Review article

Toenails as biomarker of exposure to essential trace metals: A review.

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ABSTRACT

Health problems associated with essential trace metals can result from both inadequate (i.e., low intake) and excessive exposures (i.e., from environmental and/or occupational source). Thus, measuring the exposure level is a real challenge for epidemiologists. Among non-invasive biomarkers that intend to measure long-term exposure to essential trace metals, the toenail is probably the biological matrix with the greatest potential.

This systematic review collects the current evidence regarding the validity of toenail clippings as exposure biomarker for trace metals such as boron, cobalt, copper, iron, manganese, molybdenum, selenium, silicon, vanadium and zinc. Special attention was paid to the time-window of exposure reflected by the toenail, the intraindividual variability in exposure levels over time in this matrix, and the relationship of toenail with other biomarkers, personal characteristics and environmental sources.

Our search identified 139 papers, with selenium and zinc being the most studied elements. The variability among studies suggests that toenail levels may reflect different degrees of exposure and probably correspond to exposures occurred 3–12 months before sampling (i.e., for manganese/selenium). Few studies assessed the reproducibility of results over time and, for samples obtained 1–6 years apart, the correlation coefficient were between 0.26 and 0.66. Trace metal levels in toenails did not correlate well with those in the blood and urine and showed low-moderate correlation with those in the hair and fingernails.

Available data suggests that for some elements (Se, Mn, Zn) toenail concentrations reflect long-term external exposures in fairly reproducible levels, while for other metals, this association has not yet been assessed. Among dietary factors, only toenail selenium showed clear associations with the intake of supplements or specific foods. The toenail levels could also represent occupational exposure, for instance, Mn exposure in welders. The scarcity of information on other essential trace elements, together with the great heterogeneity among studies makes the validation of the usage of toenails as biomarkers of exposure to these elements difficult. Standardization of sample collection, quality control, analytical techniques and reporting procedures might facilitate further research focused on the clear understanding of the significance of essential levels in this promising matrix and would enhance its utility in epidemiological research.

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1. Introduction

Essential trace metals/metalloids either are needed to maintain physiologically important functions, or are part of organic structures with vital functions in humans (Mertz, 1981). However, in many cases, excessive levels of these elements also pose a serious health risk. The typical source of these elements is diet, but occupational (e.g., Mn in welders) and environmental sources (e.g., environmental release of Zn by metal production industries or from combustion of coal in power stations) may also contribute to high exposure levels. Therefore, measurement of exposure at the individual level is a critical aspect in the research of the role of these elements in human health.

According to the World Health Organization (WHO) (WHO, 1996), the list of essential trace metals/metalloids -which will be called as metals in this review paper, since most of the elements studied belong to this group-, includes chromium (III) (Cr) [now under discussion] (Nigra et al., 2016), copper (Cu), cobalt (Co), iron (Fe), molybdenum (Mo), selenium (Se), zinc (Zn), and [manganese (Mn), which was added in 2001 to this group (Institute of Medicine (US), 2001). Vanadium (V), silicon (Si) and boron (B), not strictly considered essential elements, are often studied with them due to their potential health benefits (WHO, 1996; US EPA O, 2014).

A common approach to measure the exposure level to these essential trace metals is the use of biomarkers due to several reasons: they reflect both known and inadvertent exposures; they are not affected by recall bias, and they integrate all sources (i.e., diet, air and water) and routes of contact (Santonen et al., 2015). Among these, toenails are non-invasive matrices that have become quite popular in large epidemiological studies for their logistic advantages, namely very easy collection and storage and less influence of external contamination than fingernails and hair (Karagas et al., 2000). In addition, the slow rate of growth of toenails has made these suitable candidates for evaluating longer term exposures than other biomarkers such as blood or urine, a key issue in chronic diseases research (Hopps, 1977; Sukumar, 2006). However, the validity of these assumptions is unclear and the usefulness of measurement of essential trace metals in toenails as a biomarker of exposure is still uncertain. In this review, we condensed available data on essential trace metal levels in toenails and summarized the evidence on their validity as biological matrices of exposure. We paid special attention to a) stability over time and time-window of exposure, two aspects critical in evaluating long-term chronic exposures; b) the relationship with other commonly used biomarkers, such as blood and urine and; c) the association with personal characteristics and several sources, in order to better understand the factors that module or determine the levels of essential trace metals in this substrate.

2. Material and methods

This review is reported in accordance with the PRISMA publication standards (Moher et al., 2009) and the protocol was registered in PROSPERO, the international prospective register of systematic reviews (registration number CRD42018085822) (University of York, 2018).

2.1. Identification of studies

We conducted a systematic literature search for peer-reviewed papers providing original data on essential trace metal concentrations in toenails. The flow diagram of the study selection process is shown in Fig. A1 (Appendix A). Two reviewers (EG and BP) independently screened abstracts, reviewed full-text articles, extracted data and performed quality assessments. Initially, we searched the databases PubMed/MEDLINE, Web of Science and Scopus from inception to December 31, 2017, using the following exact searches: #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 aluminium OR molybdenum OR manganese OR iron OR silicon OR boron; #4: #1 AND #2 AND #3. This search retrieved 2632 references. Then, we manually reviewed the reference lists of all included studies and identified 52 additional articles. Studies that reported original quantitative data on toenail metal concentrations in humans in English or Spanish were considered eligible. When the type of nail (fingernail/toenail) was not specified, the corresponding author was contacted for clarification. After exclusion of duplicates, 276 articles met the general inclusion criteria. From these, for the purpose of this review, we narrowed our scope to focus on the papers (139) with information on essential trace metals (Co, Cu, Fe, Mn, Mo, V and Zn) or metalloids (B, Se, Si); we did not include Cr due to its disputed essentiality (Nigra et al., 2016) and the carcinogenic role of Cr (VI) (IARC, 2012).

2.2. Data collection

Data from included studies were extracted into a customized spreadsheet. According to a purpose-designed protocol, the following data were extracted from each study: a) *basic information* (first author, country, year of publication, research project, studied trace metals); b) *design features* (type of epidemiological study, main objective, sample size, population sample method, participant characteristics, informed consent request, ethical committee approval); c) *sample and analytical information* (toenail type (i.e., big toe, all toes), sample preparation, analytical method, quality control measures, limits of detection and availability of other biological specimens with trace metal data); d) *metal concentrations*, i.e., measures of central tendency (geometric or arithmetic mean, median (p50)) and dispersion (standard deviation (SD) or range), when available; and e) *correlation with other biomarkers, with personal characteristics, with environmental data, or with previous toenail measures.*

Most studies reported metal levels in micrograms per gram (μg/g), but many authors chose to provide other units of concentration, namely 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). This variability in the units used to express metal concentrations was not related to any specific element or technique. For this review, we converted all units into μg/g to allow for an easier comparison among studies.

3. Results

3.1. Study characteristics

We identified a total of 139 manuscripts published between 1975 and 2017, which provided levels of essential metals in toenails, from 89 different research projects (number of papers per research project ranged from 1 to 9; 25 projects had 2 or more manuscripts). Almost 40% of the articles evaluated exposure either in the USA (49 papers, with data from 25 research projects) or in Canada (6 manuscripts, with data from 4 research projects) and another 39% of the papers included information from studies conducted in Europe (the Netherlands −13 manuscripts from 4 research projects-; Italy −7 papers from 4 projects-; and Poland −5 manuscripts from 5 research projects-were the most common locations). The remaining studies (21%) presented toenail essential metal levels from other countries, with a higher proportion of Asian countries in the recent years. One research project combined
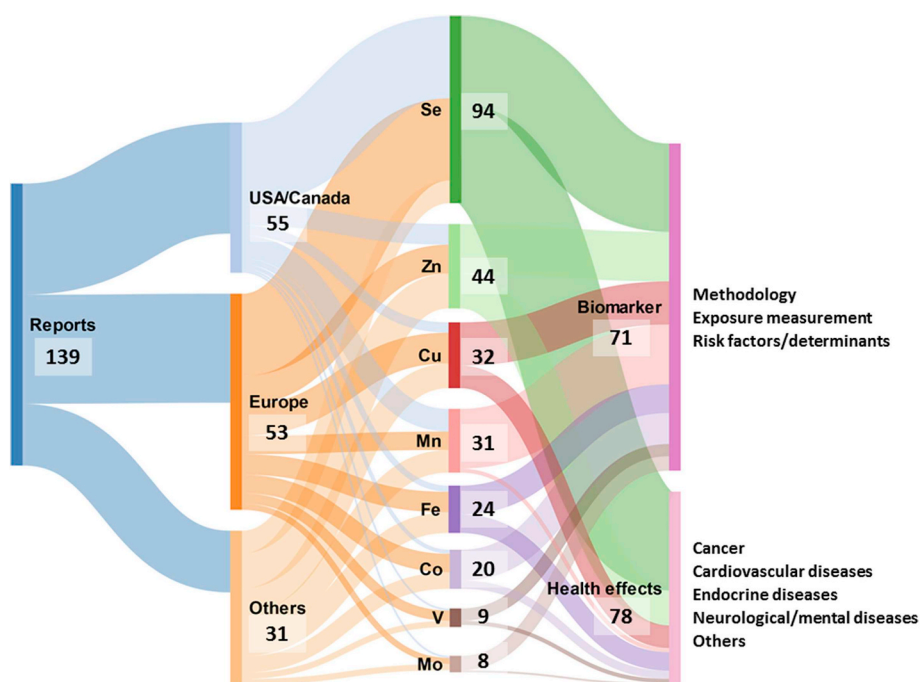
populations from more than one continent (EURAMIC study). The number of manuscripts has increased in the last decade (See Fig. A2, Appendix A), evidencing a growing interest in this biomarker. The characteristics of each paper, sorted by research study and year of publication, are detailed in Appendix A, Table A1. Search results are summarized in Fig. 1.

The majority of the research projects (n = 48) were focused on a single element, usually selenium. Overall, Se was the most studied essential trace element (n = 94 reports), followed by Zn (n = 44), Cu (n = 32), Mn (n = 31), Fe (n = 24), Co (n = 20), V (n = 9) and Mo (n = 8), while no data were found about toenail concentrations of B or Si. Regarding the aims of the articles, 71 used toenails as biomarkers of exposure to one or more essential metals or tried to identify their determinants, while 78 studied the association between toenail essential metal levels, mainly Se and Zn, and different health problems or biological characteristics (i.e., cholesterol levels). The most common outcome studied was cancer (Garland et al., 1995; Ghadirian et al., 2000), although other articles evaluated cardiovascular (Kardinaal et al., 1997), metabolic (Park and Seo, 2016), or hematologic effects (Lee et al., 2016), as well as neurologic (Meramat et al., 2017) or mental-health related problems (Colangelo et al., 2014) (Appendix A, Table A1).

The number of participants in each study was highly variable: 33 research projects included less than 100 individuals, 46 studies, between 100 and 1000 and 9 recruited more than 1000 participants (range: 12–9267). In one project (only 1 paper published), the sample size was not specified (Abdulrahman et al., 2012). Baseline characteristics of these subjects were heterogeneous across studies and depended on the aim of each investigation. Thus, each paper provided information describing some features of the specific population under study, such as age, sex, race, socioeconomic status, occupation, or dwelling place (See Appendix A, Table A1). However, in some cases, this description was limited to geographical area of recruitment, omitting basic data such as age or sex of the participants.

Regarding study design, most papers presented cross-sectional analyses (n = 59, which also included baseline levels in longitudinal projects), followed by case-control (30 reports) studies; prospective designs (case-cohort: 9 reports; nested case-controls: 13 reports; cohort: 25 reports) and randomized trials (3 reports). Convenience sampling was the typical strategy for recruitment and only 17 research projects reported participation rates, ranging from 41.8% (O'Rorke et al., 2012) to 98% [22]; usually, in case-control studies participation was lower among controls.

Concerning ethical considerations, 47 articles declared having approval of an ethics committee and informed consent explicitly appeared as an inclusion criterion in 49 papers.

3.2. Analytical methodology: sample collection, nail preparation, analysis and quality control (Table A1)

Toenails clippings -which are the last end of the nail and constitute only a fraction of the total nail-were obtained using stainless-steel clippers or scissors. In regard to sample storage, studies that included information about this issue indicated that were kept in paper envelopes or in plastic bags/vials (polyethylene or non-specified), usually at room temperatures. The effects of long-term storage (6 years) were evaluated only for Se by St-Pierre et al., who concluded that the loss of humidity occurred with long-term storage led to increased Se concentrations (St-Pierre et al., 2006).

The influence of sampling date has not been commonly studied. Isolated reports have suggested that Zn levels might be higher in winter (Campos et al., 2008) and that there might be significant differences in metal toenail levels depending on the season of sampling collection, for Cu, but not for Zn (Wilhelm et al., 1991) or Se (Baskett et al., 1995).

Most of the projects (n = 40) did not identify the specific type of toenails analyzed. Among those that did, the majority (n = 36 studies) collected clippings from all toes; 8 projects used nails from big toes and, in another two studies, specimens from big toes and from the other toes

were evaluated separately. Two projects provided partial information, reporting sampling from both feet (Ghadirian et al., 2000; Vinceti et al., 2005) or from right foot (Vinceti et al., 2012), or using nails from different feet for analysis of each metal, without specifying which toes were considered (Vinceti et al., 2005). Possible differences in metal levels among toes have only been explored for Se, comparing the big toe to the rest of toes (Baskett et al., 2001; Kok et al., 1989; Longnecker et al., 1993) or with a pool of all toes (van 't Veer et al., 1990), without finding significant variations. Also for this element, a high correlation between Se concentrations in the right and left toenails was observed in one study (r = 0.74) (Steven Morris et al., 1983).

In regard to the amount of bio-specimen, most papers (n = 105) did not provide any summary or descriptive data (i.e., mean or range) about the toenail mass used for the analyses. However, several authors (Kardinaal et al., 1997; Steven Morris et al., 1983; Mordukhovich et al., 2012; Platz et al., 2002; Sanders et al., 2014) remarked that the limit of detection (LOD) for trace metal determinations was dependent on toenail mass and at least 25 reports indicated that a minimum weight was required for the analyses, which was only specified in 15 papers (i.e., 10 mg in 12 of them). In some studies (Lee et al., 2016; Abdulrahman et al., 2012; Al-Saleh and Billedo, 2006; Goullé et al., 2009; Hartman et al., 2002; Michaud et al., 2002; Morris and Crane, 2013; Saat et al., 2013; Wongwit et al., 2004), researchers stated they analyzed aliquots of toenail within a mass range (mostly 10–50 mg). It should be noted that, according to some investigators, the weight of the clippings not only limits the possibility of measurement of trace metals, but also bias the levels obtained. Thus, Baskett et al. described an apparent systematic bias in metal concentrations (Se, in this case) that were inversely proportional to the mass of the sample (Baskett et al., 1995), which occurred in clipping samples weighing 23 mg or less. Additionally, Saint Pierre et al. (St-Pierre et al., 2006) found an inverse correlation between sample weight and Se concentration, while Colangelo et al. reported that toenail mass was positively associated with toenail Se levels (Colangelo et al., 2014). In some of the studies, this possible influence of nail weight in trace metal concentrations was considered and was corrected for. Thus, some authors adapted analytical procedures to fit small samples (Baskett et al., 1995); in other studies, toenail weight was considered as a potential confounding factor (Colangelo et al., 2014), or measured levels were normalized based on sample weight (Brockman et al., 2009). Also, regression models were fitted with log-transformed toenail element levels (the dependent variable) against the nail weight (the independent variable) (St-Pierre et al., 2006), or the residual of each observation was added to the predicted mean toenail value and the result was exponentiated (Garland et al., 1993, 1995, 1996).

In most studies, toenails were subjected to pretreatment after clipping and storage, before analysis, and the methods used were highly variable. Table A1 (Appendix A) presents a summary of this information, derived from each report included in the review. Nail polish in samples was generally removed with acetone and visible dirt was manually cleaned. Direct effects of nail polish (Ghadirian et al., 2000; van 't Veer et al., 1990; Krogh et al., 2003) or debris (van 't Veer et al., 1990) was assessed only for Se, and these factors did not seem to influence toenail Se concentrations. In order to reduce external contamination, toenails were cleaned by washing with detergent, deionized water, methanol, Triton solution, acetone, or sodium dodecylsulfate, assisted by a sonicator or an ultrasound bath. Subsequently, samples were dried in an oven, air-dried or freeze-dried.

Neutron activation analysis (NAA or instrumental NAA) was the most commonly used technique for element measurement (46 studies), followed by inductively coupled plasma spectrometry (ICP-MS, ICP-OES, ICP-AES) (29 studies) and atomic absorption spectrometry (AAS) (14 studies) (Appendix A, Table A1). In these two last cases, digestion of

samples was performed in nitric acid, with or without chlorhydric acid, in perchloric acid, or in hydrogen peroxide, when needed; some reports specified a microwave digestion system or a sonicator. Certain research projects, like CARDIA, CLUE II, or ORDET, employed different techniques depending on the metals studied. Less common techniques used were thermal neutron flux (Graham et al., 1991) and acid digestion fluorometry (Hartman et al., 2002; Michaud et al., 2002; Alfthan et al., 1992; Männistö et al., 2000; Ovaskainen et al., 1993).

Sixty reports mentioned quality control procedures, which included the use of certified reference material (urine or hair) or homemade nail reference material, recovery analysis, procedural blanks, duplicate samples, or spike samples.

3.3. Essential trace metal concentrations in toenails across populations

Tables B1–B8 (Appendix B) present the levels of each essential metal in each study and the subgroup of participants (mean (SD), median, range) extracted from the 139 studies, included in this review. Their main data are shown graphically in Fig. 2.

Only 18 (9.5%) research projects, mostly those which used IPC-MS, provided information on LOD, and even fewer (n = 4), specified limits of quantification (LOQ). The LODs were calculated from procedural blank analyses, usually as three standard deviations from the mean blank reading (Al-Saleh and Billedo, 2006; Krogh et al., 2003; Herman et al., 2013; Przybylowicz et al., 2012; Ntihabose et al., 2017; Bouchard et al., 2017). Among the studies that reported LODs for specific metals, for Co, LODs ranged from 0.0003 (Goullé et al., 2009) to 0.01 μg/g (Chanpiwat et al., 2015); for Cu, from 0.009 (Przybylowicz et al., 2012) to 0.12 μg/g (Chanpiwat et al., 2015); for Fe, from 1.55 (Przybylowicz et al., 2012) to 2.93 μg/g (Chanpiwat et al., 2015); for Mn, from 0.001 (Goullé et al., 2009) to 0.33 μg/g (Chanpiwat et al., 2015); for Mo, from 0.0004 (Goullé et al., 2009) to 0.02 μg/g (Chanpiwat et al., 2015); for Se, from 0.0022 (Emmanuelle et al., 2012) to 0.02 μg/g (Goullé et al., 2009); and for Zn, from 0.01 (Goullé et al., 2009) to 0.279 μg/g (Przybylowicz et al., 2012). Only one study specified the LOD for V, which was 0.001 μg/g (Goullé et al., 2009). The percentage of samples with quantities under LOD, when available, depended on the element studied. It was low or inexistent for Zn and Se; in contrast, some studies reported a significant proportion of samples with quantities under the LOD for other metals, i.e., Cu, Fe, Mn and V (See Appendix B, Tables B1–B8).

Among the elements studied, Co, Mo, Se and V had the lowest levels, and most studies found mean values < 1 μg/g (Fig. 2a,e,f and g; Tables B1, B5, B.6, B.7). However, a couple of studies reported exposed populations with higher mean Co concentrations: metal workers in two towns of northern Italy (AMs: 18.90 and 53.79 μg/g (Sabbioni et al., 1994),); and young adults living near a mining area in Zambia (GM: 1.39 μg/g) (Ndilila et al., 2014). Morris et al. also reported exceptionally high Se levels (AM 8.27 μg/g) among people in USA who consumed misformulated supplements with excessive Se concentrations (Morris and Crane, 2013). In general, mean Se levels were higher in studies from USA-Canada, when compared with other countries.

Fe toenail concentrations (Table B3 and Fig. 2c) showed the highest variability across studies, with median levels ranging from 8.8 μg/g in a group of 60–80 year-old women from Spain (Sureda et al., 2017) to exceptionally high levels (median: 1434 μg/g) in subjects living in contaminated areas of Cambodia (Chanpiwat et al., 2015).

Mean Cu and Mn levels were usually below 10 μg/g (Tables B.2 and B.4, Fig. 2b–d, respectively), while mean Zn levels (Table B.8, Fig. 2h) ranged mostly from 50 to 200 μg/g. The highest Cu, Mn and Zn concentrations were found among subjects living in rural areas near a highly industrialized city in Pakistan (AM: 26.2 μg/g for Cu, 52.1 for Mn and 298 for Zn) (Mohmand et al., 2015). High concentrations of Mn
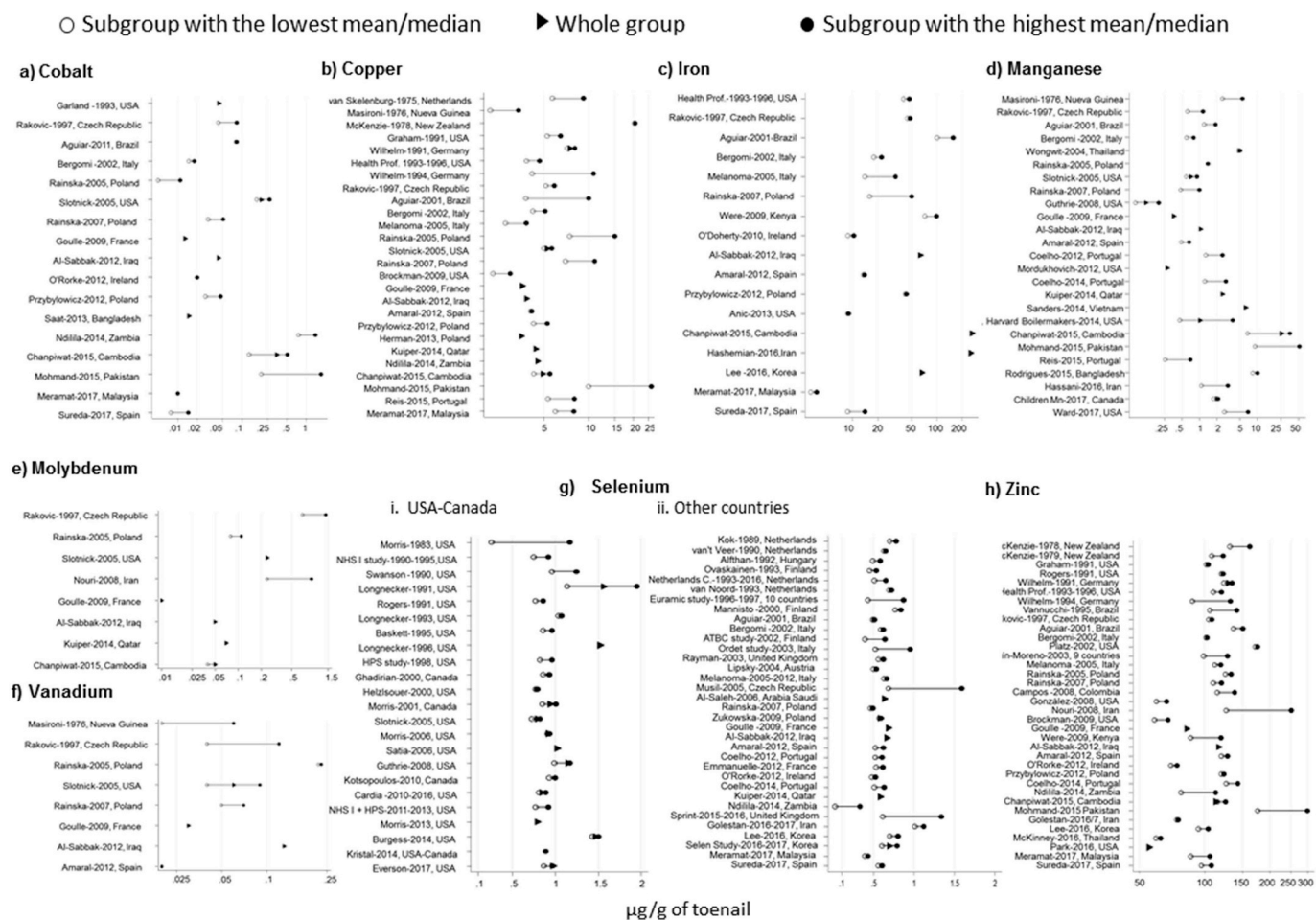
Fig. 2. Essential metal levels [mean or median (µg/g dry weight] in human toenails (1975–2017).

were observed in individuals living in highly polluted areas of Cambodia (AM: 43.9 µg/g) (Chanpiwat et al., 2015) and among welders from a local boilermaker union in the USA (AM: 26.9–55.5 µg/g) (Laohaudomchok et al., 2011).

3.4. Toenail as a biomarker of integrated long-term exposure: time-window of exposure and intraindividual stability over time (Tables 1 and 2)

The time-frame of exposure covered by toenails, investigated only for Se and Mn, was explored in studies that identified a specific moment in which the exposure occurred, which allowed to calculate the time elapsed until detection in toenail samples. Selenium was the most studied element and was evaluated in three research projects.

In the USA, 12 young men participated in a research conducted to evaluate the effect of one-year intake of Se-supplemented whole wheat bread on Se toenail levels. The participants were classified into three groups: those with high-dose (4.91 µmol Se/d), medium-dose (2.61 µmol Se/d) and low-dose (0.41 µmol Se/d), and the concentration of Se in toenail clippings was measured every 1–2 weeks for 2 years (Longnecker et al., 1993). Se peak levels were detected in the big toenail after 24–37 weeks vs. 12–24 weeks in other toes; this difference was attributed to the shorter nail bed in smaller nails. Selenium concentration in the big toenail was still high, even after one year of intake termination and remained over baseline for two years; this suggests that toenail clippings could provide a

time-integrated measure of Se intake for over 26–52 weeks, serving as a good biomarker of Se intake for retrospective studies. Other studies included 10 middle-aged men and women provided with Se-76 supplementation, and the peak Se concentrations in toenails were observed at 16–32 (Baskett et al., 1995, 2001) and 16–50 (Baskett et al., 1998) weeks. Peak concentrations were also reported by Morris et al. at 34 weeks after ingestion of high Se misformulated products, while, in this study, baseline levels were recovered after 59 weeks (Morris and Crane, 2013). For Mn, the time-frame of exposure was evaluated in 3 studies conducted among occupationally exposed workers (welders). Exposure time reflected by toenail Mn concentrations was estimated between 7 and 9 (Grashow et al., 2014) and 7–12 months (Laohaudomchok et al., 2011; Ward et al., 2017) (Table 2).

Since one year is an insufficient period for the study of exposure for most chronic diseases, it is crucial to identify the extent to which individual point measurements of trace metals in toenails represent toenail concentration levels in the same person in the previous years.

This stability of essential trace metals over time was evaluated in 7 reports by estimating the within-person correlation among samples obtained at different moments (Table 1) (Baskett et al., 1995; Garland et al., 1993; Krogh et al., 2003; Hunter et al., 1990a; Rodrigues et al., 2015; Xun et al., 2010a). The usage of correlation coefficients to assess reproducibility is not ideal, but no studies used the intra-class correlation coefficient.

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

Toenail metal	Author	Year	N	Toenails reproducibility over time *	Hair	Urine	Whole blood	Serum	Plasma	Finger nail	Other toenails	Feces	Cord blood	Placenta	Saliva
Co	Garland[e]	1993	127	r = 0.35 (6-year)	r = 0.38 (ns)										
	Sabbioni	1994	115				r = 0.25 (ns)								
	Chanpiwat[e]	2015	180		r = 0.20	r = −0.08 (ns)									
Cu	Wilhelm	1991	461		r = 0.18										
	Garland[e]	1993	127	r = 0.26 (6-year)	r = 0.26										
	Herman	2013	30		r = 0.26										
	Kuiper	2014	239			(ns)									
	Chanpiwat[e]	2015	180		r = 0.10 (ns)	r = −0.08 (ns)									
Fe	Garland	1993	127	r = 0.43 (6-year)	r = 0.36										
	Chanpiwat[e]	2015	180			r = −0.03 (ns)									
Mn	Wongwit[f]	2004	135				r = 0.05 (ns)								
	Kuiper	2014	239			(ns)						(ns)			
	Coelho[e]	2014	122		r = 0.32					r = 0.23					
	Chanpiwat[e]	2015	180		r = 0.14	r = −0.10 (ns)									
	Rodrigues[e]	2015	711	r = 0.37–0.41 (6/7 months)[b]		r = 0.65					Mother-infant r = 0.39		r = 0.14		
	Hassani[g]	2016	83		r = 0.40		r = 0.65								
	Ntihabose	2017	268												r = 0.14
Mo	Kuiper	2014	239			(ns)									
	Chanpiwat[e]	2015	180		r = 0.08 (ns)	r = 0.00 (ns)									
Se	Hunter	1990b	868	r = 0.60 (5-year)			r = 0.30 (ns)				Left-Right r = 0.74; Big-Small (nd); Big-All (nd)				
	Morris	1983	62		r = −0.3 (ns)										
	Kok	1989	168												
	Van't Veer	1990	372					r = 0.89							
	Longnecker	1991	142			r = 0.60	r = 0.91								
	Alfthan	1992	132							r = 0.57					
	Garland	1993	127	r = 0.48 (6-year)											
	Longnecker	1993	12												
	Baskett	2001	11												
	Krogh	2003	80	r = 0.57 (1-year)[c]											
	Satia[e]	2006	220						r = 0.55						
	Al Saleh[d]	2006	691					r = −0.16							
	Xun	2010b	69	r = 0.56 (20-year)											
	Vinceti[e]	2012	105								Big-Small (nd)				
	Coelho[e]	2014	122						r = 0.27		Left-Right **				
	Kuiper[f]	2014	239			(ns)				r = 0.33					
	Rayman[e]	2015	230				r = 0.45								
	Punshon[ae]	2016	554											h	
V	Rainska	2007	33		r = 0.61										
Zn	Mckenzie	1979	110		(ns)	(ns)									
	Wilhelm[a]	1991	461		r = 0.03 (ns)										
	Garland	1993	127	r = 0.58 (6-year)											
	Chanpiwat[e]	2015	180		r = −0.02 (ns)	r = 0.08 (ns)									
	Punshon[a]	2016	554											(ns)	

N = number of participants (samples) in the study; r = correlation coefficient; (ns) = p > 0.05 except in Champiwat (2015) (p > 0.01) or author only stated that correlation was not statistically significant; (nd) = author stated that there were no differences. * = between parentheses is expressed the intervale of time between both measurements.

[a] Log transformed.
[b] Pregnant women: first trimester vs one month post-partum.
[c] Not modified by age, menopausal status, smoking or acetone treatment.
[d] No significant differences between mean levels in both specimens using t-test.
[e] Spearman correlation.
[f] Pearson correlation.
[g] Partial correlation test.
[h] = strong positive significant correlation with maternal toenails. Not significant with infant toenails.

For most elements, this information was obtained from a single analysis carried out in 127 female nurses participating in the Nurse Health Study I (NHSI), which measured 5 trace metals (Co, Cu, Fe, Se and Zn) in 2 samples of toenails collected 6 years apart. Correlation values were around 0.5 for Zn, Se and Fe and less than 0.4 for Co and Cu (Garland et al., 1993).

In the case of Se and Mn, our search identified additional studies that evaluated the reproducibility of their measurements in different moments of time. For Se, the studies we identified reported a Pearson correlation coefficient of 0.57 among samples collected around 1 year apart from 80 women in the ORDET prospective study of whom 40 were pre-menopausal and 40 were postmenopausal (Krogh et al., 2003); a correlation coefficient of 0.60 using samples collected approximately 5 years apart, from the NHS I cohort (Hunter et al., 1990a); and a correlation coefficient of 0.56 using toenail Se samples collected 20 years apart from 64 participants in the CARDIA project (Xun et al., 2010a). Another exploratory research stated that Se levels were very stable in toenail samples from 2 men and 2 women, followed up for 15 months prior to Se supplementation (Baskett et al., 1995). For Mn, two studies have been conducted in this context: a study which reported correlation coefficients between 0.37 and 0.41 in pregnant women, with samples taken during the first trimester of pregnancy and one month after delivery (Rodrigues et al., 2015) and another exploratory analysis that evaluated clippings of the five toenails from the same individual, collected four times over a 9-month period, with a large variability in the Mn levels (Guthrie et al., 2008).

3.5. Correlation of trace elements in toenails with other biological matrices (Table 1)

To better understand toenail metal levels as biomarkers of exposure to essential trace elements, it is important to explore their relationship with other substrates commonly used in this field, especially blood and urine. A total of 20 studies with a variable number of participants (range: 30–868) evaluated the correlation of trace elements in toenails with other biological matrices collected concurrently (i.e., whole blood, serum, plasma, urine, hair, fingernails, feces, cord blood, placenta and saliva) (Table 1).

Hair: Hair was the biological matrix more often compared with toenails (n = 10), probably due to its shared non-invasiveness and its similar keratin-based composition. For Mo, Se or Zn, no significant associations have been observed between levels in this substrate and in toenails (Wilhelm et al., 1991; Steven Morris et al., 1983; Chanpiwat et al., 2015; Kuiper et al., 2014; McKenzie, 1979). Other metals, such as Co and Cu, showed weak positive (< 0.30) or null correlation between both biomarkers (Wilhelm et al., 1991; Herman et al., 2013; Chanpiwat et al., 2015; Sabbioni et al., 1994). In contrast, the association was moderate (between 0.32 and 0.40) for Mn (Ntihabose et al., 2017; Chanpiwat et al., 2015) and Fe (Chanpiwat et al., 2015) and strong (r = 0.61) for V, (Rainska et al., 2007), although the interpretation of the latter result was limited by the small sample size of the study (n = 33).

Urine: Our search identified two studies which revealed strong positive correlations between metal levels in toenails and urine for Mn (r = 0.65 (Hassani et al., 2016)) and Se (r = 0.60 (Longnecker et al., 1991)). In contrast, Co, Cu, Fe, Mo and Zn in toenails and in urine were not found to be correlated in other studies (Chanpiwat et al., 2015; Kuiper et al., 2014; McKenzie, 1979).

Blood: Surprisingly, there were only data comparing these two matrices for Se, Mn, Co and Zn. In the case of Se, four studies showed positive and significant correlations with whole blood (r = 0.91 (Longnecker et al., 1991) and r = 0.45 (Rayman et al., 2015)); serum (r = 0.89 (Longnecker et al., 1991)); and plasma (r = 0.55 (Satia et al., 2006)). However, in the study by Al Saleh et al. a negative correlation between log-transformed Se concentrations in toenails and serum was reported (r = −0.16 (Al-Saleh et al., 2006)). Regarding Mn, Hassani

et al. described a strong correlation between toenails and whole blood levels (r = 0.65 (Hassani et al., 2016)), but both biomarkers were not found to be related in a sample of welders studied by Wongwit et al. (2004); moreover, Rodrigues et al. reported a low correlation between infant toenails and cord blood concentrations (r = 0.14 (Rodrigues et al., 2015)). Finally, whole blood Co (Sabbioni et al., 1994) and serum Zn (McKenzie, 1979) levels were not significantly correlated with the corresponding toenail concentrations.

Fingernails: Only three studies evaluated the correlation between toenails and fingernails, showing a low correlation for Mn (r = 0.23 (Coelho et al., 2014)) and a medium correlation for Se (r = 0.33 (Coelho et al., 2014) and r = 0.57 (Alfthan et al., 1992)). In these studies, as well as in the studies by Baskett et al. for Se (Baskett et al., 1995, 1998, 2001), fingernail concentrations were almost twice as high as those from toenails.

Other matrices: For Mn levels in toenails, a weak correlation has been reported with the concentration in saliva (Ntihabose et al., 2017) and no correlation with levels in feces (Wongwit et al., 2004). A moderate correlation has been reported between infant and maternal toenail Mn levels (r = 0.39 (Rodrigues et al., 2015)). In the case of Se, a positive correlation was observed between maternal toenail and placenta Se concentrations (Punshon et al., 2016).

3.6. Correlation of essential metals with other trace metals in toenails (Table A2)

The correlation among essential trace elements in toenails or with other toxic metals was explored in 14 studies (Table A2, Appendix A). Most of the reported correlations were low-moderate (below 0.40) or non-significant, both for essential and non-essential elements. Among the essential metals group, the strongest correlations were observed between Fe and Co (r = 0.81) (Rainska et al., 2007) and between Mn and V (r = 0.40) (Masironi et al., 1976). Regarding the association between essential and toxic metals, Mn had the highest proportion of strong correlations (with aluminium (Al) (Guthrie et al., 2008), arsenic (As) (Mordukhovich et al., 2012; Sanders et al., 2014), barium (Ba) (Kuiper et al., 2014), cadmium (Cd) (Mordukhovich et al., 2012; Sanders et al., 2014), chromium (Cr) (Sanders et al., 2014), lead (Pb) (Mordukhovich et al., 2012) and uranium (U) (Kuiper et al., 2014)). Other strong correlations were reported for Co and tungsten (W) (Sabbioni et al., 1994), Cu and Cd (Wilhelm et al., 1991), Cu and Pb (Wilhelm et al., 1991; Kuiper et al., 2014), Se and As (negative correlation) (Burgess et al., 2014), V and Al (Masironi et al., 1976) and V and scandium (Sc) (Rainska et al., 2007).

3.7. Determinants of essential metals in toenails

Identification of the exposure sources or factors related to them is crucial in understanding the information provided by the measurement of essential metal levels in toenails. Most of the studies reported on this issue, although the huge variability in the variables studied, populations, designs and indicators made the calculation of quantitative summary estimators practically impossible. Notwithstanding, we have tried to summarize this information in order to give a general view of the published results. For this purpose, we have designed two tables that present, for each combination of metal and factor studied, the identification (i.e., author and date) of each report and the information about their possible relationship. Table 2 includes data for non-dietary factors and Table 3 includes the corresponding associations with intake of supplements, dietary estimates, foods and nutrients.

3.7.1. Personal and anthropometric characteristics (Table 2)

Age: For toenail Se, most of the studies showed either no changes with age (Kardinaal et al., 1997; Colangelo et al., 2014; van 't Veer et al., 1990; Alfthan et al., 1992; Ovaskainen et al., 1993; Satia et al., 2006; Everson et al., 2017; Hashemian et al., 2017; Kristal et al., 2014;

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Table 2

Studies (Author year) reporting association of toenail essential trace metals to personal characteristics and non-dietary exposures.

Metal	Personal characteristics					Non-dietary lifestyle & social factors			Other environmental exposures				
	Age	Sex	Ethnicity	BMI	Reproductive factors	Physical activity	Tobacco use	Socioecon/ Educative level	Water	Residential exposure	Dust/Air	Occupational Exposure →	Time since exp
Co	▼ Rakovic 1997	♂ Rakovic 1997 Slotnick 2005 Sureda 2017				▲ ♀ Sureda 2017			▲ Ndilila 2014 ▼ Champiwat 2015	▲ Champiwat 2015	▲ Ndilila 2014	▲ Sabbioni 1994 Ø Menezes 2004a Rakovic 1997 Rainska 2005, 2007	
Cu	Ø Slotnick 2005 Reis 2015 ▼ Rakovic 1997	♀ Rakovic 1997 Ø Masironi 1976 McKenzie 1978 Reis 2015							▲ McKenzie 1978 Ndilila 2014 Reis 2015 Chanpiwat 2015	▲ Ndilila 2014 Chanpiwat 2015 Mohmand 2015 Ø Reis 2015	▲ Ndilila (soil) Ø Reis 2015	▲ Menezes 2004a Rainska 2005	
Fe	▼ Rakovic 1997	Ø Rakovic 1997 Sureda 2017		▲ Garland 1996	▼ Garland 1996 *Age first birth*	▲ ♀ Sureda 2017 -♂ Sureda 2017			▲ Champiwat 2015	▲ Rakovic 1997 Rainska 2007 Were 2009		▲ Rakovic 1997	
Mn	▲ Laohaudomchok 2011 Coelho 2014 Ø Grashow 2014 Ward2017 ▼ Masironi 1976 Slotnick 2005 Reis 2015	Ø Masironi1976 Reis 2015 ♀ Rakovic 1997 Coelho 2014	▲ *White* Laohaudomchok2011 Mordukovitch 2012	Ø Ward 2017	▲ Rodrigues 2015 *Parity*		▲ Coelho 2014 Ø Wongwit 2004 Grashow 2014 Ward 2017 ▼ Rakovik 1997	▲ Rodrigues 2015	▲ Champiwat 2015 Rodrigues 2015 Ntihabose 2017	▲ Rakovic 1997 Coelho 2012 Coelho 2014 Sanders 2014 Chanpiwat 2015 Ø Reis 2015	▲ Reis 2015 Ø Hassani 2016	▲ Menezes 2004b Laohaudomchok 2011 →7-12 m Coelho 2012,2014 Grashow 2014 → 7-9 m Hassani 2016 Ward 2017 →7-12 m Ø Rakovic 1997 Rainska 2005	
Mo	Ø Nouri 2008 ▼ Rakovic 1997	♀ Rakovic 1997							▲ Champiwat 2015	▲ Nouri 2008	▲ Rakovic 1997	▲ Rakovic 1997 Ø Rainska 2005	

Metal	Personal characteristics					Non-dietary lifestyle & social factors			Other environmental exposures				
	Age	Sex	Ethnicity	BMI	Reproductive factors	Physical activity	Tobacco use	Socioecon/ Educative level	Water	Residential exposure	Dust/Air	Occupational Exposure →	Time since exp
Se	▲ Slotnick 2005 Rayman 2015 Ø Swanson 1990 Van't Veer 1990 Alfthan 1992 Ovaskainen 1993 Van der Brandt 1993b Kaardinal 1997 Lipsky 2004 Satia 2006 Morris 2001,2006 Xun 2010a Colangelo 2014 Kristal 2014 Everson 2017 Hashemian 2017	♂ Park 2011 Ø Satia 2006 Sureda 2017	▲ *White* Kristal 2014 Everson 2017♀ Ø Satia 2006	▲ Park 2011 Ø Hunter 1990a Ovaskainen 1993 Van der Brandt 1993b Kaardinal 1997 Lipsky 2004 Morris 2006 Satia 2006 Colangelo 2014 Kristal 2014 Hashemian 2017	▲ Van Noord 1993 *Parity* Hunter 1990b *Age menarche* Ø Krogh 2003 *Menopausal status*	Ø Satia 2006 Xun 2010a Hashemian 2017 Sureda 2017	Ø Ovaskainen 1993 Virtanen 1996 Lipsky 2004 Everson 2017	▲ Xun 2010b, 2011 Colangelo 2014 Rayman 2015	▲ Emmanuelle 2012	▲ Morris 1983 Hunter 1990a Yoshizawa 1998 Michaud 2002 Morris 2006 Xun 2010b, Xun 2011 Park 2011, Emmanuelle 2012 Ndilila 2014 Colangelo 2014 Hashemian 2017 Ø Coelho 2014		Ø Coelho 2014	

(*continued on next page*)

Table 2 (*continued*)

Metal	Personal characteristics					Non-dietary lifestyle & social factors			Other environmental exposures				
	Age	Sex	Ethnicity	BMI	Reproductive factors	Physical activity	Tobacco use	Socioecon/ Educative level	Water	Residential exposure	Dust/Air	Occupational Exposure →	Time since exp
	▼ Hunter 1990a Garland 1995 Zukowska 2009 Park 2011 Park K 2016 Jang 2017	♀ Swanson 1990 Van der Brandt 1993b Baskett 2001 Morris 2001,2006 Rainska 2007 Zukowska 2009 Xun 2010a, b Lee 2016	▼ *Afroamerican* Xun 2010a, 2011 Colangelo 2014 Kristal 2014	▼ Zukowska 2009 Xun 2010a Vincetti 2015			▼ Hunter 1990a,b Swanson 1990 Van der Brandt 1993b Van Noord 1993 Garland 1995 Virtanen 1996 Kardinaal 1997 Ghadirian 2000 Krogh 2003 Morris 2001,2006 Satia 2006 Zukowska 2009 Park 2011 Xun 2010a,b,2011 Emmanuelle 2012 Colangelo 2014	▼ Everson 2017					
V	▼ Masironi 1976 Rakovic 1997 Slotnick 2005	Ø Masironi 1976 ♀ Rakovic 1997 Slotnick 2005								Ø Rainska 2007		Ø Menezes 2004a Rainska 2005	
Zn	▲ Garland 1996 Martin Moreno 2003 Park JS 2016	♂ Campos 2008 Gonzalez 2008				▲ Park JS 2016 ♀ Sureda 2017	▲ Campos 2008	▲ Park JS 2016		▲ Willhelm 1991 Nouri 2008 Were 2009 Ndilila 2014 Mohmand 2015	▲ Rainska 2005 Ndilila 2014	▲ McKenzie 1979	
	Ø Nouri 2008 Campos 2008 Gonzalez 2008 Hashemian 2017	Ø McKenzie 1978 Rakovic 1997 Przybylowicz 2012 Park JS 2016 Hashemian 2017 Meramat 2017 Sureda 2017	Ø Gonzalez 2008	Ø Vincetti 2015 Park JS 2016 Hashemian 2017		Ø Hashemian 2017	Ø Martin Moreno 2003 Park JS 2016	Ø Hashemian 2017	Ø McKenzie 1978 Chanpiwat 2015			Ø Rakovic 1997 Rainska 2005	
	▼ Rakovic 1997 Coelho 2014	♀ Bergomi 2002 Rainska 2007 Lee 2016	▼ *Afroamerican* Park JS 2016					▼ Martin Moreno 2003					

▲: Positive; Ø: No association; ▼: Negative; BMI: body max index; Socioecon: socioeconomic; exp: exposure; ♀: women; ♂: men.

Lipsky et al., 2004; Morris, 2001; Morris et al., 2006; Swanson et al., 1990; van den Brandt et al., 1993; Xun et al., 2010b), or lower levels in elder individuals (Garland et al., 1995; Park and Seo, 2016; Hunter et al., 1990b; Jang et al., 2017; Park et al., 2011; Żukowska et al., 2009). Toenail concentrations of V were also inversely associated with age (Masironi et al., 1976; Rakovic et al., 1997; Slotnick et al., 2005) and a similar result was reported in the only study evaluating Co and Fe (Rakovic et al., 1997). The effect of age was inconsistent for Cu, Mo, Mn and Zn.

Sex: Women generally had higher toenail Se concentrations than men (Lee et al., 2016; Baskett et al., 2001; Xun et al., 2010a; Rainska et al., 2007; Morris, 2001; Morris et al., 2006; Swanson et al., 1990; van den Brandt et al., 1993; Xun et al., 2010b; Żukowska et al., 2009). For Cu, Mo, Mn and V, the studies showed either higher levels in women (Coelho et al., 2014; Rakovic et al., 1997; Slotnick et al., 2005) or no variation by sex (Masironi et al., 1976; McKenzie et al., 1978; Reis et al., 2015). Fe levels were similar in both sexes (Sureda et al., 2017; Rakovic et al., 1997). For Zn, the available data showed very inconsistent results, with some reports finding no differences by sex (Park and Seo, 2016; Meramat et al., 2017; Przybylowicz et al., 2012; Sureda et al., 2017; Hashemian et al., 2017; Rakovic et al., 1997; McKenzie et al., 1978), while others showed higher concentrations either in women (Lee et al., 2016; Rainska et al., 2007; Bergomi et al., 2002) or in men (Campos et al., 2008; Gonzalez et al., 2008). Cobalt was the only metal for which levels were consistently higher in men (Sureda et al., 2017; Rakovic et al., 1997; Slotnick et al., 2005).

Differences by **race/ethnic group** have been evaluated for Mn and

Se in a few papers. White people usually had higher toenail levels of Mn than other groups (Mordukhovich et al., 2012; Laohaudomchok et al., 2011); for Se, in some studies, levels were found to be higher in whites (Everson et al., 2017; Kristal et al., 2014), while other studies found lower concentrations in African-Americans (Colangelo et al., 2014; Kristal et al., 2014; Xun et al., 2010b, 2011). One study did not find any differences with respect to ethnicity (Satia et al., 2006).

The influence of **body mass index** (BMI) was studied only for Se, Zn and Fe. Neither Se (Kardinaal et al., 1997; Colangelo et al., 2014; Ovaskainen et al., 1993; Satia et al., 2006; Hashemian et al., 2017; Kristal et al., 2014; Lipsky et al., 2004; Morris et al., 2006; van den Brandt et al., 1993; Hunter et al., 1990b), nor Zn (Hashemian et al., 2017; Park et al., 2016; Vinceti et al., 2015) varied with this factor, while one study reported a positive link between Fe in female toenails and BMI (Garland et al., 1996).

Only a few studies evaluated the effect of **reproductive factors**, showing that parity may be positively associated with toenail Mn (Rodrigues et al., 2015) and Se concentrations (van Noord et al., 1993), while a later age at first birth may be associated to lower Fe levels (Garland et al., 1996). An older age at menarche was found to be associated with higher Se concentrations (Hunter et al., 1990a), but menopause did not modify levels of this element in toenails (Krogh et al., 2003).

3.7.2. Non-dietary lifestyle & social factors (Table 2)

Educational level was positively correlated with higher Se concentrations (Colangelo et al., 2014; Xun et al., 2010a, 2011; Rayman

et al., 2015), while both higher education and **monthly income** were also associated with higher Mn content (Rodrigues et al., 2015). The relationship between educational level and toenail Zn levels was inconsistent (Park and Seo, 2016; Hashemian et al., 2017; Martin-Moreno et al., 2003).

Twenty out of twenty-four studies found an inverse relationship between **tobacco consumption** and toenail Se (Garland et al., 1995; Ghadirian et al., 2000; Kardinaal et al., 1997; Colangelo et al., 2014; Krogh et al., 2003; Emmanuelle et al., 2012; Hunter et al., 1990a; Xun et al., 2010a; Satia et al., 2006; Morris, 2001; Morris et al., 2006; Swanson et al., 1990; van den Brandt et al., 1993; Xun et al., 2010b; Hunter et al., 1990b; Park et al., 2011; Żukowska et al., 2009; Xun et al., 2011; van Noord et al., 1993; Virtanen et al., 1996), with a dose-response relationship reported in three of them (Kardinaal et al., 1997; van den Brandt et al., 1993; Hunter et al., 1990b). Smoking, however, seemed to be not related to toenail Mn (Wongwit et al., 2004; Grashow et al., 2014; Ward et al., 2017) or Zn concentrations (Park et al., 2016; Martin-Moreno et al., 2003), although results were not homogeneous (Campos et al., 2008; Coelho et al., 2014; Rakovic et al., 1997).

Sureda et al. reported higher levels of Co, Fe and Zn with **physical activity** only in elderly women (Sureda et al., 2017). However, this factor was not related to toenail Se (Sureda et al., 2017; Satia et al., 2006; Hashemian et al., 2017; Xun et al., 2010b).

3.7.3. Other environmental factors (Table 2)

With the aim of using toenail levels of trace metals as biomarkers of exposure, several authors evaluated the relationship between toenail trace metals levels and the diverse possible sources of environmental exposure.

Most of the metals showed variations according to **dwelling place** (Co (Chanpiwat et al., 2015), Cu (Chanpiwat et al., 2015; Ndilila et al., 2014; Mohmand et al., 2015); Fe [71,93,105]; Mo (Nouri et al., 2008); Mn [35,55,76,93,107]; Se (Colangelo et al., 2014; Steven Morris et al., 1983; Michaud et al., 2002; Emmanuelle et al., 2012; Ndilila et al., 2014; Hashemian et al., 2017; Morris et al., 2006; Xun et al., 2010b, 2011; Hunter et al., 1990b; Park et al., 2011; Yoshizawa et al., 1998) and Zn (Wilhelm et al., 1991; Ndilila et al., 2014; Mohmand et al., 2015; Were et al., 2009; Nouri et al., 2008). In this sense, **living in high-polluted areas or near industries or mines** was associated with higher levels of some essential trace elements such as Co (Chanpiwat et al., 2015), Mn (Sanders et al., 2014; Coelho et al., 2012, 2014) or Zn (Ndilila et al., 2014). In contrast, these exposures did not seem to be related to Cu, Fe, Se or V toenail concentrations (Rainska et al., 2007; Coelho et al., 2014; Reis et al., 2015).

Toenail Se was also related with the distribution of Se in **forage crops** (Hunter et al., 1990b) and **soils** (Morris et al., 2006). In 2012, after a period of Se soil fortification in Finland, an increase in toenail Se levels was observed (Michaud et al., 2002). Soil Cu concentrations were also positively associated with the toenail levels of this metal (Ndilila et al., 2014).

Some projects reported that trace metal concentrations in **indoor dust** could be important contributors to toenail levels of Co (Ndilila et al., 2014), Mn (Reis et al., 2015), Mo (Rakovic et al., 1997) and Zn (Ndilila et al., 2014; Rainska et al., 2005), while other studies reported consistent associations between Cu, Fe, Mo, Mn and Se in **drinking water** and in toenails (Ntihabose et al., 2017; Chanpiwat et al., 2015; Emmanuelle et al., 2012; Ndilila et al., 2014; Rodrigues et al., 2015; McKenzie et al., 1978; Reis et al., 2015). However, for Zn (Chanpiwat et al., 2015; McKenzie et al., 1978) and Co (Chanpiwat et al., 2015; Ndilila et al., 2014), results were inconsistent.

The role of **occupation** as a source of exposure has been assessed in several studies. In this case, the metal that received more attention was

Mn, and the research was focused especially, but not only, on welders and boilermakers (Laohaudomchok et al., 2011; Grashow et al., 2014; Ward et al., 2017; Hassani et al., 2016; Coelho et al., 2012, 2014; Menezes et al., 2004a). Toenail Mn levels reflected exposure that occurred 7–12 months before clipping collection (Laohaudomchok et al., 2011; Grashow et al., 2014; Ward et al., 2017) and were correlated with the number of welding hours (Grashow et al., 2014) and with respirable airborne Mn concentrations (Ward et al., 2017). However, no differences were observed with respect to the type of personal protection equipment employed by workers (Wongwit et al., 2004). The consistent results obtained have led some authors to try to define threshold levels to identify the workers with excessive exposures (Ward et al., 2017). For the other metals, data were obtained from a few number of studies: one on workers of a phosphate fertilizer plant (Raińska et al., 2005), two on galvanizing companies (McKenzie, 1979; Menezes et al., 2004a, 2004b), another on tungsten-tin miners (Coelho et al., 2014) and another two on mixed (Sabbioni et al., 1994) or non-specified workers (Rakovic et al., 1997). Exposed workers showed higher levels of Cu (Raińska et al., 2005; Menezes et al., 2004b) and Fe (Rakovic et al., 1997), no association for Co (Rainska et al., 2007; Rakovic et al., 1997; Raińska et al., 2005; Menezes et al., 2004b), Se (Coelho et al., 2014), or V (Raińska et al., 2005; Menezes et al., 2004b) and contradictory results for Mo (Rakovic et al., 1997; Raińska et al., 2005) and Zn (McKenzie, 1979; Rakovic et al., 1997; Raińska et al., 2005).

3.7.4. Supplements, foods and nutrients (Table 3)

The role of toenails as biomarker of **supplements** intake has been explored for several essential elements, especially for selenium. The use of Se supplements significantly increased toenail Se levels (Garland et al., 1995; Baskett et al., 1995, 1998; Brockman et al., 2009; Ovaskainen et al., 1993; Guthrie et al., 2008; Satia et al., 2006; Kristal et al., 2014; Morris, 2001; Morris et al., 2006; Xun et al., 2010b; Hunter et al., 1990b; Park et al., 2011; Żukowska et al., 2009; Yoshizawa et al., 1998). Both organic and inorganic supplementation had a positive effect on toenail levels (Ovaskainen et al., 1993), with a dose-response effect (Hunter et al., 1990b). Supplement intake explained most of the variation and was the strongest predictor of toenail Se concentrations among supplements users (Ovaskainen et al., 1993; Satia et al., 2006). In contrast, toenail levels of Cu, Mn and Zn were unaffected by supplement use (Brockman et al., 2009; Guthrie et al., 2008; Gonzalez et al., 2008; Milunsky et al., 1992).

Regarding the **dietary intake of essential metals**, some authors compared the estimated exposure to Co, Mn, Se and Zn through diet with the corresponding levels in toenails. This intake was estimated by different methods, including food frequency questionnaires (FFQs), inventories with interviews and collection of diet composites. The most studied element was Se, with half of the reports showing a direct relationship of toenail levels with global Se intake (Longnecker et al., 1993; Morris and Crane, 2013; Ovaskainen et al., 1993; Longnecker et al., 1991; Swanson et al., 1990; van den Brandt et al., 1993; Longnecker et al., 1996) and the other half reporting no association (Satia et al., 2006; Hashemian et al., 2017; Morris et al., 2006; Hunter et al., 1990b; Vinceti et al., 2015; Kotsopoulos et al., 2010). For the other three metals, most of the reports did not show a good correlation between dietary intake and toenail levels. A number of studies also provided data on the relationship between toenail trace metals and specific **foods or nutrients** (Table 3).

The information obtained through this review suggests that there is a severe publication bias in this area, with many reports providing only the results for those nutrients with significant associations, without including the results corresponding to foods that do not appear to have a relationship with the studied metal in the report or in supplementary

Table 3
Studies (Author year) reporting association of toenail essential trace metals to supplements, foods or nutrients.

	Cobalt (Co)	Copper (Cu)		Iron (Fe)		Manganese (Mn)	Molybdenum (Mo)	Selenium (Se)			Vanadium (V)	Zinc (Zn)		
	▲	▲	Ø	▼	▲	Ø	▲	▲	Ø	▼	▲	▲	Ø	▼
Oral supplements			Brockman 2009			Guthrie 2007,2008		Hunter 1990a Baskett 1995,1998, 2001 Ovaskainen 1993a Garland 1995 Yoshizawa 1998 Morris 2001, 2006 Satia 2006 Guthrie 2008 Brockman 2009 Zukowska 2009 Xun 2010a Park 2011c Kristal 2014				Milunsky 1992 Gonzalez 2008 Brockman 2009		
Total diet Estimation			Graham 1991	Ntihabose 2017		Laohaudomchok 2011 Ward 2017		Swanson 1990b Longnecker 1991 1993, 1996 Van der Brandt 1993b Ovaskainen 1993a Morris 2013	Hunter 1990a Morris 2006 Satia 2006 Kotsopoulos 2010 Vinceti 2015 Hashemian 2017		Gonzalez 2008	McKenzie 1979 Milunsky 1992 Graham 2001		
Individual foods/groups														
Breads (including cake, muffins & others)								Park 2011c						
White Rice										Park 2011c				
Vegetable intake									Hashemian 2017			Hashemian 2017	Gonzalez 2008	
Fruit Intake									Hashemian 2017			Hashemian 2017		
Tomato products									Yoshizawa 1998					
Seafood									Rayman 2015d			McKenzie 1979		
Meat & poultry									Rayman 2015d					
Beef								Park 2011c						
Offal(Liver)														
Eggs									Rayman 2015d	Park 2011c				
Dairy products									Rayman 2015d	Park 2011c				
Milk									Rayman 2015d					
Brazil nuts									Rayman 2015d					
Coffee										Virtanen 1996 Park 2011c				
Tea						Wongwit 2004								

	Cobalt (Co)	Copper (Cu)		Iron (Fe)		Manganese (Mn)	Molybdenum (Mo)	Selenium (Se)			Vanadium (V)	Zinc (Zn)		
	▲	▲	Ø	▼	▲	Ø	▲	▲	Ø	▼	▲	▲	Ø	▼
Alcohol consumption	Rakovic 1997	Garland 1996				Wongwit 2004	Rakovic 1997		Hunter 1990a Garland 1995 Ovaskainen 1993a Van der Brandt 1993b Kardinaal 1997 Satia 2006	Van't Veer 1996 Xun 2010 a,b, 2011 Park 2011c Colangelo 2014	Rakovic 1997	Park JS 2016	Martin Moreno 2003 Gonzalez 2008	
Nutrients														
Vitamin C								Xun 2010b						
Vitamin E								Ovaskainen 1993a Xun 2010b	Kaardinal 1997 Yoshizawa 1998					
Zinc								Xun 2010b				Gonzalez 2008		
Iron													Gonzalez 2008	
Magnesium											Park JS 2016			
Folic acid								Xun 2010b						
Riboflavin												Bergomi 2005		
Retinol												Bergomi 2005		
β- carotene								Ovaskainen 1993a Xun 2010b	Kaardinal 1997					
Lycopene									Yoshizawa 1998					
Calcium									Yoshizawa 1998					
Fiber												Gonzalez 2008		
Saturated fat									Yoshizawa 1998					
Polyunsaturated fatty acids								Ovaskainen 1993a						
Cholesterol		Bergomi 2005										Bergomi 2005		
Animal proteins					Bergomi 2005							Bergomi 2005	Gonzalez 2008	
Total energy intake								Van der Brandt 1993b		Ovaskainen 1993a		Park JS 2016		
Others														
Dietary mercury								Ovaskainen 1993a						

▲ : Positive; Ø: No association; ▼: Negative.
[a] Ovaskainen 1993 excluded 2 due to Se>1.0mg/kg
[b] Estimated by analysis of duplicate-plate foods
[c] 131 items grouped into 21 categories were assesssed in the food frequency questionnaire but only those shown in this table were reported
[d] Non significant after adjusment

material. According to the available information, toenail Se levels seemed to be positively associated with beef, bread, vitamin C, zinc, folic acid, β-carotene, polyunsaturated fatty acids and dietary mercury intake (Ovaskainen et al., 1993; Xun et al., 2010a; Park et al., 2011), while rice and coffee (Park et al., 2011; Virtanen et al., 1996) were related to lower toenail Se concentrations.

The association of Se with eggs, dairy products, vitamin E and total energy intake was inconsistent among studies (Kardinaal et al., 1997; Ovaskainen et al., 1993; Xun et al., 2010a; Rayman et al., 2015; van den Brandt et al., 1993; Park et al., 2011; Yoshizawa et al., 1998). Regarding other essential elements (Zn, Mn, Cu), most studies found no association with dietary variables (Graham et al., 1991;

Laohaudomchok et al., 2011; Ward et al., 2017; McKenzie et al., 1978; Milunsky et al., 1992); however, the intake of Zn, Mg, riboflavin, retinol, fiber and cholesterol was positively associated with toenail Zn levels in three studies (Gonzalez et al., 2008; Park et al., 2016; Bergomi et al., 2005), while the evidence for a correlation with animal proteins intake was inconsistent (Gonzalez et al., 2008; Bergomi et al., 2005).

Alcoholic beverages (Table 3) did not modify Zn toenail levels (Gonzalez et al., 2008; Martin-Moreno et al., 2003). For Se, the published data revealed no association (Garland et al., 1995; Kardinaal et al., 1997; Ovaskainen et al., 1993; Satia et al., 2006; van den Brandt et al., 1993; Hunter et al., 1990b) or a negative relationship with this risk factor (Colangelo et al., 2014; Xun et al., 2010a; Xun et al., 2010b; Park et al., 2011; Xun et al., 2011; van 't Veer et al., 1996). Positive associations were reported with Co, Cu, Mo and V (Garland et al., 1996; Rakovic et al., 1997).

4. Discussion

In this systematic review, we presented a comprehensive picture of the available evidence on the role of toenails as biological matrices of exposure to essential trace metals. In addition, we tabulated and homogenized published quantitative levels of essential trace metals measured in toenails in the literature, allowing for future comparisons among studies. Finally, we presented a synopsis of the evidence on factors and sources that may be associated with the concentrations of these elements in this matrix.

Toenails are gaining attention because of their indubitable logistical advantages for large epidemiological studies and because they are supposed to represent longer-term exposures compared with other biomarkers, which is an essential feature to study the involvement of certain agents in chronic diseases. Although toenails share many characteristics with fingernails, they have specific advantages that make them more desirable as a biomarker of exposure. Toenails' rate of growth is slower; thus, compared with fingernails, toenails can reflect exposures that occurred further in the past. In addition, toenails are less frequently polished with nail varnish than fingernails and participants, especially females, may be less reticent to provide a sample. Some authors (Karagas et al., 2000) consider toenails to have a lower chance of exposure to external contamination, although in any case, both toenails and fingernails need to be pretreated and cleaned before being analyzed.

Another related sample is hair, as both biological matrices have a similar composition. However, in contrast to toenails, hair is frequently altered by cosmetic procedures such as dyeing, bleaching and permanent waving, which are known to modify hair content (Cuypers and Flanagan, 2018). The moment of exposure that is explored by hair samples is also difficult to standardize since it depends on the distance from scalp, and baldness may limit the study of elder men. In contrast, there is certified reference material for hair, which is used by many laboratories for nails.

The reason why toenails have been proposed as biological matrix to evaluate past exposures is that, after binding to keratin proteins present in nails, the concentrations of the elements deposited in them seem to remain stable in time, independent of changes in metabolic activities (Hopps, 1977; Sukumar, 2006). In this case, the researchers estimate that the levels of selected metals (i.e., Mn or Se) measured in toenail clippings reflect the exposure that occurred 6–12 months earlier, a time-window of exposure congruent with the estimated time required by toenails to grow (Yaemsiri et al., 2010). However, there is another critical issue: the use of toenails as a proxy for maintained exposures, implies that point measurements of the studied metals have to correlate well with ulterior determinations of the same element in the same individual. Our review shows that the stability of toenail levels of essential trace metals over time was examined in a few number of studies, which found that for some metals (i.e., Se and Zn), there was a good correlation among measurements even after years. However, for other

elements (i.e., Fe, Mg, Mn, Co, Cu), intraindividual correlations coefficients were moderate or low, and obtained from a single study; in a third group (i.e., Mo and V), it has not been investigated. Thus, available information support the findings that for some essential metals, toenails may be a good biological matrix to measure long-term exposure, although data on this issue are scarce for other metals. Direct extrapolation of findings for one element to other elements might be risky; it implies that differences in the internal metabolism among trace elements do not play any role in their arrival and deposition in toenails. In fact, homeostasis of each essential trace element is tightly and specifically regulated because of their relevance in the organism, and this regulation may modify the relationship between exposure and the biomarker, making it more difficult to interpret.

It is also of interest to investigate the relationship of essential trace elements in toenails with their level in other commonly used biomarkers of exposure in the same individual. All but two studies showed non-significant correlations between levels in toenails and urine, suggesting either different exposure time-windows for both biospecimens or different metabolic pathways involved in the arrival of these elements to the kidney and toenail matrix. The correlation of whole blood, plasma and serum with toenails has only been assessed in a few studies, and the association was only consistent for Se. Not many reports have compared trace element concentrations in toenails with those in hair and fingernails. Surprisingly, correlations with hair or fingernail levels were also low to moderate; we expected them to be higher owing to the shared characteristics among these substrates (i.e., skin appendages with slow growth and similar composition) and their common use as long-term exposure biomarkers.

We were also interested in understanding whether toenails reflected external exposures and the sources that might be explored with them. It is noteworthy that for this substrate, there is great variability of concentrations among studies, suggesting that differences in external environmental exposures may have been reflected. In this case, because we evaluated essential elements for humans, we presumed that the diet was probably the main source of exposure in the general population. However, our review showed that mostly there was no evidence supporting a direct correlation between metal dietary intake estimates and corresponding levels in toenails; even for Se, the most frequently studied trace element, the results were quite conflicting, with half of the studies reporting no association between estimated global intake and toenail concentration. It should be noted that in many cases, dietary intake was estimated with FFQs, which are have known limitations as a tool to assess exposure to trace elements. FFQ-based individual micronutrient intake estimates have a high level of uncertainty; in addition to the possible inaccuracy of diet recording due to recall bias, such estimates are calculated with the help of food composition tables, which, in many cases, are standard and may not represent the real exposure in local settings.

In contrast, the relationship between the intake of supplements of Se and toenail concentration was very consistent, probably due to the high doses of the element in the supplements. For other elements (Zn, Mn, Cu), oral supplements were not related to toenail levels; however, there were no data for Fe, another element usually administered in supplements.

Regarding individual foods, it is difficult to review available evidence because of the obvious selective publication bias. A good example of this is the report of Park et al. on the determinants of toenail Se in NHS and NPFS participants (Park et al., 2011). The authors explain that they correlated toenail levels of this element with 21 food groups, but they only provide results for seven of them. Another limitation of assessing associations with many individual food items separately is that some associations will yield significant results just by chance (multiple comparisons).

Many exposures are related to the place of people's residence and our data indicate that the dwelling place was a factor substantially affecting toenail metal concentrations. Indoor dust, which is closely

related to environmental exposure, was also described as a non-negligible source of exposure for some metals (Co, Mn, Zn). Similarly, drinking water, which is related to the geographical area, represented an important source for some metals (Co, Cu, Fe, Mn, Se) in environments with high exposure levels. Finally, several studies showed that living near mining areas or in polluted regions significantly increased exposure to certain trace elements (Co, Mn, Zn). Based on these findings, it is of great importance that future studies consider the influence of geographical area, especially in multicentric epidemiological investigations.

Occupation is another important source of exposure to metals, which can occur through inhalation, ingestion or dermal absorption (Elder et al., 2015). However, its relevance and presence in the published literature seem less obvious in this subgroup of essential elements than for toxic metals such as Cd or As. However, workers are also exposed to these agents during specific industrial procedures and thus, occupation needs to be considered as a source of exposure to essential elements. The most studied metal in this field has been Mn and some authors have even tested the use of toenails to monitor exposure to Mn.

We also assessed the association of personal (age, sex, ethnicity, BMI) and socioeconomic and non-dietary lifestyle-related factors with metal levels. Age is one of the main factors that could modify toenail metal levels; for example, some studies suggested that age could change the rate of incorporation of elements such as Se into toenails, but also that differences between younger and elder people could reflect age-related variations in the total amount of the element in the body (Hunter et al., 1990b). Sex differences may also occur due to hormonal regulation and variations by race may be due to changes in enzyme activity. However, age, sex, ethnicity and BMI may also be associated to unidentified exposure patterns or confounders. In general, we did not identify any specific predictors of essential metals in toenails, with some exceptions (i.e., higher levels of Se in women, or inverse association with age for V). Of special interest is the inverse relationship between Se and tobacco use, which seems to be relatively consistent based on several reports and this relationship is consistent with the already described association between smoking and circulating selenium concentrations (Ellingsen et al., 2009).

In real world, mixed exposures are the rule and not the exception. The correlation among levels of different metals in toenails was explored only in a few studies. Some essential trace elements (i.e., Se) correlated negatively with toxic agents (i.e., Cd or As), suggesting that they are interrelated and share or interfere in the absorption or availability of toxic agents. Other essential metals (Co, Cu, Fe, Mn, Zn) correlated both with non-toxic and toxic metals, indicating common sources of exposure (i.e., diet or environment).

Another point of interest pertains to the quality and methodological details of reports included in this review and to the methodological issues they reflect. Our search found that relevant information such as inclusion/exclusion criteria was not always provided in the reports, making comparisons among studies difficult. Moreover, although quality control procedures have improved over time, there is no standardized protocol on toenail preparation, analyses and report, which would be essential owing to the challenges that this biomarker presents. Among them, we would highlight the absence of certified reference material for this substrate, a problem that has been addressed with diverse strategies in different studies. In addition, cleaning procedures should be homogeneously performed, as they are essential to avoid external contamination, especially for metals derived from nail polish, which may contain trace elements such as B, Fe or Zn (Favaro et al., 2005), or other elements such as hafnium, which may interfere with metal concentrations (St-Pierre et al., 2006). In addition, important information, such as limits of detection, was absent in many reports.

Regarding the analytic technique, neutron activation analysis (NAA) and inductively coupled mass spectrometry (ICP-MS) were the most frequently used techniques. In general, ICP-MS was the preferred

technique for multi-elemental analysis, although NAA was also used to measure multiple metals. The validity of both techniques for detecting trace elements is well known; however, we did not find any study comparing their performance in toenails. As we previously mentioned, quantitative data on metal concentrations were most frequently reported using arithmetic means. However, the distribution of toenail metal concentration does not frequently follow a normal distribution and outliers are frequent. Consequently, geometric means or medians should be preferred when reporting results. Few studies reported the percentage of samples under LOD; probably, most samples had detectable levels of essential metals because of the low LOD that INAA and IPC-MS usually have, but if that were not the case, the lack of this information could impair the comparability among studies or affect the results. Another limitation was how LODs were determined, without giving a true indication of detectability, since the matrix effect is not being taken into account.

A relatively surprising finding was the general lack of information about sample mass, as it is known that the LOD and the metal concentrations in toenails are affected by sample size (Colangelo et al., 2014). Moreover, toenail type was frequently omitted, probably due to the assumption that metals are equally distributed in big and small toes. However, as their growth rate is different (Yaemsiri et al., 2010; Edwards and Schott, 1937), the time-windows represented by them is also different (Longnecker et al., 1991, 1993). Regarding which strategy would be better, we could state that using only big toes allows to explore a more defined and homogenous period of exposure; on the other hand, it is more probable to have a low amount of toenail mass available for the analyses. Notwithstanding, at least for Se, available research indicates that concentrations are similar among toes (Kok et al., 1989; Longnecker et al., 1993; van 't Veer et al., 1990). New investigations are needed to confirm if this statement applies to the other metals.

One of the main strengths of our review is its wide scope, which provides an overview of the existing information about the role of toenails as biological matrices of exposure to all essential metals. However, its major limitation is that the great heterogeneity of the studies, with respect to exposure or personal features of the subjects precluded any quantitative pooling of the results. Nevertheless, our tables intend to be useful instruments for those interested in investigating a specific metal, allowing anyone to easily locate all the studies that provide information in this context. Another limitation could be the exclusion of a number of studies that did not state the type of nail analyzed (i.e., fingernail or toenail), an issue that was not clarified by the corresponding authors after our request (see Fig. A1, flow diagram). In this case, we opted for being specific.

5. Conclusions

In summary, this review provided evidence on the role of toenails as biological matrices of exposure to essential metals. For some metals (Se, Mn, Zn), there is evidence that toenail metal concentrations can reflect long-term external exposures and the levels are reproducible, although for other elements, this information is unknown. There remain many uncertainties on the potential role of socioeconomic, lifestyle-related and other factors that affect the metal levels in toenails. Se levels can reflect exposure to certain foods or nutrients from diet or supplements and are modified by tobacco exposure; also Mn concentration can also indicate occupational exposure. Toenail levels of most of the essentials metals studied could also be affected by environmental factors such as pollution and the concentration of metals in soils or water, although reports are scarce for many trace elements. Standardization of sample collection, quality control, analytical techniques and reporting procedures might help boost research and better understand the implications of essential levels in this promising matrix, and would enhance the use of toenails in epidemiological research.

Conflicts of interest

None.

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CRediT authorship contribution statement

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-Baz:** Writing - original draft, Writing - review & editing. **Inmaculada Salcedo-Bellido:** Investigation, Methodology, Writing - review & editing. **Ana Navas-Acien:** Investigation, Methodology, Writing - review & editing. **Virginia Lope:** Writing - original draft, Writing - review & editing. **José Luis Gómez-Ariza:** Investigation, Methodology, Writing - review & editing. **Roberto Pastor:** Investigation, Methodology, Writing - review & editing. **Marina Pollán:** Investigation, Methodology, Writing - review & editing. **Beatriz Pérez-Gómez:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Validation, Visualization, Writing - review & editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2019.108787.

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