The association with BMI has been studied only for toenail Hg with inconsistent results: two studies described an inverse association (Mozaffarian et al, 2011, 2012) while one study reported a positive relationship (Park and Seo, 2016).

3.7.2. Lifestyle determinants

3.7.2.1. Diet. Several studies supported a positive association between Hg in toenails and fish intake (Alfthan, 1997; Garland et al., 1993; Hsi et al., 2014; Mozaffarian et al, 2011, 2012; Ohno et al., 2007; Suzuki et al., 1989; Yoshizawa et al., 2002), particularly tuna and saltwater fish (Joshi et al., 2003); tuna, dark-meat fish and other fish (MacIntosh et al., 1997); whale or shark meats (Park et al., 2016; Park and Seo, 2017); and shellfish, dark-meat fish and tuna in men (Mordukhovich et al., 2012). The chemical form of Hg was taken into account in a small number of reports; three articles had measured total Hg (Alfthan, 1997; Ohno et al., 2007; Suzuki et al., 1989) while another measured MeHg in toenails (Hsi et al., 2014). Hg levels were also positively associated with dietary intake of long-chain n-3 polyunsaturated fatty acids (Mozaffarian et al., 2012), and in particular with eicosapentaenoic and docosahexaenoic acids (Mozaffarian et al., 2011). Also, toenail Hg concentrations were positively correlated with higher intakes of protein and polyunsaturated fat (Mozaffarian et al., 2011), fruits and vegetables (Mozaffarian et al., 2012) and alcohol (Mozaffarian et al, 2011, 2012; Park and Seo, 2016); and inversely related to intakes of saturated fat, monounsaturated fat, trans fat or dietary cholesterol (Mozaffarian et al., 2011); as well as skimmed milk, mashed potatoes, tomato sauce, pizza, and pancakes (MacIntosh et al., 1997); and finally processed meat and unprocessed red meat (Mozaffarian et al., 2012). In regard to other metals, a cross-sectional study performed in 160 healthy residents in Lahore city and its suburban areas in Pakistan found that toenail Pb, but not Cd, was positively associated with fish-consumption frequency (Anwar, 2005). Higher toenail Cr levels (Garland et al., 1996), and toenail Cd, in this latter case just in men, were associated with higher alcohol consumption (Mordukhovich et al., 2012).

3.7.2.2. Physical activity. Increased physical activity was associated with higher toenail Cr in the general population (Bai et al., 2015), and in active women (Sureda et al., 2017). For toenail Hg, physical activity did not show a consistent association: in the Nurse Health Study/Health Professionals Follow-up Study levels were higher among those reporting more METS/week (Mozaffarian et al, 2011, 2012), while other authors have found higher Hg in toenails in inactive women (Sureda et al., 2017) or no difference by level of exercise (Park and Seo, 2016). No association was found with Ni levels (Sureda et al., 2017).

3.7.2.3. Smoking status. Data on the association between smoking and toxic metals in toenails are scarce. Tobacco consumption was associated with higher Hg concentrations in one study (Park and Seo, 2016), but not in another two (Mozaffarian et al., 2011; Suzuki et al., 1989), while Al (Hinwood et al., 2008) and Pb levels (Anwar, 2005) seemed to be positively associated with smoking. Surprisingly, the three studies that evaluated active smoking and toenail Cd levels did not find any evidence of association (Anwar, 2005; Everson et al., 2017; Mordukhovich et al., 2012), although their numbers of smokers were low.

3.7.3. Environmental determinants

The included studies occasionally evaluated specific exposure sources or selected environments, namely: i) **Drinking water**, which showed inconsistent results for Ni (Chanpiwat et al., 2015; Ndilila et al., 2014) and Pb (Chanpiwat et al., 2015; Wilhelm et al., 1991)), higher toenail Al levels in non-bore water drinkers compared to bore-water users (Hinwood et al., 2008), a positive association for U (Karpas et al. 2005a, 2005b), and a null association with Cr (Chanpiwat et al., 2015); ii) **Residential exposure,** which, in many cases, explored geographical variation in toenail levels by place of residence, with the three metals with most reports being Cr (Chanpiwat et al., 2015; Coelho et al., 2014; Johnson et al., 2011; Mohmand et al., 2015; Sanders et al., 2014), Ni (Chanpiwat et al., 2015; Coelho et al., 2014; Johnson et al., 2011; Mohmand et al., 2015; Slotnick et al., 2005) and Pb (Chanpiwat et al., 2015; Mohmand et al., 2015; Ndilila et al., 2014; Were et al., 2009; Wilhelm et al., 1991); iii) Metal content in **dust and air,** which was positively associated with levels in toenails for Cd (Mohmand et al., 2015; Ndilila et al., 2014; Wong et al., 2014), Pb (Mohmand et al., 2015; Ndilila et al., 2014) and Cr (Mohmand et al., 2015); and iv) **Occupational exposures,** which were associated with increased toenail Al and Cr levels in galvanizers (Menezes et al., 2004); with Cd, Ni and Pb in welders (Grashow et al., 2014); and with Hg in dentistry (Duncan et al., 2011; Joshi et al., 2003; Yoshizawa et al., 2002); in contrast, toenail Cd, Cr, Ni, Pb (Coelho et al., 2012, 2014) and Hg levels (Coelho et al., 2014) were not higher among miners , nor toenail Al levels in workers from a fertilizer plant (Raińska et al., 2005). **Other specific determinants for Hg** included dental amalgam fillings-use and recent vaccination (<1 year) that were positively and negatively associated respectively with Hg levels in toenails (Al-Saleh and Al-Sedairi, 2011).

3.8. Toxic metals in toenails and health effects

A total of 39 studies evaluated the association between metal levels in toenails and health outcomes; among them, the most commonly studied metals were Hg (n = 21), Cd (n = 14) and Cr (n = 13), while cardiovascular & metabolic (n = 19), followed by cancer (n = 8) and neurologic endpoints (n = 6) were the main health outcomes (Supplementary Material, Table S3).

4. Discussion

In this report we summarize the available evidence to evaluate the possible use of toenail measurements as biomarkers of exposure for Al, Hg, Be, Ni, Pb, Cd, Cr, Tl, and U. We provide a structured breakdown of the studies published from 1976 to 2017 that report quantitative levels of these toxic metals in toenails, their correlation with other matrices, exposure time-windows, and the factors that may be associated with them. Our data suggest that, for Hg, levels in toenails might be a useful option to evaluate exposure; however, for most of the other toxic metals, information is still scarce.

Interest in toenails has increased over time, with Hg being the most frequently studied metal, probably due to its ubiquity in the environment, persistency, bioaccumulation and toxicity. In fact, Hg ranked in third position of the most toxic elements and has high bioaccumulation potential (US Department of Health and Human Services, Public Health Service., 1999).

Toenails are a potential useful and non-invasive tool to identify highly and chronically exposed individuals in epidemiological studies. This is clearer for toxic than for essential metals, as in this latter group, the association between exposure and toenail essential metal concentrations could be hampered by the tight regulation of their homeostasis in the organism (Gutiérrez-González et al., 2019).

Another point of interest pertains to the characteristics of the studies reported in this review. Population profiles, selection strategy, samples sizes and participation rate were heterogeneous. If toenail metal levels are intended to be used for biomonitoring, participation rates are key for guaranteeing the representativeness of the target populations. Low participation can result in selection bias, which would hamper the external validity of the results.

Among the different biospecimens, toenails have obvious logistic advantages; in addition, despite the need for pretreatment and cleaning prior to analysis, toenails are supposed to be less exposed to external contamination than fingernails or hair (Sukumar, 2006), and do not suffer procedures such as dyeing, bleaching or permanent waving, common in hair (Cuypers and Flanagan, 2018). Nevertheless, the real appeal of toenails as candidates to represent past or long-term exposure for epidemiologists lies in two facts: trace elements levels are assumed to remain stable once incorporated in the keratin structure of nails, independently of metabolic activities (Sukumar, 2006), and toenails have a slow growth rate (Adair et al., 2006). For some of the metals studied in this review (Pb, Cd and Ni), it has been reported that toenails may reflect exposures that occurred 7–12 months before (Grashow et al., 2014). However, 12 months may not be enough to estimate exposure in the study of most chronic diseases, so it is very important to establish if a single determination of toxic metal levels in toenails could work as a proxy of toxic-metal levels in the same person's toenails; this may be established by studying repeated measurements over time. Up to 2017, there were only two studies which had evaluated this issue. Thus, at different times in the same individuals these studies found moderate (Al, Cr, Hg) (Garland et al., 1993) to strong (Hg) correlations (Hinners et al., 2012) between measurements. Notwithstanding, changes over time of toxic metal levels in toenails do not necessarily mean that the biomarker is not adequate to measure exposure. These variations may be due to changes over time in the sources of exposure (e.g. dietary intake, environmental exposure), as well as to changes in metabolism, excretion, interaction with other trace elements or storage mechanisms.

Another approach to better understand the information provided by toenail levels is to study their relationship with concentrations measured in other commonly used biomarkers of exposure. Thus, most studies found a strong to moderate correlation for Hg or U levels between toenails and hair or fingernails, probably due to their similar characteristics such as slow growth and analogous composition – which is why they are considered as longer-term exposure biomarkers. However, this was not the case for the other elements studied. For blood, in the two elements in which it was assessed – Hg and Pb – the correlation was moderate in most studies, while in urine, only Hg seemed to be associated with toenail levels, which could reflect this element's body burden. This lack of association found with other metals could be due to the different exposure time-windows explored by the matrices, to the involvement of different metabolic pathways during their transit in the body or storage mechanisms that decrease the correlation. Also, to explain the variability in the correlation between toxic metals in different matrices, studying the different chemical forms of these elements is worthwhile, since they could influence the accumulation of toxic metals in toenails. In fact, it has been reported that MeHg has a strong affinity for thiol groups, which are present in nails (Guallar et al., 2002). This could explain the results of Suzuki et al. who found stronger correlations with total mercury in comparison to inorganic mercury. Moreover, the absence of standardized protocols for toenail processing – including cleaning procedures to avoid external contamination – and the different detectability of metals among biological matrices, could also explain the absence of correlation with toenails.

However, it is difficult to get a clear picture of the data on toxic metals in toenails. Many studies were limited due to small sample sizes, and a proportion of the reports included in this review did not provide information about population characteristics (including inclusion and exclusion criteria), the type of toenail analyzed – each toenail grows at a different rate (Dykyj, 1989; Hinners et al., 2012) – or about toenail weight, which might be a relevant confounder that can also modify the detection limits (Park and Seo, 2016). Another very relevant source of variability among the studies is the heterogeneity in the laboratory methodology and techniques used for measuring toenail metals, including the processing of samples and the statistical analysis and reporting of results. In this sense, sampling, preparation of toenails and washing procedures, which varied widely among the studies, are crucial for removing exogenous contaminants from toenails' surfaces – as well as nail polish which can contain Cd, Cr, Pb, Hg and Ni (Corazza et al., 2009; Grosser et al., 2011); these procedures should be homogeneous. The absence of standardized methods (Morais et al., 2012; Rauf and Hanan, 2009) calls for caution concerning the comparability of studies' metal levels. Also, there are no certified reference materials for this matrix, and a common approach to address this limitation would be useful. With respect to the analytic technique, and although toxic metal levels are usually measured with NAA, INAA or ICP-MS – which are capable of measuring trace elements with adequate precision (Adair et al., 2006; He, 2011) – we cannot rule out variability due to the type of analysis used; this is because there are no studies that compare the various methods' performance in the same samples.

If we focus on the factors that might be related to levels of the selected metals, in general none of the personal characteristics evaluated, including sex and age, seem to have a great influence, in contrast with what has been found for other biomarkers (i.e. Cd in urine). One of the main characteristics that could influence toenail toxic-metal levels is age, which could modify the rate of incorporation of these elements into that biological matrix. However, these results are not homogeneous and a minor number of studies did not report an association between age and Cd, Cr, Hg and Ni levels in toenails, which could be due to unadjusted analysis without considering other factors that could modify these levels, or to variations in the exposure over time. Regarding lifestyle-related factors, we did not identify any specific determinant of toxic metals in toenails. However, possible confounding factors may not have been considered in the analyses. This is the case with socioeconomic status in the studies that analyzed the association between toxic metals in toenails and physical activity. This point, only considered in one study, could be important since socioeconomic status has been related to physical habits in several studies (Chen et al., 2015; Lee et al., 2007). Therefore, results for the relation between physical activity and toxic metals levels in toenails should be viewed with caution.

Perhaps the most consistent association in our review is the relationship between fish intake and Hg concentrations; in contrast, studies failed to find an association between tobacco and toenail Cd, which might be due to the small number of smokers included in those studies. On the other hand, available data seem to support the possibility that toenail concentrations may be a suitable biomarker of environmental exposures, with variability according to exposures linked to the place of residence and to occupational exposure for specific metals. Thus, Al and Cr levels in toenails were associated with galvanizers, Cd, Ni and Pb with welders and Hg concentrations with dentists. Regarding occupation, Pb, Hg, Al and Cd were the elements most studied in this field. Finally, dust/air, closely related to environmental exposure, was also reported as a possible source for some toxic metals (Cd, Pb, Cr).

One of the main strengths of our review is its comprehensive approach, which allows us to provide a global perspective of the available information on levels of these toxic metals in toenail levels. However, its major limitation, as already explained, is that the great heterogeneity of the studies precluded any quantitative pooling of the results. However, our tables provide useful information for each non-essential toxic metal in toenails, and can be a useful instrument for those who may consider using this biomarker. An additional limitation is the exclusion of articles where the type of nail used could not be established (fingernail or toenail) (see Figure S1, flow diagram) even after contacting the corresponding authors.

5. Conclusions

The use of toenails as biomarkers of exposure to toxic metals has increased over time, but there is still excessive heterogeneity among the studies and analytical methods. Excluding Hg, the evidence supporting the use of toenails as biomarkers of cumulative exposure to toxic metals is insufficient. Large studies including longitudinal determinations of toxic metals, as well as clear, standardized analytical procedures, are needed to draw solid conclusions about the suitability of toenails as biomarkers of exposure to these substances.

Credit author statement

Inmaculada Salcedo-Bellido: Data curation, Formal analysis, Investigation & Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. Enrique Gutiérrez-González: Data curation, Formal analysis, Investigation & Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. Esther García-Esquinas: Data curation, Formal analysis, Funding acquisition, Writing – review & editing. Nerea Fernández de Larrea-Laz: Writing – original draft, Writing – review & editing. Ana Navas-Acien: Investigation, Methodology, Funding acquisition, Writing – review & editing. Maria Téllez-Plaza: Writing – original draft, Writing – review & editing. Roberto Pastor-Barriuso: Investigation, Methodology, Writing – review & editing. Virginia Lope: Writing – original draft, Writing – review & editing. José Luis Gómez Ariza: Investigation, Methodology, Writing – review & editing. Tamara García-Barrera: Investigation, Methodology, Writing – review & editing. Marina Pollán: Investigation, Methodology, Writing – review & editing. Jose Juan Jiménez Moleón: Data curation, Formal analysis, Validation, Visualization, Writing – review & editing. Beatriz Pérez-Gómez: Conceptualization, Data curation, Formal analysis, Funding acquisition, Validation, Visualization, Writing – review & editing.

Funding sources

This work was supported by FIS grants PI12/00150, PI17CIII/00034, PI18/00287 (Instituto de Salud Carlos III, State Secretary of R + D + I and European Union (ERDF/ESF, "Investing in your future")), P42ES010349 and P30ES009089 (National Institute of Environmental Health Sciences).

Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.111028.

The total number of articles included in the review is represented in the first column. The place where studies were performed is shown in the second column. The number of articles that assessed each toxic metal is illustrated in the third column (many articles included more than one element). The main objective of articles is shown in the last column (studies may share both objectives).

References

Abdulrahman, F.I., Akan, J.C., Chellube, Z.M., Waziri, M., Abdulrahman, F.I., Akan, J.C., Chellube, Z.M., Waziri, M., 2012. Levels of heavy metals in human hair and nail samples from Maiduguri Metropolis, Borno State, Nigeria. World Environ. 2, 81–89. https://doi.org/10.5923/j.env.20120204.05.

Adair, B.M., Hudgens, E.E., Schmitt, M.T., Calderon, R.L., Thomas, D.J., 2006. Total arsenic concentrations in toenails quantified by two techniques provide a useful biomarker of chronic arsenic exposure in drinking water. Environ. Res. 101, 213–220. https://doi.org/10.1016/j.envres.2005.08.004.

Alfthan, G.V., 1997. Toenail mercury concentration as a biomarker of methylmercury exposure. Biomark. Biochem. Indic. Expo. Response Susceptibility Chem. 2, 233–238. https://doi.org/10.1080/135475097231607.

Al-Saleh, I., Al-Sedairi, A.A., 2011. Mercury (Hg) burden in children: the impact of dental amalgam. Sci. Total Environ. 409, 3003–3015. https://doi.org/10.1016/j.scitotenv.2011.04.047.

Anwar, M., 2005. Arsenic, cadmium and lead levels in hair and toenail samples in Pakistan. Environ. Sci. Int. J. Environ. Physiol. Toxicol. 12, 71–86.

Bai, J., Xun, P., Morris, S., Jacobs, D.R., Liu, K., He, K., 2015. Chromium exposure and incidence of metabolic syndrome among American young adults over a 23-year follow-up: the CARDIA Trace Element Study. Sci. Rep. 5, 15606. https://doi.org/10.1038/srep15606.

Ballatori, N., 2002. Transport of toxic metals by molecular mimicry. Environ. Health Perspect. 110, 689–694. https://doi.org/10.1289/ehp.02110s5689.

Bergomi, M., Vinceti, M., Nacci, G., Pietrini, V., Brätter, P., Alber, D., Ferrari, A., Vescovi, L., Guidetti, D., Sola, P., Malagu, S., Aramini, C., Vivoli, G., 2002. Environmental exposure to trace elements and risk of amyotrophic lateral sclerosis: a population-based case-control study. Environ. Res. 89, 116–123. https://doi.org/10.1006/enrs.2002.4361.

Björkman, L., Lundekvam, B.F., Laegreid, T., Bertelsen, B.I., Morild, I., Lilleng, P., Lind, B., Palm, B., Vahter, M., 2007. Mercury in human brain, blood, muscle and toenails in relation to exposure: an autopsy study. Environ. Health Glob. Access Sci. Source 6, 30. https://doi.org/10.1186/1476-069X-6-30.

Brockman, J.D., Brown, J.W.N., Morrell, J.S., Robertson, J.D., 2016. Measurement of uranium isotope ratios in keratinous materials: a noninvasive bioassay for special nuclear material. Anal. Chem. 88, 8765–8771. https://doi.org/10.1021/acs.analchem.6b02144.

Campanella, B., Colombaioni, L., Benedetti, E., Di Ciaula, A., Ghezzi, L., Onor, M., D'Orazio, M., Giannecchini, R., Petrini, R., Bramanti, E., 2019. Toxicity of thallium at low doses: a review. Int. J. Environ. Res. Publ. Health 16, 4732. https://doi.org/10.3390/ijerph16234732.

Carneiro, M.F.H., Grotto, D., Batista, B.L., Rhoden, C.R., Barbosa, F., 2011. Background values for essential and toxic elements in children's nails and correlation with hair levels. Biol. Trace Elem. Res. 144, 339–350. https://doi.org/10.1007/s12011-011-9102-1.

Chanpiwat, P., Himeno, S., Sthiannopkao, S., 2015. Arsenic and other metals' presence in biomarkers of cambodians in arsenic contaminated areas. Int. J. Environ. Res. Publ. Health 12, 14285–14300. https://doi.org/10.3390/ijerph121114285.

Chen, M., Wu, Y., Narimatsu, H., Li, X., Wang, C., Luo, J., Zhao, G., Chen, Z., Xu, W., 2015. Socioeconomic status and physical activity in Chinese adults: a report from a community-based survey in Jiaxing, China. PloS One 10, e0132918. https://doi.org/10.1371/journal.pone.0132918.

Choi, A.L., Weihe, P., Budtz-Jørgensen, E., Jørgensen, P.J., Salonen, J.T., Tuomainen, T.-P., Murata, K., Nielsen, H.P., Petersen, M.S., Askham, J., Grandjean, P., 2009. Methylmercury exposure and adverse cardiovascular effects in Faroese whaling men. Environ. Health Perspect. 117, 367–372. https://doi.org/10.1289/ehp.11608.

Coelho, P., Costa, S., Costa, C., Silva, S., Walter, A., Ranville, J., Pastorinho, M.R., Harrington, C., Taylor, A., Dall'Armi, V., Zoffoli, R., Candeias, C., Ferreira da Silva, E., Bonassi, S., Laffon, B., Teixeira, J.P., 2014. Biomonitoring of several toxic metal(loid)s in different biological matrices from environmentally and occupationally exposed populations from Panasqueira mine area. Portugal. Environ. Geochem. Health 36, 255–269. https://doi.org/10.1007/s10653-013-9562-7.

Coelho, P., Costa, S., Silva, S., Walter, A., Ranville, J., Sousa, A.C.A., Costa, C., Coelho, M., García-Lestón, J., Pastorinho, M.R., Laffon, B., Pásaro, E., Harrington, C., Taylor, A., Teixeira, J.P., 2012. Metal(loid) levels in biological matrices from human populations exposed to mining contamination–Panasqueira Mine (Portugal). J. Toxicol. Environ. Health 75, 893–908. https://doi.org/10.1080/15287394.2012.690705.

Corazza, M., Baldo, F., Pagnoni, A., Miscioscia, R., Virgili, A., 2009. Measurement of nickel, cobalt and chromium in toy make-up by atomic absorption spectroscopy. Acta Derm. Venereol. 89, 130–133. https://doi.org/10.2340/00015555-0595.

Cuypers, E., Flanagan, R.J., 2018. The interpretation of hair analysis for drugs and drug metabolites. Clin. Toxicol. Phila. Pa 56, 90–100. https://doi.org/10.1080/15563650.2017.1379603.
Dórea, J.G., 2020. Neurotoxic effects of combined exposures to aluminum and mercury in early life (infancy). Environ. Res. 188, 109734. https://doi.org/10.1016/j.envres.2020.109734.
Duncan, A., O'Reilly, D.S., McDonald, E.B., Watkins, T.R., Taylor, M., 2011. Thirty-five year review of a mercury monitoring service for Scottish dental practices. Br. Dent. J. 210, E2. https://doi.org/10.1038/sj.bdj.2011.49.
Dykyj, D., 1989. Anatomy of the nail. Clin. Podiatr. Med. Surg. 6, 215–228.
Elder, A., Nordberg, G.F., Kleinman, M., 2015. Routes of exposure, dose, and toxicokinetics of metals. In: Nordberg, G.F., Fowler, B.A., Nordberg, M. (Eds.), Handbook on the Toxicology of Metals, fourth ed. Academic Press, San Diego, pp. 45–74.
Everson, T.M., Kappil, M., Hao, K., Jackson, B.P., Punshon, T., Karagas, M.R., Chen, J., Marsit, C.J., 2017. Maternal exposure to selenium and cadmium, fetal growth, and placental expression of steroidogenic and apoptotic genes. Environ. Res. 158, 233–244. https://doi.org/10.1016/j.envres.2017.06.016.
Garland, M., Morris, J.S., Colditz, G.A., Stampfer, M.J., Spate, V.L., Baskett, C.K., Rosner, B., Speizer, F.E., Willett, W.C., Hunter, D.J., 1996. Toenail trace element levels and breast cancer: a prospective study. Am. J. Epidemiol. 144, 653–660. https://doi.org/10.1093/oxfordjournals.aje.a008977.
Garland, M., Morris, J.S., Rosner, B.A., Stampfer, M.J., Spate, V.L., Baskett, C.J., Willett, W.C., Hunter, D.J., 1993. Toenail trace element levels as biomarkers: reproducibility over a 6-year period. Cancer Epidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol. 2, 493–497.
Gibb, H., Haver, C., Kozlov, K., Centeno, J.A., Jurgenson, V., Kolker, A., Conko, K.M., Landa, E.R., Xu, H., 2011. Biomarkers of mercury exposure in two eastern Ukraine cities. J. Occup. Environ. Hyg. 8, 187–193. https://doi.org/10.1080/15459624.2011.556984.
Goullé, J.P., Saussereau, E., Mahieu, L., Bouige, D., Groenwont, S., Guerbet, M., Lacroix, C., 2009. Application of inductively coupled plasma mass spectrometry multielement analysis in fingernail and toenail as a biomarker of metal exposure. J. Anal. Toxicol. 33, 92–98. https://doi.org/10.1093/jat/33.2.92.
Grashow, R., Zhang, J., Fang, S.C., Weisskopf, M.G., Christiani, D.C., Cavallari, J.M., 2014. Toenail metal concentration as a biomarker of occupational welding fume exposure. J. Occup. Environ. Hyg. 11, 397–405. https://doi.org/10.1080/15459624.2013.875182.
Grosser, Z., Davidowski, L., Thompson, L., 2011. The determination of metals in cosmetics. PerkinElmer Appl Note 1, 1–6.
Guallar, E., Jiménez, F.J., van 't Veer, P., Bode, P., Riemersma, R.A., Gómez-Aracena, J., Kark, J.D., Arab, L., Kok, F.J., Martín-Moreno, J.M., EURAMIC-Heavy Metals and Myocardial Infraction Study Group, 2005. Low toenail chromium concentration and increased risk of nonfatal myocardial infarction. Am. J. Epidemiol. 162, 157–164. https://doi.org/10.1093/aje/kwi180.
Guallar, E., Sanz-Gallardo, M.I., van't Veer, P., Bode, P., Aro, A., Gómez-Aracena, J., Kark, J.D., Riemersma, R.A., Martín-Moreno, J.M., Kok, F.J., Heavy Metals and Myocardial Infarction Study Group, 2002. Mercury, fish oils, and the risk of myocardial infarction. N. Engl. J. Med. 347, 1747–1754. https://doi.org/10.1056/NEJMoa020157.
Gutierrez-Bedmar, M., Martínez-González, M., Muñoz-Bravo, C., Ruiz-Canela, M., Mariscal, A., Salas-Salvadó, J., Estruch, R., Corella, D., Borau, F., Fito, M., Lapetra, J., Serra-Majem, L., Pinto, X., Alonso-Gómez, Á., Portolés, O., Fiol, M., Bulló, M., Castañer, O., Ros, E., Gómez-Gracia, E., 2017. Chromium exposure and risk of cardiovascular disease in high cardiovascular risk subjects – nested case-control study in the prevention with mediterranean diet (PREDIMED) study. Circ. J. 81, 1183–1190. https://doi.org/10.1253/circj.CJ-17-0032.
Gutiérrez-González, E., García-Esquinas, E., de Larrea-Baz, N.F., Salcedo-Bellido, I., Navas-Acien, A., Lope, V., Gómez-Ariza, J.L., Pastor, R., Pollán, M., Pérez-Gómez, B., 2019. Toenails as biomarker of exposure to essential trace metals: a review. Environ. Res. 179 (Pt A), 108787. https://doi.org/10.1016/j.envres.2019.108787.
Hashemian, M., Poustchi, H., Pourshams, A., Khoshnia, M., Brockman, J.D., Hekmatdoost, A., Abnet, C.C., Malekzadeh, R., 2016. The nail as a biomonitor of trace element status in Golestan Cohort Study. Middle East J. Dig. Dis. 8, 19–23. https://doi.org/10.15171/mejdd.2016.02.
He, K., 2011. Trace elements in nails as biomarkers in clinical research. Eur. J. Clin. Invest. 41, 98–102. https://doi.org/10.1111/j.1365-2362.2010.02373.x.
Hinners, T., Tsuchiya, A., Stern, A.H., Burbacher, T.M., Faustman, E.M., Mariën, K., 2012. Chronologically matched toenail-Hg to hair-Hg ratio: temporal analysis within the Japanese community (U.S.). Environ. Health 11, 81. https://doi.org/10.1186/1476-069X-11-81.
Hinwood, A., Horwitz, P., Rogan, R., 2008. Human exposure to metals in groundwater affected by acid sulfate soil disturbance. Arch. Environ. Contam. Toxicol. 55, 538–545. https://doi.org/10.1007/s00244-007-9076-3.
Hsi, H.-C., Jiang, C.-B., Yang, T.-H., Chien, L.-C., 2014. The neurological effects of prenatal and postnatal mercury/methylmercury exposure on three-year-old children in Taiwan. Chemosphere 100, 71–76. https://doi.org/10.1016/j.chemosphere.2013.12.068.
IARC, 2012. Arsenic, Metals, Fibres, and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 100C.
Johnson, N., Shelton, B.J., Hopenhayn, C., Tucker, T.T., Unrine, J.M., Huang, B., Christian, W., Zhang, Z., Shi, X., Li, L., 2011. Concentrations of arsenic, chromium, and nickel in toenail samples from Appalachian Kentucky residents. J. Environ. Pathol. Toxicol. Oncol. Off. Organ Int. Soc. Environ. Toxicol. Cancer 30, 213–223. https://doi.org/10.1615/jenvironpatholtoxicoloncol.v30.i3.40.
Joshi, A., Douglass, C.W., Kim, H.-D., Joshipura, K.J., Park, M.C., Rimm, E.B., Carino, M. J., Garcia, R.I., Morris, J.S., Willett, W.C., 2003. The relationship between amalgam restorations and mercury levels in male dentists and nondental health professionals. J. Publ. Health Dent. 63, 52–60. https://doi.org/10.1111/j.1752-7325.2003.tb03474.x.
Karpas, Z., Lorber, A., Sela, H., Paz-Tal, O., Hagag, Y., Kurttio, P., Salonen, L., 2006. Determination of 234U/238U ratio: comparison of multi-collector ICPMS and ICP-QMS for water, hair and nails samples, and comparison with alpha-spectrometry for water samples. Radiat. Protect. Dosim. 118, 106–110. https://doi.org/10.1093/rpd/nci318.
Karpas, Z., Lorber, A., Sela, H., Paz-Tal, O., Hagag, Y., Kurttio, P., Salonen, L., 2005a. Measurement of the 234U/238U ratio by MC-ICPMS in drinking water, hair, nails, and urine as an indicator of uranium exposure source. Health Phys. 89, 315–321. https://doi.org/10.1097/01.hp.0000165450.76676.10.
Karpas, Z., Paz-Tal, O., Lorber, A., Salonen, L., Komulainen, H., Auvinen, A., Saha, H., Kurttio, P., 2005b. Urine, hair, and nails as indicators for ingestion of uranium in drinking water. Health Phys. 88, 229–242. https://doi.org/10.1097/01.hp.0000149883.69107.ab.
Kuiper, N., Rowell, C., Nriagu, J., Shomar, B., 2014. What do the trace metal contents of urine and toenail samples from Qatar's farm workers bioindicate? Environ. Res. 131, 86–94. https://doi.org/10.1016/j.envres.2014.02.011.
Lee, R.E., Cubbin, C., Winkleby, M., 2007. Contribution of neighbourhood socioeconomic status and physical activity resources to physical activity among women. J. Epidemiol. Community Health 61, 882–890. https://doi.org/10.1136/jech.2006.054098.
Lee, O., Moon, J.H., Kim, S.H., Chung, Y.S., Sun, G.M., 2016. Toenail elemental analysis of Korean young adults by instrumental neutron activation analysis. J. Radioanal. Nucl. Chem. 307, 2571–2575. https://doi.org/10.1007/s10967-015-4638-8.
Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gotzsche, P.C., Ioannidis, J.P.A., Clarke, M., Devereaux, P.J., Kleijnen, J., Moher, D., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 339, b2700. https://doi.org/10.1136/bmj.b2700.
Lin, G., Sun, Y., Long, J., Sui, X., Yang, J., Wang, Q., Wang, S., He, H., Luo, Y., Qiu, Z., Wang, Y., 2020. Involvement of the Nrf2-Keap1 signaling pathway in protection against thallium-induced oxidative stress and mitochondrial dysfunction in primary hippocampal neurons. Toxicol. Lett. 319, 66–73. https://doi.org/10.1016/j.toxlet.2019.11.008.
Loh, M.M., Sugeng, A., Lothrop, N., Klimecki, W., Cox, M., Wilkinson, S.T., Lu, Z., Beamer, P.I., 2016. Multimedia exposures to arsenic and lead for children near an inactive mine tailings and smelter site. Environ. Res. 146, 331–339. https://doi.org/10.1016/j.envres.2015.12.011.
Lukiw, W.J., Kruck, T.P.A., Percy, M.E., Pogue, A.I., Alexandrov, P.N., Walsh, W.J., Sharfman, N.M., Jaber, V.R., Zhao, Y., Li, W., Bergeron, C., Culicchia, F., Fang, Z., McLachlan, D.R.C., 2019. Aluminum in neurological disease – a 36 year multicenter study. J. Alzheimer's Dis. Park. 8 https://doi.org/10.4172/2161-0460.1000457.
MacIntosh, D.L., Williams, P.L., Hunter, D.J., Sampson, L.A., Morris, S.C., Willett, W.C., Rimm, E.B., 1997. Evaluation of a food frequency questionnaire-food composition approach for estimating dietary intake of inorganic arsenic and methylmercury. Cancer Epidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol. 6, 1043–1050.
Masironi, R., Koirtyohann, S.R., Pierce, J.O., Schamschula, R.G., 1976. Calcium content of river water, trace element concentrations in toenails, and blood pressure in village populations in New Guinea. Sci. Total Environ. 6, 41–53. https://doi.org/10.1016/0048-9697(76)90005-X.
Menezes, M., Maia, E.C.P., Albinati, C.C.B., Sabino, C.V.S., Batista, J.R., 2004. How suitable are scalp hair and toenail as biomonitors? J. Radioanal. Nucl. Chem. 259, 81–86. https://doi.org/10.1023/B:JRNC.0000015810.22775.72.
Mohmand, J., Eqani, S.A.M.A.S., Fasola, M., Alamdar, A., Mustafa, I., Ali, N., Liu, L., Peng, S., Shen, H., 2015. Human exposure to toxic metals via contaminated dust: bio-accumulation trends and their potential risk estimation. Chemosphere 132, 142–151. https://doi.org/10.1016/j.chemosphere.2015.03.004.
Morais, S., E Costa, F.G., De Lourdes Pereira, M., 2012. Heavy metals and human Health. In: Oosthuizen, J. (Ed.), Heavy Metals and Human Health, Environmental Health - Emerging Issues and Practice, first ed. InTech, Croatia, pp. 227–246.
Mordukhovich, I., Wright, R.O., Hu, H., Amarasiriwardena, C., Baccarelli, A., Litonjua, A., Sparrow, D., Vokonas, P., Schwartz, J., 2012. Associations of toenail arsenic, cadmium, mercury, manganese, and lead with blood pressure in the normative aging study. Environ. Health Perspect. 120, 98–104. https://doi.org/10.1289/ehp.1002805.
Morton, J., Mason, H.J., Ritchie, K.A., White, M., 2004. Comparison of hair, nails and urine for biological monitoring of low level inorganic mercury exposure in dental workers. Biomarkers 9, 47–55. https://doi.org/10.1080/13547500410001670312.
Mozaffarian, D., Shi, P., Morris, J.S., Grandjean, P., Siscovick, D.S., Spiegelman, D., Willett, W.C., Rimm, E.B., Curhan, G.C., Forman, J.P., 2012. Mercury exposure and risk of hypertension in US men and women in 2 prospective cohorts. Hypertension 60, 645–652. https://doi.org/10.1161/HYPERTENSIONAHA.112.196154.
Mozaffarian, D., Shi, P., Morris, J.S., Spiegelman, D., Grandjean, P., Siscovick, D.S., Willett, W.C., Rimm, E.B., 2011. Mercury exposure and risk of cardiovascular disease in two U.S. cohorts. N. Engl. J. Med. 364, 1116–1125. https://doi.org/10.1056/NEJMoa1006876.
Ndilila, W., Callan, A.C., McGregor, L.A., Kalin, R.M., Hinwood, A.L., 2014. Environmental and toenail metals concentrations in copper mining and non mining communities in Zambia. Int. J. Hyg Environ. Health 217, 62–69. https://doi.org/10.1016/j.ijheh.2013.03.011.

Nigra, A.E., Ruiz-Hernandez, A., Redon, J., Navas-Acien, A., Tellez-Plaza, M., 2016. Environmental metals and cardiovascular disease in adults: a systematic review beyond lead and cadmium. Curr. Environ. Health Rep. 3, 416–433. https://doi.org/10.1007/s40572-016-0117-9.

Nordberg, G.F., Fowler, B.A., Nordberg, M. (Eds.), 2015. Toxicology of Metals: Overview, Definitions, Concepts, and Trends, Handbook on the Toxicology of Metals, fourth ed. Academic Press, San Diego, pp. 1–12.

Nygaard, U.C., Li, Z., Palys, T., Jackson, B., Subbiah, M., Malipatlolla, M., Sampath, V., Maecker, H., Karagas, M.R., Nadeau, K.C., 2017. Cord blood T cell subpopulations and associations with maternal cadmium and arsenic exposures. PloS One 12, e0179606. https://doi.org/10.1371/journal.pone.0179606.

Ohno, T., Sakamoto, M., Kurosawa, T., Dakeishi, M., Iwata, T., Murata, K., 2007. Total mercury levels in hair, toenail, and urine among women free from occupational exposure and their relations to renal tubular function. Environ. Res. 103, 191–197. https://doi.org/10.1016/j.envres.2006.06.009.

Osorio-Rico, L., Santamaria, A., Galván-Arzate, S., 2017. Thallium toxicity: general issues, neurological symptoms, and neurotoxic mechanisms. In: Aschner, M., Costa, L.G. (Eds.), Neurotoxicity of Metals, Advances in Neurobiology. Springer, Cham, Switzerland, pp. 345–353.

Park, J.S., Xun, P., Li, J., Morris, S.J., Jacobs, D.R., Liu, K., He, K., 2016. Longitudinal association between toenail zinc levels and the incidence of diabetes among American young adults: the CARDIA Trace Element Study. Sci. Rep. 6, 23155. https://doi.org/10.1038/srep23155.

Park, K., Seo, E., 2017. Toenail mercury and dyslipidemia: interaction with selenium. J. Trace Elem. Med. Biol. 39, 43–49. https://doi.org/10.1016/j.jtemb.2016.07.005.

Park, K., Seo, E., 2016. Association between toenail mercury and metabolic syndrome is modified by selenium. Nutrients 8, 424. https://doi.org/10.3390/nu8070424.

Platz, E.A., Helzlsouer, K.J., Hoffman, S.C., Morris, J.S., Baskett, C.K., Comstock, G.W., 2002. Prediagnostic toenail cadmium and zinc and subsequent prostate cancer risk. Prostate 52, 288–296. https://doi.org/10.1002/pros.10115.

Przybylowicz, A., Chesy, P., Herman, M., Parczewski, A., Walas, S., Piekoszewski, W., 2012. Examination of distribution of trace elements in hair, fingernails and toenails as alternative biological materials. Application of chemometric methods. Cent. Eur. J. Chem. 10, 1590–1599. https://doi.org/10.2478/s11532-012-0089-z.

Punshon, T., Li, Z., Marsit, C.J., Jackson, B.P., Baker, E.R., Karagas, M.R., 2016. Placental metal concentrations in relation to maternal and infant toenails in a U.S. Cohort. Environ. Sci. Technol. 50, 1587–1594. https://doi.org/10.1021/acs.est.5b05316.

Rainska, E., Biziuk, M., Bode, P., Dlugolecki, P., Astel, K., 2007. An evaluation of endemic exposure of citizens living in near a Gdansk phosphatic fertilizer plant. Pol. J. Environ. Stud. 16, 243–250.

Raińska, E., Biziuk, M., Sarbu, C., Szczepaniak, K., Frontasyeva, M.V., Culicov, O., Bode, P., Astel, A., 2005. Assessment of phosphatic fertilizer production impact on occupational staff based on NAA of hair, nails, and inhald particles. J. Environ. Sci. Health Part A Tox. Hazard. Subst. Environ. Eng. 40, 2137–2152. https://doi.org/10.1080/10934520500234635.

Rakovic, M., Foltýnová, V., Pilecká, N., Glagolicová, A., Kucera, J., 1997. Assessment of metals and metalloids in skin derivatives of volunteers from capital city of Prague, Czech Republic. Sb. Lek. 98, 107–114.

Rauf, M.A., Hanan, A., 2009. Quality assurance considerations in chemical analysis. Qual. Assur. J. 12, 16–21. https://doi.org/10.1002/qaj.435.

Ritchie, K.A., Burke, F.J.T., Gilmour, W.H., Macdonald, E.B., Dale, I.M., Hamilton, R.M., McGowan, D.A., Binnie, V., Collington, D., Hammersley, R., 2004. Mercury vapour levels in dental practices and body mercury levels of dentists and controls. Br. Dent. J. 197, 625–632. https://doi.org/10.1038/sj.bdj.4811831 discussion 621.

Ritchie, K.A., Gilmour, W.H., Macdonald, E.B., Burke, F.J.T., McGowan, D.A., Dale, I.M., Hammersley, R., Hamilton, R.M., Binnie, V., Collington, D., 2002. Health and neuropsychological functioning of dentists exposed to mercury. Occup. Environ. Med. 59, 287–293. https://doi.org/10.1136/oem.59.5.287.

Saat, N.Z.M., Chow, S.Y., Ghazah, A.R., Lubis, S.H., 2013. Study of heavy metal levels in nails and hairs among vegetable farmers in Malaysia. Res. J. Appl. Sci. 8, 449–455. https://doi.org/10.3923/rjasci.2013.449.455.

Sakamoto, M., Chan, H.M., Domingo, J.L., Oliveira, R.B., Kawakami, S., Murata, K., 2015. Significance of fingernail and toenail mercury concentrations as biomarkers for prenatal methylmercury exposure in relation to segmental hair mercury concentrations. Environ. Res. 136, 289–294. https://doi.org/10.1016/j.envres.2014.09.034.

Sanders, A.P., Miller, S.K., Nguyen, V., Kotch, J.B., Fry, R.C., 2014. Toxic metal levels in children residing in a smelting craft village in Vietnam: a pilot biomonitoring study. BMC Publ. Health 14, 114. https://doi.org/10.1186/1471-2458-14-114.

Schreier, H.M.C., Hsu, H.-H., Amarasiriwardena, C., Coull, B.A., Schnaas, L., Téllez-Rojo, M.M., Tamayo y Ortiz, M., Wright, R.J., Wright, R.O., 2015. Mercury and psychosocial stress exposure interact to predict maternal diurnal cortisol during pregnancy. Environ. Health 14, 28. https://doi.org/10.1186/s12940-015-0016-9.

Signes-Pastor, A.J., Gutiérrez-González, E., García-Villarino, M., Rodríguez-Cabrera, F. D., López-Moreno, J.J., Varea-Jiménez, E., Pastor-Barriuso, R., Pollán, M., Navas-Acien, A., Pérez-Gómez, B., Karagas, M.R., 2020. Toenails as a biomarker of exposure to arsenic: a review. Environ. Res. 110286 https://doi.org/10.1016/j.envres.2020.110286.

Slotnick, M.J., Nriagu, J.O., Johnson, M.M., Linder, A.M., Savoie, K.L., Jamil, H.J., Hammad, A.S., 2005. Profiles of trace elements in toenails of Arab-Americans in the Detroit area, Michigan. Biol. Trace Elem. Res. 107, 113–126. https://doi.org/10.1385/BTER:107:2:113.

Solenkova, N.V., Newman, J.D., Berger, J.S., Thurston, G., Hochman, J.S., Lamas, G.A., 2014. Metal pollutants and cardiovascular disease: mechanisms and consequences of exposure. Am. Heart J. 168, 812–822. https://doi.org/10.1016/j.ahj.2014.07.007.

Sukumar, A., 2006. Human nails as a biomarker of element exposure. In: Ware, G.W., Nigg, H.N., Doerge, D.R. (Eds.), Reviews of Environmental Contamination and Toxicology. Springer, New York, pp. 141–177.

Sureda, A., Bibiloni, M.D.M., Julibert, A., Aparicio-Ugarriza, R., Palacios-Le Blé, G., Pons, A., Gonzalez-Gross, M., Tur, J.A., 2017. Trace element contents in toenails are related to regular physical activity in older adults. PloS One 12, e0185318. https://doi.org/10.1371/journal.pone.0185318.

Suzuki, T., Watanabe, S., Matsuo, N., 1989. Comparison of hair with nail as index media for biological monitoring of mercury. Sangyō Igaku Jpn. J. Ind. Health 31, 235–238. https://doi.org/10.1539/joh1959.31.235.

Tellez-Plaza, M., Guallar, E., Navas-Acien, A., 2018. Environmental metals and cardiovascular disease. BMJ 362, k3435. https://doi.org/10.1136/bmj.k3435.

US Department of Health and Human Services, Public Health Service, 1999. Toxicological Profile for Mercury. US Department of Health and Human Services, Atlanta.

Were, F.H., Njue, W.M., Murungi, J., Wanjau, R., 2009. Comparison of some essential and heavy metals in the toenails and fingernails of school-age children in Kenya. Bull. Chem. Soc. Ethiop. 23, 117–122. https://doi.org/10.4314/bcse.v23i1.21308.

Wilhelm, M., Hafner, D., Lombeck, I., Ohnesorge, F.K., 1991. Monitoring of cadmium, copper, lead and zinc status in young children using toenails: comparison with scalp hair. Sci. Total Environ. 103, 199–207. https://doi.org/10.1016/0048-9697(91)90145-5.

Wong, J.Y.Y., De Vivo, I., Lin, X., Grashow, R., Cavallari, J., Christiani, D.C., 2014. The association between global DNA methylation and telomere length in a longitudinal study of boilermakers. Genet. Epidemiol. 38, 254–264. https://doi.org/10.1002/gepi.21796.

Yaemsiri, S., Hou, N., Slining, M.M., He, K., 2010. Growth rate of human fingernails and toenails in healthy American young adults. J. Eur. Acad. Dermatol. Venereol. JEADV 24, 420–423. https://doi.org/10.1111/j.1468-3083.2009.03426.x.

Yang, L.E., 2019. Chronic exposure to toxic metals as a risk factor for Alzheimer's disease: a review. Chronic Disease 11–13.

Yoshizawa, K., Rimm, E.B., Morris, J.S., Spate, V.L., Hsieh, C., Spiegelman, D., Stampfer, M.J., Willett, W.C., 2002. Mercury and the risk of coronary heart disease in men. N. Engl. J. Med. 347, 1755–1760. https://doi.org/10.1056/NEJMoa021437.