

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

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Table A.1: Systematic review on essential trace metals in toenails. Main characteristics of included research studies by research project and publication year

Note: all the reports of the same research study are presented together. The complete reference of the reports is listed at the end of this table.

Reference	Project	Metals	Study design	N° Participants	IC	EC	Other biomarkers	Toenail preparation	Toenail type	Analit. Method	LD	LQ	QQ	Main objective	Health effect	
van Stekelenburg-1975 Netherlands		Cu	Ca-Con	75	Patients with cystic fibrosis & healthy control children			Cleaned by scrapping debris, washed with acetone & deionized water, dried at 115°	NS	AAS				Health effects	Other	
Masironi-1976 Nueva Guinea		Cu Mn V	Cross	157	Families residing along Blackwater-Korosameri & Wogupmeri-Karawari river (high calcium content)			Washed in 3 % analytical grade hydrogen peroxide in absolute alcohol.	Big toes	NAA				Health effects	CV	
McKenzie-1978 New Zealand		Cu Zn	Cross	48	Polynesian adults resident in the Tokehau Islands (both sexes), diet with low content of animal protein		Hair Serum Urine	Mechanic cleaning, washed in detergent, rinsed in deionized water, EDTA & HNO ₃ - HClO ₄ digestion	NS	AAS				Health effects BM evaluation	CV Metab.	
McKenzie-1979 New Zealand		Zn	Cross	110	Healthy adults (not oyster eaters); oyster openers (& eaters), galvanizing workers (industrial exposure) & patients of accidents & several diseases		Hair Serum Urine	Mechanic cleaning washing in detergent, rinsed in deionized water ,EDTA & HNO ₃ - HClO ₄ digestion	NS	AAS				BM evaluation		
Morris-1983 USA		Se	Cross	62	Residents in high (South Dakota), intermediate (Boston, Georgia) & low (New Zealand) Se areas	Y	Blood Hair	Cleaned & rinsed with demineralized water	All toes	NAA			Y	BM evaluation		
Morita-1986 Japan		Fe Cu Zn	Cross	6	Renal disease patients in treatment with Germanium elixir and healthy persons.		Hair Fingernail	Washed, dried	NS	ICP-AES			Y	Health effects	Other	
Kok-1989 Netherlands		Se	Ca-Con	168	Acute myocardial infarction cases and age-sex matched healthy controls (<75 yrs)		Erythrocytes Plasma	Cleaned by scraping off any debris.	All toes	NAA			Y	Health effects BM evaluation	CV Metab.	
Hunter -1990a USA	NHS I	Se	Cross	715	Age-region matched Se supplement users & non users; cancer free NHS I subsample			Cleaned by sonication in distilled water & acetone	All toes	NAA			Y	BM evaluation		
Hunter – 1990b USA		Se	N ca-con	868	Incident breast cancer female cases & age-matched controls in NHSI cohort (30-55 yrs).			Cleaned by sonication in distilled water & acetone	All toes	NAA				Health effects	Cancer	
Garland -1993 USA		Co Cu Fe Se Zn	Coh	127	Sub-sample of Hunter 1990a			Cleaned by sonication in deionized water	All toes	INAA				BM evaluation		
Garland -1995 USA		Se	N ca-con	1960	Incident cancer female cases & age-matched controls in NHSI cohort (30-55 years).			Cleaned by sonication in deionized water	All toes	INAA				Health effects	Cancer	
Garland -1996 USA		Cu Fe Zn	N ca-con	892	Hunter 1990a breast cancer cases & control participants			Cleaned by sonication in deionized water	All toes	INAA				Health effects	Cancer	
van't Veer-1990 Netherlands		Se	Ca-Con	372	Breast cancer cases & controls (25-44 or 55-64 yrs)		Erythrocytes Plasma		All toes	INAA			Y	Health effects	Cancer	
Swanson -1990 USA	Se	Cross	44	Adults residing in Wyoming & South Dakota (high Se area) & in South Dakota ranches with selenosis in livestock	Y	Y	Blood Serum	Cleaned	All toes	NAA			Y	BM evaluation		
Longnecker-1991 USA	SOUTH DAKOTA	Se	Cross	142	Swanson -1990 participants + new set of highly exposed residents of these areas	Y	Y	Blood Serum Urine	Cleaned with ultrasound in a bath of distilled water	All toes	NAA			Y	Health effects	Metab. Other
Longnecker-1996 USA		Se	Cross	77	Subsample of Longnecker 1991			Blood Serum Urine	Cleaned with ultrasound in distilled water	All toes	NAA			Y	BM evaluation	
Graham-1991 USA	MACS cohort	Cu Zn	N ca-con	162	Homosexual men (HIV-, HIV+ with & without AIDS)		Serum	Cleaned by sonication in distilled water & acetone	NS	TNF				Health effects	Other	
Wilhelm-1991 Germany	Duisgurg/ Westfalen children	Cu Zn	Cross	461	Children (3-7 yrs) living in a polluted industrial area (Duisburg) and a rural area (Westfalen)		Hair	Mechanic washing in Triton solution, distilled water, acetone /methanol, digested with HNO ₃	All toes	AAS			Y	BM evaluation		
Wilhelm-1994 Germany		Cu Zn	Coh	47	Children of Wilhelm-1991 & their parents two years later.		Hair	Washed in Triton solution, bidistilled water & acetone/methanol, digested with HNO ₃	All toes	AAS			Y	BM evaluation		

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Rogers-1991 USA		Se Zn	Ca-Con	893	Oral cavity cancer cases & age-gender frequency-matched controls 20 -74 years			Cleaned in an ultrasonic bath using reagent grade deionized water.	Big toes	INAA				Health effects	Cancer
Rogers-1993 USA		Fe Zn Co	Ca-Con	893	Participants of Rogers 1991 & laryngeal & e esophageal cancer cases			Cleaned in an ultrasonic bath using reagent grade deionized water.	Big toes	INAA				Health effects	Cancer
Alfthan-1992 Hungary		Se	Cross	132	Hungarian blood donors (both sexes, 10-61 yrs)		Blood Fingernails	Cleaned with sodium dodecyl-sulfate, ultrasonicated & rinsed with purified water.	All toes	ADF			Y	BM evaluation	
Milunsky -1992 USA		Zn	Ca-Con	1804	Women at 15-20 weeks gestation who delivered a baby with neural tube defect & mothers of healthy babies matched by maternal age & delivery year			Acetone, cleaned with HNO ₃ solution, rinsed with deionized water	NS	INAA				Health effects	Other
Longnecker-1993 USA		Se	Clinical trial	12	Non-smoking healthy white males aged 22-64 years, who were given enriched Se bread		Y Blood Serum	Cleaned with ultrasound in distilled water	Big toe Other toes	NAA				BM evaluation	
van den Brandt-1993a Netherlands	NETHERLANDS COHORT	Se	Ca-coh	2829	Incident lung cancer cases & control sub-cohort (56-69 yrs)			Ultrasonic cleaning with acetone, distilled water	All toes	INAA			Y	Health effects	Cancer
van den Brandt-1993b Netherlands		Se	Ca-coh	2910	Incident stomach & colorectal cancer cases & control sub-cohort (56-69 yrs)			Ultrasonic cleaning with acetone, distilled water,	All toes	INAA			Y	Health effects	Cancer
van den Brandt-1993c Netherlands		Se	Cross	2459	Control sub-cohort of van den Brandt-1993b			Ultrasonic cleaning with acetone, distilled water.	All toes	INAA			Y	BM evaluation	
van den Brandt-1994 Netherlands		Se	Ca-coh	1603	Incident breast cancer cases & female control sub-cohort (56-69 yrs)			Ultrasonic cleaning with acetone, distilled water	All toes	INAA			Y	Health effects	Cancer
Zeegers-2002 Netherlands		Se	Ca-coh	2890	Incident bladder cancer cases & control sub-cohort of van den Brandt-1993a			Ultrasonic cleaning with acetone, distilled water	All toes	INAA			Y	Health effects	Cancer
van den Brandt-2003 Netherlands		Se	Ca-coh	1751	Incident prostate cancer cases & male control sub-cohort of van den Brandt-1993a			Ultrasonic cleaning with acetone, distilled water	All toes	INAA			Y	Health effects	Cancer
Geybels-2013 Netherlands		Se	Ca-coh	2074	Advanced prostate cancer cases & male control sub-cohort of van den Brandt-1993a		Y Y	Ultrasonic cleaning with acetone, distilled water	All toes	NAA			Y	Health effects	Cancer
Geybels -2014 Netherlands		Se	Ca-coh	1865	Participants of Geybels 2013 with genotyping data		Y Y	Ultrasonic cleaning with acetone, distilled water	All toes	NAA			Y	Health effects	Cancer
Maasland-2016 Netherlands		Se	Ca-coh	2458	Incident head and neck cancer cases & control sub-cohort of van den Brandt-1993a		Y Y	Ultrasonic cleaning with acetone, distilled water	All toes	NAA			Y	Health effects	Cancer
van Noord-1993 Netherlands		DOM project	Se	N ca-con	414	Breast cancer cases, age-matched & randomly selected controls from screening cohort (55-70 yrs)			Ultrasound washing with acetone & demineralized water	Big toes	INAA				Health effects
Ovaskainen-1993 Finland		Se	Cross	166	Helsinki men 55-69 yrs (low selenium area)		Y	Washed (neutral detergent), 1% dodecyl sulphate, rinsed (purified water)	All toes	ADF			Y	BM evaluation	
Sabbioni -1994 Italy		Co	Cross	115	Subjects occupationally exposed to hard metal dusts, 15-65 yrs		Blood Pubic hair Urine	Washed with purified water, acetone & water again	NS	NAA			Y	BM evaluation	
Baskett -1995 USA	Missouri University Research Reactor study	Se	Coh	4	Subsample of Baskett 1998 (2 men and 2 women)		Fingernails	NS	All toes	INAA			Y	BM evaluation	
Baskett- 1998 USA		Se	Cross	11	11 Missouri University Research coworkers		Fingernails Whole blood Serum	NS	All toes	INAA				BM evaluation	
Baskett- 2001 USA		Se	Coh	11	Participants of Baskett 1998		Fingernails	NS	Big toes Other toes	INAA				BM evaluation	

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Vannucchi-1995 Brazil		Zn	Cross	81	Alcoholic adults with pellagra & healthy controls 21-54 yrs (both sexes)		Y Y	Hair Plasma Urine	Washed by the method of Reilly & Harrison, HNO ₃ digestion	NS	AAS			Health effects	Other
van't Veer-1996 5 European countries	EURAMIC	Se	Ca-Con	721	Postmenopausal breast cancer cases & age-region matched controls (50-75 yrs)		Y Y		Unspecified cleaning	All toes	INAA		Y	Health effects	Cancer
Virtanen -1996 8 Euro Countries+Israel		Se	Ca-Con	1025	Van't Veer female & Kardinaal 1997 male controls					All toes	INAA		Y	BM evaluation	
Kardinaal-1997 10Euro.Countries+Israel		Se	Ca-Con	1412	Men with a first acute myocardial infarction & controls < 70 yrs		Y Y			All toes	INAA		Y	Health effects	CV
Strain-1997 Northern Ireland		Se	Ca-Con	186	Irish postmenopausal breast cancer patients and age-matched healthy controls 50-75 yrs			Y	Cleaned	All toes	INAA		Y	Health effects	Cancer Other
Martin-Moreno-2003 8 Euro. Countries+Israel		Zn	Ca-Con	1408	Men with a first acute myocardial infarction & male controls of Kardinaal 1997		Y Y			All toes	INAA		Y	Health effects	CV Metab.
Rakovic-1997 Czech Republic			Co Cu Fe Mn Mo V Zn	Cross	262	Mixed group (Patients of the faculty hospital, pregnant women, retired persons, students) 13-89 years		Y	Scalp hair Pubic hair	Washed in acetone & deionized water	NS	INAA		Y	BM evaluation
Yoshizawa-1998 USA	HPFS	Se	N ca-con	181	Incident prostate cancer cases & age-smoking status matched controls (40 -75 yrs)		Y		Cleaned by sonication in deionized water	All toes	INAA			Health effects	Cancer
Rajpathak-2005 USA		Se	N ca-con	1247	Men with prevalent diabetes, men with prevalent diabetes & cardiovascular disease & age-smoking status matched controls (40 -75 yrs)		Y		Cleaned by sonication in deionized water	All toes	INAA			Health effects	CV
Ghadirian -2000 Canada	Canadian case-control study	Se	Ca-Con	1736	Incident breast (35-79 yr) , prostate (35-84 yr) & colon cancer patients + age-sex matched controls					Both feet	NAA			Health effects	Cancer
St-Pierre-2006 Canada		Se	Cross	87	Subsample of Ghadirian 2000				None or washed with Triton X-100 diluted 1/200 in Milli-Q deionized water, rinsed Milli-Q deionized water, acetone. Air-dried	Both feet	NAA			BM evaluation	
Helzlsouer-2000 USA	CLUE II	Se	N ca-con	350	Incident prostate cancer cases & age-race & recruitment date matched male controls >45 yrs		Y		Digested with HNO ₃ by using a microwave digestion system	Big toes	NAA			Health effects	Cancer
Platz-2002 USA		Zn	N ca-con	342	Incident prostate cancer cases, & controls of Helzlsouer-2000		Y		Digested with HNO ₃ by using a microwave digestion system	Big toes	AAS			Health effects	Cancer
Mannisto -2000 Finland	Kuopio Breast Cancer Study	Se	Ca-Con	722	Incident breast cancer cases & age-rurality matched controls		Y Y		Cleaned with 1% sodium dodecylsulphate for, then rinsed with demineralized water	All toes	ADF		Y	Health effects	Cancer
Aguiar- 2001 Brasil		Co Cu Fe Mn Se n	Cross	32	Cystic fibrosis and healthy children (1-12)			Fingernails	Scintillation flask with non-ionic detergent Triton X100 solution & mechanical shaking. Washed distilled water & acetone	NS	INAA			Health effects	Other
Morris 2001 Canada	Canadian Study of Diet Lifestyle & Health	Se	Cross	755	Alumni from the Universities of Alberta, Toronto, and Western Ontario and Canadian Cancer Society members.				Nail polish removed with acetone, sonicated in high-purity water, strained while rinsing with water & freeze-dried	NS	INAA		Y	BM evaluation	
Bergomi -2002 Italy		Co Cu Fe Mn Se Zn	Ca-Con	62	Incident amyotrophic lateral sclerosis cases & age-sex matched controls		Y Y		Washed with Triton solution in a sonicator & then with deionized water	NS	ICP-OES INAA		Y	Health effects	Other
Hartman-2002 Finland	α-Tocopherol β-Carotene Cancer Prevention Study	Se	N ca-con	500	Lung cancer cases & age, date & intervention group assignment matched controls				Cleaned with 1% sodium dodecylsulphate for, then rinsed with demineralized water	All toes	ADF		Y	Health effects	Cancer
Michaud -2002 Finland		Se	N ca-con	90	Male bladder cancer cases & age-treatment- date of recruitment matched controls in SouthWest Finland				Cleaned with 1% sodium dodecylsulphate for, then rinsed with demineralized water	All toes	ADF		Y	Health effects	Cancer

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Krogh-2003 Italy	ORDET	Se	Coh	80	Sub-sample of a cohort of Italian women to evaluate diet, hormones and breast cancer (pre & post-menopausal)			Acetone if nail polish. Sonicated in Triton X100 solution, deionized water, digestion with HNO ₃ in a microwave system	All toes	AAS	Y		Y	BM evaluation	
Vinceti-2015 Italy		Se	N ca-con	621	Incident female diabetes cases (type2) & age-matched control women (35-70) in ORDET cohort			Washed in high purity water, acetone, Triton using an ultrasonic bath	All toes	INAA			Y	Health effects	Metab.
Rayman-2003 United Kingdom		Se	Ca-Con	106	Pregnant women with early symptoms of preeclampsia and age, gestational age and parity matched controls			Placed in acid-washed beaker, washed with acetone and distilled deionized water in a sonic bath, dried.	All toes	INAA			Y	Health effects	Other
Menezes -2004a Brazil	Brazil galvanizing factory	Co Cu Fe Mn Zn	Cross	48	Workers in galvanizing factories & non-exposed subjects			Washed and dried	NS	INAA			Y	BM evaluation	
Menezes-2004b Brazil		Cu Fe	Cross	48	Participants of Menezes 2004a			Hair Urine	NS	INAA			Y	BM evaluation	
Lipsky-2004 Austria		Se	Ca-Con	150	Prostate cancer cases & consecutively recruited control urologic patients >45 yrs			Washing with ultrapure water, microwave assisted digestion with HNO ₃ & HClO ₄	NS	ICP-MS			Y	Health effects	Cancer
Wongwit-2004 Thailand		Mn	Cross	182	Welders working in a thermal plant in direct contact with Mn			Washed with acetone twice on a mechanical shaker, digested with HNO ₃	NS	AAS				BM evaluation	
Bergomi -2005 Italy	MELANOMA Case-Control study	Cu	Ca-Con	116	Incident melanoma cases & sex-age matched population based controls			Washed with Triton solution in a sonicator & then digested in HNO ₃ & deionized H ₂ O	NS	ICP-OES			Y	Health effects	Cancer
		Fe Se Zn							Washed with Triton solution in a sonicator		INAA				Cancer
Vinceti-2005 Italy		Cu	Ca-Con	116	Participants of Bergomi 2005			Washed in Triton solution, deionized water & HNO ₃ digestion.	Both feet	ICP-OES			Y	Health effects	Cancer
		Fe Se Zn							Cleaned with diethyl-ether, bidistilled water & acetone		INAA				
Vinceti-2012 Italy		Se	Ca-Con	105	Participants of Bergomi 2005			Cleaned with diethyl-ether, bi-distilled water & acetone	Right foot	INAA			Y	BM evaluation Health effects	Cancer
Musil -2005 Czech Republic		Se	Ca-Con	52	Acute pancreatitis & colorectal cancer cases and age-sex matched controls, 23-78 yrs			Erythrocytes Plasma	Big toes	NAA				Health effects	Cancer Other
Slotnick-2005 USA		Co Cu Mn Mo Se V	Cross	259	Arab-Americans adults and children residing in a highly industrialized area			Washing, rinsed with acetone, digested in HNO ₃	All toes	ICP-MS			Y	BM evaluation	
Rainska-2005 Poland		Co Cu Mn Mo V Zn	Cross	26	Workers in a phosphatic fertilizer plant & controls			Washed in acetone–water–water–water–acetone	NS	INAA			Y	BM evaluation	
Al-Saleh-2006 Arabia Saudi		Se	Cross	691	Subjects participating in a cross-sectional study about Se & vitamin status			Cleaned with detergent, rinsed with deionised water, digested with HNO ₃ , HCl	Big toes	AAS	Y		Y	BM evaluation	
Le Marchand-2006 USA		Se	Ca-Con	278	Caucasian melanoma cases 18-79 yrs & race-sex-age matched population based controls			Y Y Blood	NS	INAA				BM evaluation Health effects	Cancer
Morris-2006 USA		Se	Cross	3575	Volunteers living in 111 of Missouri's 114 counties			Y Fingernails	Freezed	NS	INAA			BM evaluation	
Satia-2006 USA	VITAL study	Se	Coh	220	Sub-sample of members of a cohort to research dietary supplement use and cancer risk			Y Plasma	Cleaned with ultrasound in a bath of distilled water	All toes	INAA			Y	BM evaluation
González-2008 USA		Zn	Cross	212	Participants of Satia 2006					All toes	INAA				BM evaluation
Rainska-2007 Poland		Co Cu Mn Fe Se V Zn	Cross	33	Subjects living near a fertilizer plant & controls			Hair	Washed in acetone–water–water–water–acetone+ultrasound bath	NS	INAA			Y	BM evaluation

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Guthrie-2007, 2008 USA	One source cohort study	Mn Se	Coh	126	Consumers of Multivitamin-mineral supplement (containing Se/Mn/Cu/Zn) & sex- age-bmi-smoking status matched controls (both sexes, volunteers)			Sonicated in HNO ₃ solution, decanted & sonicated in water, rinsed with milliQ-water	NS	INAA	Y		Y	BM evaluation	
Brockman-2009 USA		Cu Se Zn	Coh	126	Participants of Guthrie 2007			Sonicated in HNO ₃ solution, decanted & sonicated in water, rinsed with milliQ-water	NS	INAA	Y		Y	BM evaluation	
Campos -2008 Colombia		Zn	Ca-Con	443	Incident gastric cancer patients & hospital controls			Cleaned with neutral detergent & rinsed with deionized water, digested in HNO ₃	NS	ICP-MS			Y	Health effects	Cancer
Nouri-2008 Iran		Mo Zn	Ca-Con	100	Esophageal cancer patients, family members & matched controls of 2 areas with different risk			Cleaned with acetone, alcohol, & distilled water. HNO ₃ digestion	NS	AAS			Y	BM evaluation Health effects	Cancer
Goullé -2009 France		Co Cu Mn Mo Se V Zn	Cross	50	Healthy volunteers (both sexes)			Fingernails Washed with water, acetone decontamination, HNO ₃ digestion	NS	ICP-MS	Y			BM evaluation	
Were-2009 Kenya		Fe Zn	Cross	33	Children <6 yrs in urban & rural areas in Kenya			Fingernails Soaked in non-ionic liquid soap, acetone & rinsed in deionised distilled water. Digestion with HNO ₃	NS	AAS	Y		Y	BM evaluation	
Żukowska-2009 Poland		Se	Cross	336	Randomly selected inhabitants of Pomeranian District and from Lubuskie District.			Scratched with a quartz knife. Cleaned by acetone and deionized water plus ultrasonic bath & drying	All toes	INAA			Y	BM evaluation	
Kotsopoulos-2010 Canada		Se	Ca-Con	50	Female BRCA1 healthy mutation carriers and sex-matched non-carriers family members			Washed in Triton solution, rinsed with deionized water & acetone, drying.	NS	NAA				Health effects	Other
Xun -2010a USA	CARDIA trace element study cohort	Se	Coh	4032	American young adults (18–30 yrs) of 4 USA regions recruited for a cohort study on psychological and lifestyle CV risk factors in young adults			Washed with 10% HNO ₃ & deionized water, then rinsed	All toes	INAA			Y	Health effects	CV
Xun -2010b USA		Se	Coh	3112	Participants of Xun 2010a			Washed with 10% HNO ₃ & deionized water, then rinsed	All toes	INAA			Y	Health effects	Other
Xun -2011 USA		Se	Coh	4252	Participants of Xun 2010a			Washed in a sonicator with HNO ₃ & deionized water, then rinsed	All toes	INAA				BM evaluation	
Colangelo-2014 USA		Se	Coh	3735	Participants of Xun 2010a			Washing in a sonicator with deionized water	All toes	INAA				Health effects	Other
Park -2016a USA		Se Zn	Coh	3960	Participants of Xun 2010a free of diabetes at baseline			Washing in a sonicator with HNO ₃ & deionized water, then rinsed	All toes	ICP-MS				Health effects	Metab.
O'Doherty-2010 Ireland	FINBAR	Fe	Ca-Con	534	Esophageal adenocarcinoma cases, Barrett's esophagus patients & age-matched randomly selected controls			Washed with deionized water & 10% HNO ₃ using a sonicator	Big toes	INAA			Y	Health effects	Cancer Other
O'Rorke-2012 Ireland		Co Se Zn	Ca-Con	595	Participants of O'Doherty 2010 & reflux esophagitis patients			Washed with deionised water & 10% HNO ₃ using a sonicator	Big toes	INAA			Y	Health effects	Cancer Other
Laohaudomchok-2011 USA		Mn	Cross	49	Active & retired members of a boilermaker union & welder apprentices in Quincy with retrospectively constructed job-history (USA)			Washed in Triton X-100, rinsed repeatedly in Milli-Q water, digested in HNO ₃	All toes	ICP-MS				BM evaluation	
Grashow-2014 USA	Harvard Boilermakers Longitudinal Study	Mn	Coh	48	Participants of Laohaudomchok-2011			Sonicated in 1% Triton X-100, rinsed in Milli-Q water, dried, digested in HNO ₃	All toes	ICP-MS	Y		Y	BM evaluation	
Wong-2014 USA		Mn	Coh	87	Boilermakers, male, unionized apprentices or journeymen, > 18 yrs				All toes	ICP-MS			Y	Health effects	Other
Wong-2015 USA		Mn	Coh	25	Boilermakers, male, unionized apprentices or journeymen, >18 yrs				All toes	ICP-MS			Y	Health effects	CV

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Mozaffarian-2011 USA	NHS I + HPFS	Se	N ca-con	6854	Incident CV disease or stroke cases & age-race-smoking cohort matched control (dentist excluded)	Y	Y		Cleaned by sonication in deionized water	All toes	NAA			Health effect	CV	
Park-2011 USA		Se	Cross	3902	Mozaffarian 2011 controls				Cleaned by sonication in deionized water	All toes	NAA			BM evaluation		
Mozaffarian-2012 USA		Se	Coh	6045	Mozafarian 2011 participants (hypertension at toenail sampling excluded) + new set of controls	Y	Y		Cleaned by sonication in deionized water	All toes	NAA			Health effects	CV	
Park-2012 USA		Se	Coh	7165	Mozafarian 2011& 2012 participants (diabetes at toenail sampling excluded)		Y		Cleaned by sonication in deionized water	All toes	NAA			Health effects	Metab.	
Mozaffarian-2013 USA		Se	Coh	9267	Mozafarian 2011 & 2012 participants (diabetes at toenail sampling excluded)	Y	Y		Cleaned by sonication in deionized water	All toes	NAA			Health effects	Metab.	
Abdulrahman-2012 Nigeria		Cu Fe Mn Zn	Cross	NS	Assorted volunteers, including workers in an iron welder workshop, alcohol and non-alcohol drinkers			Hair Fingernails	Cleaned with Triton X-100, soaking in acetone & rinsed with deionized water, digestion with a mixture of HNO ₃ & HCl	NS	AAS		Y	BM evaluation		
Al-Sabbak-2012 Iraq		Co Cu Fe Mn Mo Se V Zn	Ca-Con	56	Parents of children with birth defects or of normal babies born in Al Basrah after 2003 invasion and bombing	Y		Hair Teeth	Washed, sonicated in acetone, rinsed several times in deionized water & acetone dried & then reconstituted in HNO ₃	NS	ICP-MS			BM evaluation		
Amaral-2012 Spain	PANKRAS EPICURO	Cu Fe Mn Se V Zn	Ca-Con	517	Pancreatic cancer cases & hospital-matched controls	Y	Y		HNO ₃ digestion, H ₂ O ₂ & deionized water	NS	ICP-MS		Y	Health effects	Cancer	
Coelho -2012 Portugal	Panasqueira Mine	Mn Se	Cross	102	Adult residents in the vicinity of Panasqueira tungsten-tin mine, male mine workers & age-sex-lifestyle and smoking matched non-exposed controls	Y	Y	Blood Fingernails Hair Urine	Mechanical cleaning, sonication with acetone, rinse with deionized water and oven-dried. Acid digestion with HNO ₃	NS	ICP-MS		Y	BM evaluation Health effects		
Coelho -2014 Portugal		Cu Fe Mn Mo Se Zn	Cross	122	Participants of Coelho -2012 & small number of new recruits in the three groups	Y	Y	Blood Fingernails Hair Urine	Acid digestion with closed vessel, microwave assisted, HNO ₃ addition.	NS	ICP-MS ICP-OES		Y	BM evaluation		
Emmanuelle -2012 France		Se	Coh	78	Residents in area with high levels of Se in drinking water & non-exposed subjects matched by age, sex and social status	Y	Y		Sonicated in a detergent & ultrapure water. Dried & digested with graphite heating block system, adding HNO ₃ & H ₂ O ₂	NS	ICP-MS	Y	Y	Y	BM evaluation	
Mordukhovich-2012 USA	NORMATIVE AGING	Mn	Cross	639	Male army veterans without any chronic condition at recruitment in 1963 providing toenail sample between 1999-2009	Y	Y		Sonicated in Triton-x solution, rinsed with distilled deionized water	All toes	ICP-MS	Y	Y	Health effects	CV	
Przybylowicz-2012 Poland		Co Cu Fe Zn	Cross	42	Healthy volunteers (both sexes)			Hair Fingernails	Washed in water, Triton X-100, methanol in ultrasonic bath. HNO ₃ digestion	NS	ICP-MS	Y	Y	Y	BM evaluation	
Anic 2013 USA		Fe	Ca-Con	600	Incident multiform glioblastoma or anaplastic astrocytoma cases & friends and other non-blood related controls	Y	Y		Immersed in 10% (v/v) HNO ₃ , sonicated, decanted, immersed in 18MΩ-cm water, sonicated & rinsed with 18MΩ-cm water	Big toes	INAA		Y	Health effects	Cancer	
Herman-2013 Poland		Cu	Cross	30	Healthy volunteers of both sexes from the urban areas of Krakow.			Hair Fingernails	Washed in distilled water, Triton X-100, CH ₃ OH in ultrasonic bath, dried. HNO ₃ digestion	NS	AAS	Y	Y	Y	BM evaluation	
Morris-2013 USA	Selenium Supplement Intoxication Study	Se	Coh	45	USA Subjects that answered call looking for users of certain multivitamin supplements with known misformulated Se levels	Y	Y	Fingernails	NS	All toes	NAA			BM evaluation/ Health effects	Other	
Saat-2013 Bangladesh		Co	Cross	80	Bangladesh vegetable male farmers randomly selected from a list of registered farmers employed >1 year (18-80 yrs)			Hair Fingernails	Soaked in Triton 100 & acetone, rinsed with deionized water & acetone, dried & digested in HNO ₃ & H ₂ O ₂	NS	ICP-MS			BM evaluation Health effects	CV	

Reference	Project	Metals	Study design	N° Participants	IC	EC	Other biomarkers	Toenail preparation	Toenail type	Analit. Method	LD	LQ	QQ	Main objective	Health effect
Burgess-2014 USA		Se	Cross	55			Urine	Washed with acetone, Triton X-100 & water, HNO ₃ digestion	NS	ICP-MS	Y		Y	Health effects	Other
Kristal-2014 USA	SELECT	Se	Ca-coh	4761	Y	Y		NS	All toes	INAA			Y	Health effects	Cancer
Kuiper-2014 Qatar		Cu Mn Mo Se	Cross	239	Y	Y	Urine	Cleaning with sonication & rinsed with acetone, HNO ₃ digestion	All toes	ICP-MS	Y		Y	BM evaluation	
Ndilila-2014 Zambia		Co Cu Se Zn	Cross	86	Y	Y		Autoclaved, ultrasonicated with acetone & Milli-Q water, rinsed, dried, digested in HNO ₃ & H ₂ O ₂	All toes	ICP-MS			Y	BM evaluation	
Sanders-2014 Vietnam		Mn	Cross	20	Y	Y	Blood	Washed with double distilled water, acetone, dried, digestion with HNO ₃ & HCl	NS	ICP-MS				BM Evaluation	
Chanpiwat-2015 Cambodia		Co Cu Fe Mn Mo Zn	Cross	180	Y	Y	Hair Urine	Immersed in Triton X-100, sonicated, washed with milli-Q water, dried, digested with HNO ₃	All toes	ICP-MS	Y		Y	BM evaluation	
Mohmand-2015 Pakistan		Co Cu Mn Zn	Cross	30		Y	Hair Serum	HNO ₃ digestion	NS	ICP-MS			Y	BM evaluation	
Rayman-2015 United Kingdom	SPRINT	Se	Clinical trial	230	Y	Y	Blood	Washed with acetone, distilled deionized water in a sonic bath.	All toes	INAA			Y	BM evaluation Health effects	Other
Mao-2016 United Kingdom		Se	Clinical trial	227	Y	Y	Blood	Washed with acetone, distilled deionized water in a sonic bath.	All toes	INAA			Y	Health effects	Other
Reis-2015 Portugal		Cu Mn	Cross	30	Y	Y		Washed rinsed in Milli-Q water & methanol, dried, digestion with HNO ₃ & H ₂ O ₂	All toes	ICP-MS			Y	BM evaluation	
Rodrigues-2015 Bangladesh		Mn	Coh	711	Y	Y	Cord blood Hair	Placed in glass beakers with Triton X-100 solution in ultrasonic bath, rinsed in deionized water, oven-dried, digested with ultrahigh purity HNO ₃ & diluted deionized water	All toes	ICP-MS	Y		Y	BM evaluation	
Hashemian-2016 Iran	GOLESTAN Cohort Study	Fe Se Zn	Cross	30				Acetone, HNO ₃ in a sonicator, then rinsed, water & sonicated	All toes	INAA			Y	BM evaluation	
Hashemian-2017 Iran		Se Zn	N ca-con	443	Y	Y			All toes	INAA			Y	Health effects	Cancer
Hassani-2016 Iran		Mn	Cross	83	Y	Y	Blood Urine	Sonication in Tritone X-100 solution, washed with deionized water & dried. HNO ₃ , H ₂ O ₂ , HCl digestion	All toes	AAS	Y	Y		BM evaluation Health effects	Other
Lee -2016 Korea		Fe Se Zn	Cross	73	Y	Y		Washed with acetone, then demineralized water in a sonicator, rinsed and freeze-dried	NS	INAA			Y	BM evaluation Health effects	CV. Metab. Other
McKinney-2016 Thailand		Zn	Ca-Con	190	Y				NS	INAA				Health effects	Other

Reference	Project	Metals	Study design	N° Participants	IC	EC	Other biomarkers	Toenail preparation	Toenail type	Analit. Method	LD	LQ	QQ	Main objective	Health effect
Park-2016b Korea	SELEN study	Se	Cross	501	Participants of a cohort study of middle-aged adults living in urban & rural south-eastern areas of South Korea		Y Y	Inspected to eliminate contaminated and cleaned	All toes	INAA			Y	Health effects	Metab.
Park-2017 Korea		Se	Coh	501	Participants of Park 2016b		Y Y	Washed in a sonicator with deionized water	All toes	INAA			Y	Health effects	Metab.
Jang-2017 Korea		Se	Coh	501	Participants of Park 2016b		Y Y	Washed in a sonicator with deionized water	All toes	INAA			Y	Health effects	Metab.
Punshon 2016 USA	NHBC	Mn Se Zn	Cross	687	Recent mothers (2 weeks post-partum)+ 8 weeks newborns residing & drinking well water in New Hampshire (↑As in water)		Y Y	Placenta	Manual removal of visible dirt, ultrasonic bath using Triton X-100, acetone, deionized water, and dry.	NS	ICP-MS	Y		BM evaluation	
Bouchard -2017 Canada	New Brunswick Children	Mn	Cross	259	Children (6–13 yrs) consuming well water with high levels of Mg in southeastern New Brunswick.		Y Y	Hair Saliva	Sonicated in Triton X-100, rinsed with Milli-Q water, digested in HNO ₃ -HCl	All toes	ICP-MS	Y	Y	Health effects	Other
Ntihakose-2017 Canada		Mn	Cross	274	Participants of Bouchard 2017		Y Y	Hair Saliva	Sonicated in Triton X-100, rinsed with Milli-Q water, digested in HNO ₃ -HCl	All toes	ICP-MS	Y	Y	BM evaluation	
Everson-2017 USA	RHODE ISLAND	Se	Coh	173	Healthy mothers >18 yrs with singleton, viable, non-pathologic pregnancies born at ≥37 weeks gestation		Y Y		Washed in a Triton X-100 & acetone, deionized water, digested with HNO ₃	All toes	ICP-MS		Y	Health effects	Other
Meramat-2017 Malaysia	NEURO PROTECTIVE	Co Cu Fe Se Zn	Cross	235	Malaysian subjects > 60 yrs participants in study on healthy longevity		Y Y		Washing in Triton-X, deionized water, acetone & rinsing in deionized water & dried in oven. Digestion in HNO ₃ & H2O2	All toes	ICP-MS		Y	Health effects	Other
Sureda-2017 Spain		Co Fe Se Zn	Cross	100	Active and inactive adults 55-80 yrs with no previous cardiovascular disease		Y Y		Cleaned with acetone, distilled deionized water & acetone again	NS	INAA		Y	BM evaluation	
Ward-2017 USA		Mn	Cross	80	Male welders occupationally exposed to Mn (21-61) & sex- age-matched factory controls(18-61)		Y Y		Sonicated in 1% Triton X-100, rinsed in deionized water, digested in HNO ₃	All toes	ICP-MS		Y	BM evaluation	

Cross: Cross-sectional; Ca-Con: case-control; N ca-con: nested case-control; Coh: cohort; Ca-Coh: Case-cohort; CS: convenience sample; V: volunteers; NS: non specified; N°:number; Y: yes; IC: informed consent; EC: ethics committee; LD: limit of detection; LQ: limit of quantification; QQ: quality control; NHSI: Nurse Health Study (Women); HPFS: Health professional Follow up Study (Men); NHBC: New Hampshire Cohort; ICP-MS: Inductively Coupled Plasma Mass Spectrometry ; ICP-AES: Inductively Coupled Plasma Atomic Emission Spectroscopy ; ICP-OES: Inductively Coupled Plasma Optical Emission Spectroscopy ; INAA: Instrumental Neutron Activation Analysis ; NAA: Neutron Activation Analysis ; ADF: Acid Digestion Fluorimetry; AAS: Atomic Absorption Spectroscopy; TNF: Thermal Neutron Flux; BM: Biomarker; CV: Cardiovascular effects. Metab: Metabolic effects.

Figure A.1: Systematic review flow-chart

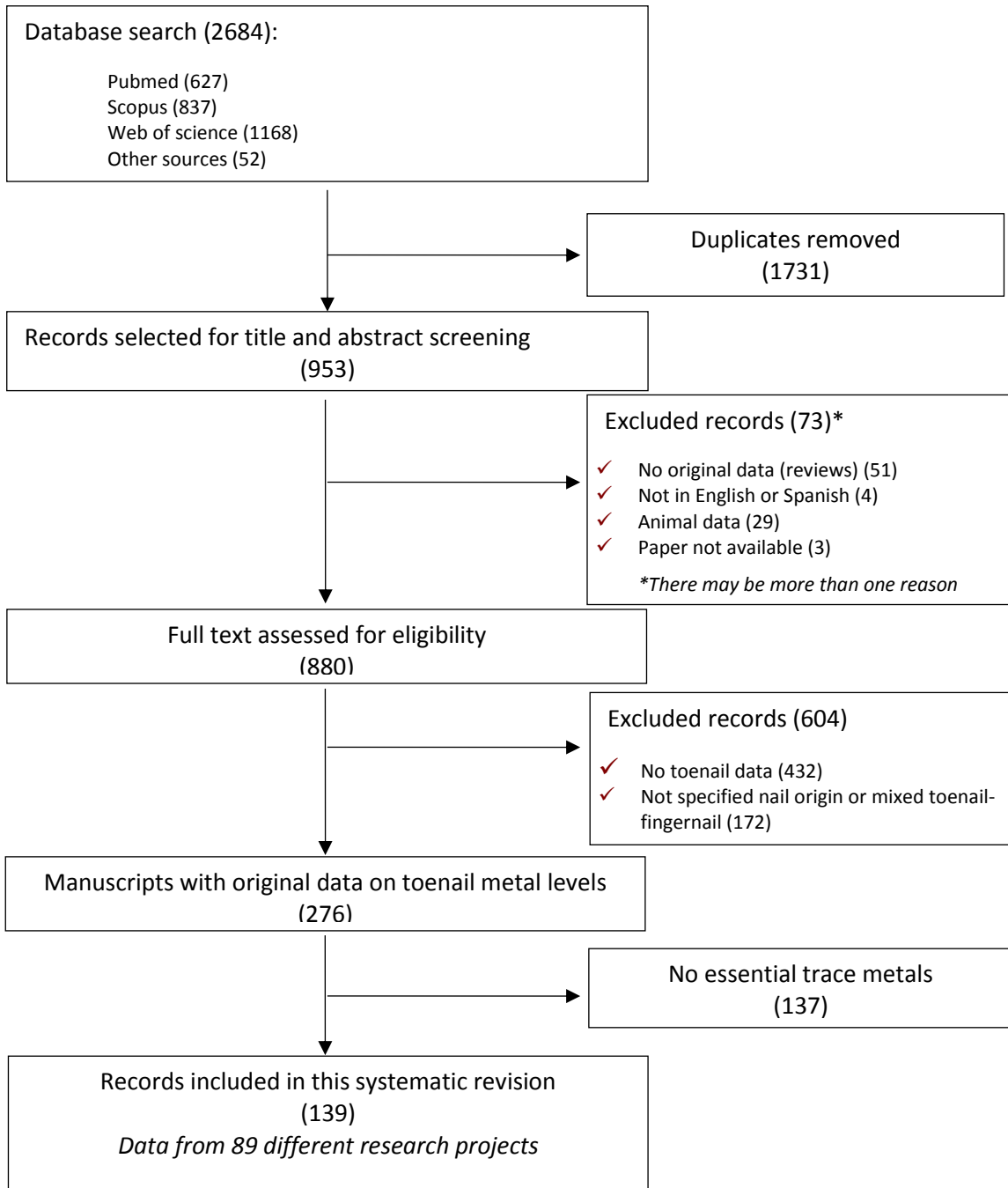


Figure A.2: Temporal evolution of number of published reports with data on essential trace elements in toenails by metal (1975-2017).

