

This is a pre print version of the following article:

Dietary intake of cadmium, chromium, copper, manganese, selenium and zinc in a Northern Italy community / Filippini, T; Cilloni, S; Malavolti, M; Violi, F; Malagoli, C; Tesauro, M; Bottecchi, I; Ferrari, A; Vescovi, L; Vinceti, M. - In: JOURNAL OF TRACE ELEMENTS IN MEDICINE AND BIOLOGY. - ISSN 0946-672X. - 50:(2018), pp. 508-517. [10.1016/j.jtemb.2018.03.001]

*Terms of use:*

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

20/09/2024 22:21

(Article begins on next page)

**Title: Dietary intake of cadmium, chromium, copper, manganese, selenium and zinc in a Northern Italy community**

**Authors:**

Tommaso Filippini<sup>a</sup>, Silvia Cilloni<sup>a</sup>, Marcella Malavolti<sup>a</sup>, Federica Violi<sup>a</sup>, Carlotta Malagoli<sup>a</sup>, Marina Tesauro<sup>b</sup>, Ilaria Bottecchi<sup>a</sup>, Angela Ferrari<sup>a</sup>, Luciano Vescovi<sup>c</sup>, Marco Vinceti<sup>a,d</sup>

**Affiliations:**

<sup>a</sup>CREAGEN, Environmental, Genetic and Nutritional Epidemiology Research Center, Section of Public Health - Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, 287 Via Campi, 41125 Modena, Italy;

<sup>b</sup>Department of Biomedical, Surgical and Dental Sciences, University of Milan, Italy.

<sup>c</sup>IREN, Reggio Emilia and Piacenza, Italy;

<sup>d</sup>Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA.

**Corresponding author:** Marco Vinceti, CREAGEN – Section of Public Health - Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Via Campi 287, 41125 Modena, Italy (Tel. +39 059 2055481; fax +39 059 2055483; E-mail marco.vinceti@unimore.it)

## **Abstract**

This study provides the dietary intakes of six trace elements (cadmium, chromium, copper, manganese, selenium and zinc), generally characterized by both nutritional and toxicological features depending on their exposure. Being diet the most relevant source of exposure to trace elements in non-professionally exposed subjects, we measured content of these trace elements in foods composing the typical Italian diet using inductively coupled plasma-mass spectrometry, and assessing dietary habits using a validated semi-quantitative food frequency questionnaire we eventually estimated dietary daily intake of trace elements in a Northern Italian community.

In the 890 analyzed food samples, the main contributors to cadmium intake are cereals, vegetables and sweets, while cereals, beverages and vegetable are to primary source of manganese. The primary contributors for copper are cereals, fresh fruits and vegetables, while for chromium are beverages, cereals and meat. The main source of selenium intake are cereals and meat, followed by fish, seafood and milk and dairy products, while of zinc intake are meat, cereals, milk and dairy products. In our Italian population sample, the estimated median (interquartile range) dietary daily intakes are 5.00 (3.17-7.65), 56.70 (36.08-86.70) and 66.53 (40.04-101.32) µg/day for cadmium, chromium and selenium, and corresponding figures are 0.98 (0.61-1.49), 2.34 (1.46-3.52) and 8.50 (5.21-12.48) mg/day for copper, manganese and zinc.

The estimated intakes are generally within the average intake reported in other European populations, and in such cases well above the daily dietary intakes recommended by national international agencies, avoiding the risk of excess or deficiency. The present estimated intake data can be used to examine a specific trace element of interest and would afford enhanced health protection from those trace elements characterized by both nutritional and toxicological effects.

## **Keywords**

trace elements, selenium, cadmium, chromium, manganese, copper, zinc, dietary intake, nutritional epidemiology, food analysis.

## **Introduction**

The relevance of trace elements in human health and disease is well documented [1]. Depending of their role within the metabolism, trace elements are generally classified in essential and non-essential. In particular, six trace elements, i.e. cadmium, chromium, copper, manganese, selenium and zinc, were selected due to their intriguing relation with human health showing either nutritional and toxicological effects [2-9]. Two of these elements are also included as prioritized substances within the Human Biomonitoring Initiative at the European level [10].

Diet is generally recognized as being the main source of exposure to trace elements. Some exceptions are the high exposure in occupationally exposed workers, e.g. to cadmium [11, 12] and chromium [13, 14], and smoking. Moreover, additional relevant contribution from outdoor and indoor pollution was also pointed out for cadmium, manganese and selenium [15-20]. Being diet most relevant source of exposure to the above mentioned trace elements in non-occupationally exposed subjects, the systematic evaluation, the periodic and updated evaluation of their content in foods composing population diet is a key element for a comprehensive assessment of their intake levels and of possible consequent health risks [21].

In the present study, we assessed the dietary intake of these trace elements in a Northern Italian community, taking into account their concentrations in foods and the dietary habits of the community.

## **Methods**

### *Food collection and analysis*

We determined the trace element content in the food items characterizing the usual diet of a Northern Italian population. Relevant food items characterizing the diet of this community were selected from previous population-based studies addressing the dietary habits of subjects from Northern Italy, with particular reference of Emilia Romagna Region [22]. We purchased samples of the food items in local markets, large supermarkets, and grocery stores as well as in community canteens from Reggio Emilia and Modena provinces. Food collection started in October 2016 and ended in February 2017. In order to avoid contamination of metals from food containers, plastic tubes or jars were used and plastic cutlery implement during the collection. Food samples were homogenised in a food blender (equipped with a stain less-steel blade) to ensure the homogeneity and for each food sample, specimen in six different point from the plate were collected for subsequent analyses.

We placed portions of the samples (0.5-1.0 g) in quartz containers previously washed with MilliQ water and HNO<sub>3</sub>. Food samples were liquid-ashed (5 ml HNO<sub>3</sub> + 5 ml H<sub>2</sub>O<sub>2</sub>) in a microwave digestion system, then we stored them in a plastic tube and diluted to 50 ml with deionised water before analyses. We performed trace element determination using inductively coupled plasma-mass spectrometer 7500 Agilent. All reagents were of analytical grade and deionised water was used throughout. We performed all the analyses in duplicate and quality controls including both blanks (solution of MilliQ water) and a control solution of tap-water additionally enriched with 22 ppb of each element under investigation. Limit of quantification was 0.02 µg/kg for cadmium, chromium and selenium, while 0.5 µg/kg for copper, manganese and zinc. Corresponding limit of detection (LOD) was quantified in 0.007 µg/kg and 0.17 µg/kg.

Therefore, we reported the concentrations of investigated trace elements according to the food consumption pattern typical of this Italian population, as previously described [23, 24]. The final list of foods included cereals, meat, milk and dairy products, eggs, fish and seafood, vegetables, legumes, potatoes, fresh fruits, dry fruits, sweets and beverages.

#### *Study population and estimation of daily element intake*

We carry out the evaluation of dietary habits of Northern Italy community in a representative sample of the Emilia-Romagna Region population [25, 26]. Briefly, the large sample population was randomly selected from the database of the Emilia-Romagna region National Health Service directory, namely from the provinces of Bologna, Ferrara, Modena, Parma, and Reggio Emilia. The final population was made up by 719 subjects, 319 males and 400 females with mean age 55.3 years, range 18-87 years.

In this population, we assessed the total daily intake and for food categories through the assessment of food intake by using a validated semi-quantitative food frequency questionnaire (FFQ) specifically developed for the Central-Northern Italian population [27, 28]. Briefly, the EPIC (European Prospective Investigation into Cancer and Nutrition) questionnaire assessed the frequency and amount of consumption of 188 food items over the previous year, and allowed the frequency and quantity of consumption of foodstuffs and the related intake of nutrients and contaminants to be calculated using an *ad hoc* software [26, 29].

By combining the analytical results of trace elements determination in foods and of the dietary assessment performed through with the EPIC FFQ, we assessed daily trace element intake using the equation presented below:

$$Total\ daily\ dietary\ exposure\ \left(\frac{\mu g}{day}\right) = \sum \frac{food\ intake\ \left(\frac{g}{day}\right) \times element\ food\ content\ \left(\frac{\mu g}{kg}\right)}{1000}$$

We estimated daily dietary exposure for each category and for total dietary exposure, reporting median and interquartile range of intake.

## Results

We determined trace element content of 890 food samples. Table 1 shows the distribution of investigated trace elements in food categories. All concentrations were found to be above the limit of detection for chromium, copper, and zinc, while four samples were below the LOD for manganese and selenium, and 25 for cadmium. For cadmium, the higher median content was detected in cereals followed by potatoes, while the highest concentrations were found in dry fruits, totally driven by pine nuts levels, in sweets (due to high content in dark chocolate) and eventually in seafood, due to high levels in samples of shellfish and cephalopods, as shown in Supplementary Figure S1. The high cadmium concentration in meat were almost totally driven by levels in offal samples (Supplementary Figure S2).

Chromium showed high median content in three food categories: oils and fats, due to high concentrations in seed oils (i.e. mixed, sunflower and peanut), sweets, which showed the maximum levels in dark chocolate, and meat. The highest chromium levels were found in dry fruits, especially in nuts, and in beverages, due to high concentration in such spirits and liqueurs.

The highest median content of selenium was found in fish and seafood, with elevated levels in fish of big size, e.g. fresh and canned tuna, showing values generally above 1 mg/kg, mackerel and perch fish, and crustaceans (Supplementary Figure S1). High selenium levels were also found in eggs, due to higher concentrations in the yolk, and in meat samples, with higher content in offal, followed by processed and red meat (Supplementary Figure S2). Vegetables generally showed a low content of this trace element, which in turn was higher in Se-accumulator vegetables (i.e. cabbage, onion and garlic) that revealed four- to ten-fold higher levels, with median content of 18.87 µg/kg (IQR: 5.62-65.90), and especially in mushrooms with a median content of 106.37 µg/kg (IQR: 129.00-151.64) (Supplementary Figure S3).

Copper showed the both median and maximum levels in dry fruits, due to pine nuts, hazelnuts and nuts content, followed by legumes, where copper-rich samples were soy beans, black-eyed beans/peas and lentils. Sweets were generally at low content of copper, except for high concentration in dark chocolate (Supplementary Figure S4).

Similarly, manganese levels were high in almost all dry fruits, especially pine nuts, followed by nuts, hazelnuts, nuts and in addition almonds, in legumes, with the highest levels in chickpeas, followed by soybeans, beans in general (black-eyed, black peas, 'borlotto' and ingot/'cannellino' beans), and finally in cereals. Despite the general low content of manganese in beverages, tea shows the highest content in coffee (3.41 mg/kg, IQR: 1.96-3.40) and tea (1.61 mg/kg IQR: 0.78-1.12).

Zinc generally showed the higher median content in dry fruits, meat, followed by milk and dairy products, cereals and eggs, while the highest values were found in dry fruits, especially pine nuts, peanuts, nuts and almonds, and in all kind of meat.

We estimated the mean consumption of foods carried in our representative sample population of the Emilia-Romagna Region (Table 2). The contribution of the most representative food groups of the total diet were cereals, vegetables, fresh fruit, meat, milk and dairy products. Table 3 shows the estimated daily intake (median and interquartile range) of investigated trace elements in the total diet and according to the different food categories in overall study population, with sex-specific estimates substantially similar to the those obtained in the overall population (Supplementary Table S1).

The overall trace element content in food categories, and the contribution of each food category to the trace element daily intake are reported in Figure 1 for the total study population. Cereals are the primary contributor for dietary intake of cadmium (55%), manganese (46%) and copper (37%). Meat shows relevant contribution to zinc (32%), selenium (26%), chromium (14%), and copper (8%). Milk and dairy products demonstrate high contribution only to zinc (17%), selenium (14%), chromium (8%). Egg shows generally low contribution to element intake, with the highest values for selenium (4%) and zinc (2%). Fish and seafood show the highest contribution to selenium intake (17%) and cadmium (4%), followed by zinc, copper and chromium (around 1-2%). Vegetables show relevant contribution to cadmium (19%), copper (11%), manganese (10%), followed by chromium (8%), zinc (3%), and selenium (less than 1%). Legumes show the highest contribution in intake of copper (8%) and manganese (7%), while, potatoes generally show low contribution (less than 1%) to elements intake, with slight exception for copper (2.2%) and cadmium (3.7%). Fresh fruits show relevant contribution only to copper (16%) and chromium and manganese (7% each), while dry fruits show very low contribution due to the low daily intake, despite the high content demonstrated especially in copper, manganese, and zinc. Sweets (mainly due high element content in chocolate) are the primary contributors for chromium and cadmium

intake (10% each), followed by manganese (8%), copper (7%), selenium and zinc (around 3%). Oils and fats show the only high contribution to chromium intake (13%). Finally, beverages show highest contribution to intake of chromium (20%), manganese (19%), zinc (11%) and selenium (9%). Sex-specific analysis yielded generally comparable results (Supplementary Figures S5 and S6).

Finally, the comparison of total element intake estimated in the study population with European and International TDIs/TWIs is reported in Table 4.

## **Discussion**

In this study, we assessed the dietary intake of six trace elements in a Northern Italy population, by measuring trace element content in foods characterizing their usual diet and assessing the contribution of different foods to the intake of trace elements. For cadmium, cereals were by far the most relevant source, followed by vegetables, and sweets (mainly due to dark chocolate). For chromium, the similar contribution was yielded beverages, cereals, meat, oils and fats, and sweets/chocolate. Selenium estimated daily intake was mostly driven by cereals and meat, followed by fish, seafood, milk and dairy products. For copper intake was driven by cereals, followed by fresh fruits, vegetables, legumes and sweets, and in addition beverages for manganese. Zinc intake showed the highest contribution from milk and dairy products, meat and cereals.

National dietary surveys tend to provide information on average intakes of all dietary factors, including trace elements, of the whole country [21, 30, 31]. In the present study, we assessed both trace elements content in the specific foods distributed and consumed in a local community, as well as the dietary habits characterizing that community, to achieve an estimate of the average daily intake of the trace elements and their major dietary sources in a representative community of Northern Italy. Though the subjects from Emilia-Romagna Region we investigated are characterized by substantially comparable dietary habits compared with previous Italian surveys [32, 33], it should be noted that our sample population shows a slight lower intake of cereals, beverages and vegetables, while it is higher for fresh fruits, milk and dairy products.

Overall, the estimates of intake of trace elements were however generally within the average intake reported by European surveys (Table 4), avoiding the risk of excess or deficiency in the intake.

The first exception is cadmium, for which the weekly estimated intake in our population of 0.50 µg/kg of body weight (bw) is far below the average intake reported in other European surveys



(range 1.9-3.0  $\mu\text{g}/\text{kg}$  of bw) and the tolerable weekly intake of 2.5  $\mu\text{g}/\text{kg}$  of bw per week recently established European Food Safety Authority (EFSA) [34, 35] and the tolerable monthly intake of 7  $\mu\text{g}/\text{kg}$  of bw per month of the World Health Organization (WHO) [36]. Cadmium is a well-established carcinogen [11] recently linked to both neoplastic [37, 38] and non-neoplastic diseases [39-41], and a more restrictive guideline of dietary intake has been suggested in order to enhance the health protection [42]. Our results confirm previous studies showing that the primary dietary source of cadmium are cereals, followed by vegetables, mainly due to natural content in soil [43-45]. According to previous findings, we point out that sweets, and particularly chocolate are a relevant source of cadmium [45-47], though not all studies showed consistent results [31, 48].

The other elements are characterized by both nutritional and toxicological properties, depending on the levels of exposure and in such cases of the chemical species [49-52]. This is particularly true for the metalloid selenium which demonstrated an intriguing relation with human health and disease and a very narrow safe range of intake [3, 53]. In our population, daily median intake of selenium of 66.53  $\mu\text{g}/\text{day}$  is slightly higher than the reported range of intake of 31.0-65.6  $\mu\text{g}/\text{day}$  characterizing the European population [54, 55] and well above the reference intake by many international agencies [53], varying from 26  $\mu\text{g}/\text{day}$  for women and 33  $\mu\text{g}/\text{day}$  for men of WHO [56] to 70  $\mu\text{g}/\text{day}$  of EFSA [55]. This may have been due to the different (higher) food selenium content of foods distributed in this community compared with other European countries [43, 57-65]. In a previous Italian study based on the diet characterizing the entire Italian population, average selenium intake (103.6  $\mu\text{g}/\text{day}$ ) was higher than in our study [30]. However, overestimation of daily selenium intake might occur when using measurement in food samples compared to complete meals [66].

The status of trivalent chromium as an essential trace element for humans is currently under question [9], due to the involvement of insulin signaling and lipid metabolism, though most recent findings suggest more caution and point out possible pharmacological effects of chromium and chromium supplements [67, 68]. As a matter of that, EFSA did not set a reference intake for chromium due to lack of evidence of beneficial effects associated with its intake, whereas a tolerable weekly intake of 300  $\mu\text{g}/\text{kg}$  of bw/week was established for trivalent chromium. The estimated chromium median dietary intake of 56.70  $\mu\text{g}/\text{day}$  is similar to those reported in other European populations [69], but it is above the average intake reported by WHO [1] and two-fold higher than the dietary reference intake set by the Institute of Medicine [70], suggesting possible overexposure. Our results are consistent with previous findings showing that the food groups with

the highest levels of chromium are sweets (particularly dark chocolate and ice cream), oils and fats, and finally meat [46, 47, 71, 72].

Copper is considered essential to humans as it is a cofactor of many redox enzymes, including ceruloplasmin, the most abundant copper-dependent ferroxidase enzyme [73]. However, the reference value for copper dietary intake is still challenging [4], while higher level of copper are considered toxic, especially towards neurodegenerative disease [74]. The estimated daily intake of 0.98 mg/day is slightly lower the intake reported by European and International Agencies, and generally nearby the established dietary reference intake, suggesting possible risk of deficiency in our population, whereas it is well below the different established upper limits [75, 76].

Similarly, manganese is an essential trace elements involved in oxidative stress response [2], and plays a fundamental role for brain development and functioning [49, 77]. The manganese estimated daily intake of 2.34 mg/day is within the range of dietary exposure reported for adult populations in Europe [78] and other world countries [79], and it is only slightly below the dietary reference intake of 3 mg/day set by EFSA [78]. In line with previous findings, the primary contributors to manganese intake are cereals, followed by vegetables, legumes, and sweets, especially in dark chocolate [48, 71, 80]. As shown by the high content in tea and coffee sample, it should be noted their consumption could be a relevant source of manganese [81, 82], with possible risk of overexposure especially in heavy consumers tea [83].

Zinc is an essential trace elements characterized by a wide array of vital physiological functions as it plays a role in more than a hundred enzymatic reactions [84]. Being ubiquitous within every cell of human body, signs of zinc deficiency are not generally linked with a specific function [85], while its excess can result in severe neurological disease [86, 87]. The intake of zinc is largely dependent by the efficiency of its absorption and it is negatively influenced by the phytate intake [8]. The estimated daily intake of 9.09 mg/day in men and 8.03 mg/day in women is close to the EFSA recommendations of 9.4 and 7.5 mg/day in men and women, respectively , considering an average phytate intake of 300 mg/day [88], while it is slight above the dietary reference intake of 7 and 4.9 for men and women, respectively, set by WHO considering a moderate zinc bioavailability [56]. Unfortunately, we did not directly assess the phytate content in foods, but the estimation of the intake of foods which mostly account to its intake, i.e. cereals, legumes and dry fruits [89], is substantially similar with previous findings [32, 90] and did not suggest that phytate intake is particularly higher in our population to heavily decrease the zinc

bioavailability. Interestingly, we pointed out that contribution of various food to zinc dietary intake is consistent with previous Italian surveys [30, 48], except for a lower contribution from vegetables and a higher one from milk and dairy products, the latter one possibly due also by the higher intake of this category in our regional sample respect to the whole country population.

Our study has some strengths. First the large number of food samples on which the analytical determinations were based, and their collection from local, groceries as well as from supermarkets, in order to mimic the real sources of foodstuffs in the regional population. In addition, we identified food items and food categories according to the guidelines suggested for total diet studies and to previous studies on dietary trace element intake, thus improving the possibility to compare our results with other studies [91]. To do that, we also preferred to carry out separated analyses after splitting categories into subgroups, such as for vegetables and fruit, in order to better identify specifically high and low sources of trace elements.

A second strength of the study is the estimation of the trace elements content in foodstuffs composing the actual and the typical diet of Northern Italian, and Emilia-Romagna region in particular, as well we estimated the daily element intake using dietary habits evaluated in large sample out of the same regional population [25, 26]. Similar studies yielded in different regions of the same country, pointed out such differences in trace elements intake, due typical dietary habits influencing the amount and type of foodstuffs composing the usual diet [44, 92] and moreover for the possible different content in food them-self, due to geographical variations in soil and water [60, 93-95]. Moreover, we collected information of dietary habits using a validated FFQ [28], in a version specifically developed for Northern Italian population [27]. Finally, due to the large population sample, we have addressed possible sex-differences, as shown by sex-specific estimation of daily intake, though no relevant differences were pointed out, except for a general higher daily intake in men due to the higher food consumption [35, 96, 97].

Interestingly, in a previous report correlating serum levels of manganese species and foods intake, we pointed a positive correlation between both meat with inorganic manganese, and between vegetables, legumes, and to a lesser extent fruits with levels of total manganese, manganese-citrate and manganese-transferrin [19].

The study has some limitations that should be pointed out. The collection of food was performed in winter-autumn, thus seasonal variation could only be partially taken in consideration [91, 98]. For example, selenium biomarkers showed lower and higher level in winter and summer, respectively [99], possible due to different intake in food accounting for the increase selenium

intake, i.e. fish and seafood [100], though other studies did not point out any seasonal variation with intake and biomarkers of exposure [101], even in area with high exposure through drinking water [102]. Nevertheless, collection dietary habits from the study population was carried out over the whole year, thus seasonal differences are not expected to occur neither for macro [103, 104] or micro nutrients [105, 106]. Moreover, the EPIC FFQ collects information of food consumption over the entire previous year, and includes specific questions in order to take into account intake of food which are made subjects to seasonality.

Unfortunately, we were unable to differentiate species of trace elements, although the interest in element speciation in both biomarkers [49, 107, 108] and foods [109-114] is markedly increased due to the even opposite effects of various species in humans. In particular for chromium, there is a lack of data on the presence of carcinogenic hexavalent chromium in food [115], whereas it is the main form in drinking water [116]. Indeed, previous studies assessing trivalent (chromite) and hexavalent (chromate) chromium species in cereals found that chromate content in bread is nearly to the 10% of total chromium [117]. Another study found high chromate levels in brown respect white bread, and pointed out that the high temperature of toasting seems to favor the oxidation from chromite to chromate [118]. However, these results are not consistent with other studies showing no chromate content in any investigated sample [119-121]. Possible explanation of the contrasting results could be found in the instability of chromate in food, which is by-and-large a reducing medium [121].

Regarding selenium species, selenocysteine is an essential component in selenoprotein biosynthesis [122], while other organic forms such as selenomethionine [123] and inorganic forms such selenite and selenate [124] are considered the most toxic species [107, 108, 125]. Nevertheless, an elevated inorganic selenium intake through food is unlikely, since most of the selenium ingested with foods is in organic species [126], and the predominant forms in cereals, plants and meat are generally selenomethionine and selenocysteine [108, 127-129], followed by the inorganic forms, which are generally abundant in fish and seafood [126, 130-132].

We did not assess the geographic origin of purchased foods in order to explore differences in local and imported products [91] as well as the content of trace elements in drinking water. However, the use of groceries as well as large supermarket to retrieve foods should have mimed the actual habits of population, thus yielding to a close-to-real estimation of dietary intake. Trace elements in water samples are generally very low and the contribution of drinking water is generally negligible in unpolluted or non-seleniferous areas [79, 133-136], though in such cases

subjects could receive up to the 10% of the recommended dietary intake, especially for zinc and copper. About the latter one, the contribution of drinking water could vary depending also on consumption of water flushed within a distribution system that includes copper pipes [76], or drinking water could be source of such species, generally different from those retrieved in foods, as for inorganic selenium and hexavalent chromium [116, 137].

Finally, we assessed dietary intake only on adult population, excluding adolescents and children, for which the difference in dietary habits and metabolism could hamper the use of estimation based on adult subjects, as recently reported for cadmium [138].

In conclusion, the daily intake data provided by our studies can offer important information about the nutritional quality of local dietary habits. The present estimated intake data can be used to examine a specific element of interest, and would particularly afford enhanced health protection from those trace elements characterized by both nutritional and toxicological effects.

**Declaration of interest:** none

#### **Founding**

This work was supported by the Italian Association for Cancer Research (AIRC).

**Table 1.** Distribution of trace elements concentrations in food categories of the usual diet in the study population.

	Cd (µg/kg)					Cu (mg/kg)				
	5 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	95 <sup>th</sup>	5 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	95 <sup>th</sup>
Cereals	6.24	9.87	15.36	22.98	54.52	1.01	1.43	2.13	3.05	4.38
Meat	0.07	0.33	0.83	2.18	25.72	0.40	0.53	0.81	1.41	3.61
Milk and dairy products	0.05	0.15	0.31	0.55	1.61	0.04	0.21	0.38	0.63	5.96
Eggs	0.00	0.00	0.10	0.26	0.43	0.07	0.23	0.46	1.32	1.73
Fish and seafood	0.13	0.75	4.96	26.78	136.71	0.15	0.31	0.73	1.53	3.40
Vegetables	0.40	1.82	4.04	11.45	39.52	0.24	0.46	0.83	1.49	3.86
Legumes	1.09	3.25	5.10	10.4	35.74	2.01	4.40	6.00	7.12	11.44
Potatoes	1.13	4.77	10.51	23.11	71.20	0.54	0.80	1.22	1.54	2.49
Fresh fruits	0.00	0.08	0.24	0.81	3.94	0.26	0.37	0.60	1.01	2.26
Dry fruits	0.00	0.66	1.67	20.8	272.50	2.71	7.39	11.16	16.24	27.45
Sweets	0.17	1.63	6.03	27.1	233.13	0.06	0.41	0.99	4.29	17.31
Oils and fats	0.00	0.00	0.12	0.22	0.62	0.01	0.02	0.02	0.06	7.16
Beverages	0.01	0.04	0.09	0.21	0.68	0.01	0.02	0.08	0.23	0.94
	Cr (µg/kg)					Mn (mg/kg)				
	5 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	95 <sup>th</sup>	5 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	95 <sup>th</sup>
Cereals	10.37	22.33	39.50	96.02	207.12	2.71	5.03	6.92	12.08	24.27
Meat	19.33	31.82	63.09	137.80	340.99	0.06	0.13	0.22	0.34	2.38
Milk and dairy products	3.03	24.49	42.33	125.75	335.45	0.02	0.11	0.19	0.30	0.70
Eggs	2.53	8.45	10.61	15.86	67.11	0.00	0.01	0.33	0.60	1.27
Fish and seafood	9.28	13.02	25.13	66.34	188.56	0.06	0.12	0.21	0.54	1.35
Vegetables	5.81	10.82	25.46	60.15	207.82	0.36	0.72	1.33	3.06	11.15
Legumes	5.32	17.79	33.73	56.20	99.32	3.25	7.91	11.34	13.72	23.89
Potatoes	5.11	9.54	25.18	33.56	87.46	0.63	1.03	1.20	2.45	4.50
Fresh fruits	4.89	7.41	13.73	26.66	84.95	0.16	0.30	0.52	1.59	7.74
Dry fruits	13.91	20.21	34.61	249.37	563.67	5.17	13.8	18.26	31.22	139.23
Sweets	17.54	37.19	140.35	330.67	936.88	0.04	0.68	3.03	8.24	20.22
Oils and fats	11.08	48.69	286.70	372.35	877.40	0.00	0.01	0.02	0.07	0.24
Beverages	5.94	11.30	20.20	130.22	383.71	0.01	0.12	0.34	0.82	2.24
	Se (µg/kg)					Zn (mg/kg)				
	5 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	95 <sup>th</sup>	5 <sup>th</sup>	25 <sup>th</sup>	50 <sup>th</sup>	75 <sup>th</sup>	95 <sup>th</sup>
Cereals	17.61	34.08	61.67	96.87	428.86	4.19	6.08	10.54	13.36	30.25
Meat	46.80	105.87	175.80	280.53	470.26	5.54	16.58	22.29	38.03	66.18
Milk and dairy products	11.52	39.66	109.25	185.14	294.36	1.97	3.53	20.68	33.01	44.83
Eggs	73.14	173.46	193.10	1197.85	1632.66	0.01	0.29	10.32	36.24	40.82
Fish and seafood	98.45	204.51	376.40	668.08	1204.70	2.30	3.46	5.75	10.58	15.40
Vegetables	1.07	2.06	3.56	8.35	89.58	0.60	1.12	2.08	3.85	9.05
Legumes	10.00	19.82	44.43	250.63	1035.32	6.17	14.78	22.24	25.56	34.36
Potatoes	0.95	3.13	7.83	12.59	461.58	1.28	1.93	2.78	5.81	10.53
Fresh fruits	0.16	0.71	1.33	1.92	6.94	0.18	0.36	0.60	1.25	3.08
Dry fruits	3.81	15.74	35.59	64.11	623.39	6.88	15.46	25.43	40.56	82.28
Sweets	1.11	16.28	38.63	80.31	194.71	0.42	2.53	4.60	10.65	29.18
Oils and fats	0.00	0.77	1.26	2.23	94.32	0.03	0.08	0.15	0.27	0.77
Beverages	0.13	0.33	1.00	3.81	13.48	0.02	0.08	0.28	0.56	2.07

**Table 2.** Mean (standard error) of daily intake (g/day) of main food categories in the sample population of Emilia-Romagna Region.

<b>Foods</b>	<b>Total</b>	<b>Men</b>	<b>Women</b>
Cereals	188.5 (3.7)	206.5 (5.9)	174.2 (4.6)
Meat	128.4 (2.6)	142.4 (4.1)	117.2 (3.3)
Milk and dairy products	230.7 (8.1)	203.1 (10.7)	252.7 (11.6)
Eggs	15.1 (0.4)	14.6 (0.6)	15.4 (0.6)
Fish and seafood	35.1 (1.0)	35.5 (1.5)	34.9 (1.5)
Vegetables	160.7 (3.5)	156.6 (5)	164.0 (5.0)
Legumes	18.7 (0.7)	19.5 (1.1)	18.1 (0.9)
Potatoes	24.5 (0.9)	25.5 (1.5)	23.7 (1.1)
Fresh fruits	344.3 (8.2)	336.5 (11.9)	350.4 (11.4)
Dry fruits	1.7 (0.1)	1.8 (0.2)	1.6 (0.2)
Sweets	86.5 (2.8)	82.9 (4.3)	89.4 (3.5)
Oils and fats	27.2 (0.5)	27.9 (0.7)	26.7 (0.7)
Beverages	363.3 (11)	412 (15.6)	324.6 (15.1)

**Table 3.** Daily dietary intake of cadmium, chromium, selenium, copper, manganese and zinc in study population. Median and interquartile range (IQR) are reported.

	Cd ( $\mu\text{g/day}$ )		Cu (mg/day)	
	50 <sup>th</sup>	IQR	50 <sup>th</sup>	IQR
Cereals	2.77	(1.90 - 3.74)	0.36	(0.25 - 0.50)
Meat	0.07	(0.05 - 0.12)	0.08	(0.05 - 0.12)
Milk and dairy products	0.03	(0.02 - 0.04)	0.02	(0.01 - 0.03)
Eggs	0.001	(0.001 - 0.002)	0.006	(0.003 - 0.010)
Fish and seafood	0.22	(0.09 - 0.59)	0.02	(0.01 - 0.03)
Vegetables	0.97	(0.64 - 1.47)	0.11	(0.07 - 0.16)
Legumes	0.07	(0.03 - 0.13)	0.08	(0.04 - 0.15)
Potatoes	0.19	(0.11 - 0.34)	0.02	(0.01 - 0.04)
Fresh fruits	0.06	(0.04 - 0.08)	0.16	(0.10 - 0.23)
Dry fruits	0.001	(0.00 - 0.003)	0.003	(0.002 - 0.018)
Sweets	0.51	(0.22 - 0.98)	0.07	(0.03 - 0.13)
Oils and fats	0.002	(0.001 - 0.003)	0.001	(0.001 - 0.002)
Beverages	0.11	(0.07 - 0.15)	0.05	(0.03 - 0.07)
<b>Total</b>	<b>5.00</b>	<b>(3.17 - 7.65)</b>	<b>0.98</b>	<b>(0.61 - 1.49)</b>
	Cr ( $\mu\text{g/day}$ )		Mn (mg/day)	
	50 <sup>th</sup>	IQR	50 <sup>th</sup>	IQR
Cereals	9.01	(5.60 - 12.77)	1.07	(0.71 - 1.53)
Meat	8.40	(5.59 - 11.62)	0.02	(0.01 - 0.03)
Milk and dairy products	4.40	(2.41 - 8.57)	0.01	(0.01 - 0.02)
Eggs	0.14	(0.08 - 0.22)	0.004	(0.002 - 0.007)
Fish and seafood	0.72	(0.39 - 1.15)	0.006	(0.003 - 0.010)
Vegetables	4.33	(2.83 - 6.40)	0.23	(0.15 - 0.35)
Legumes	0.46	(0.21 - 0.85)	0.15	(0.07 - 0.29)
Potatoes	0.45	(0.27 - 0.81)	0.02	(0.01 - 0.04)
Fresh fruits	3.81	(2.44 - 5.37)	0.18	(0.11 - 0.25)
Dry fruits	0.01	(0.01 - 0.06)	0.005	(0.004 - 0.029)
Sweets	5.86	(3.11 - 10.64)	0.20	(0.09 - 0.35)
Oils and fats	7.75	(5.79 - 10.54)	0.001	(0.001 - 0.002)
Beverages	11.36	(7.35 - 17.70)	0.44	(0.29 - 0.61)
<b>Total</b>	<b>56.70</b>	<b>(36.08 - 86.70)</b>	<b>2.34</b>	<b>(1.46 - 3.52)</b>
	Se ( $\mu\text{g/day}$ )		Zn (mg/day)	
	50 <sup>th</sup>	IQR	50 <sup>th</sup>	IQR
Cereals	15.59	(10.02 - 24.93)	1.61	(1.11 - 2.24)
Meat	17.57	(11.69 - 24.46)	3.08	(1.93 - 4.35)
Milk and dairy products	8.99	(5.38 - 13.37)	1.42	(0.89 - 2.10)
Eggs	2.61	(1.41 - 4.09)	0.14	(0.08 - 0.22)
Fish and seafood	11.45	(6.33 - 17.80)	0.15	(0.08 - 0.26)
Vegetables	0.66	(0.43 - 1.05)	0.25	(0.17 - 0.37)
Legumes	0.60	(0.28 - 1.12)	0.30	(0.14 - 0.56)
Potatoes	0.14	(0.08 - 0.25)	0.05	(0.03 - 0.09)
Fresh fruits	0.33	(0.21 - 0.47)	0.19	(0.12 - 0.27)
Dry fruits	0.01	(0.01 - 0.06)	0.01	(0.01 - 0.04)
Sweets	2.26	(0.91 - 4.35)	0.30	(0.12 - 0.53)
Oils and fats	0.09	(0.04 - 0.16)	0.004	(0.003 - 0.005)
Beverages	6.23	(3.25 - 9.21)	1.00	(0.53 - 1.44)
<b>Total</b>	<b>66.53</b>	<b>(40.04 - 101.32)</b>	<b>8.50</b>	<b>(5.21 - 12.48)</b>



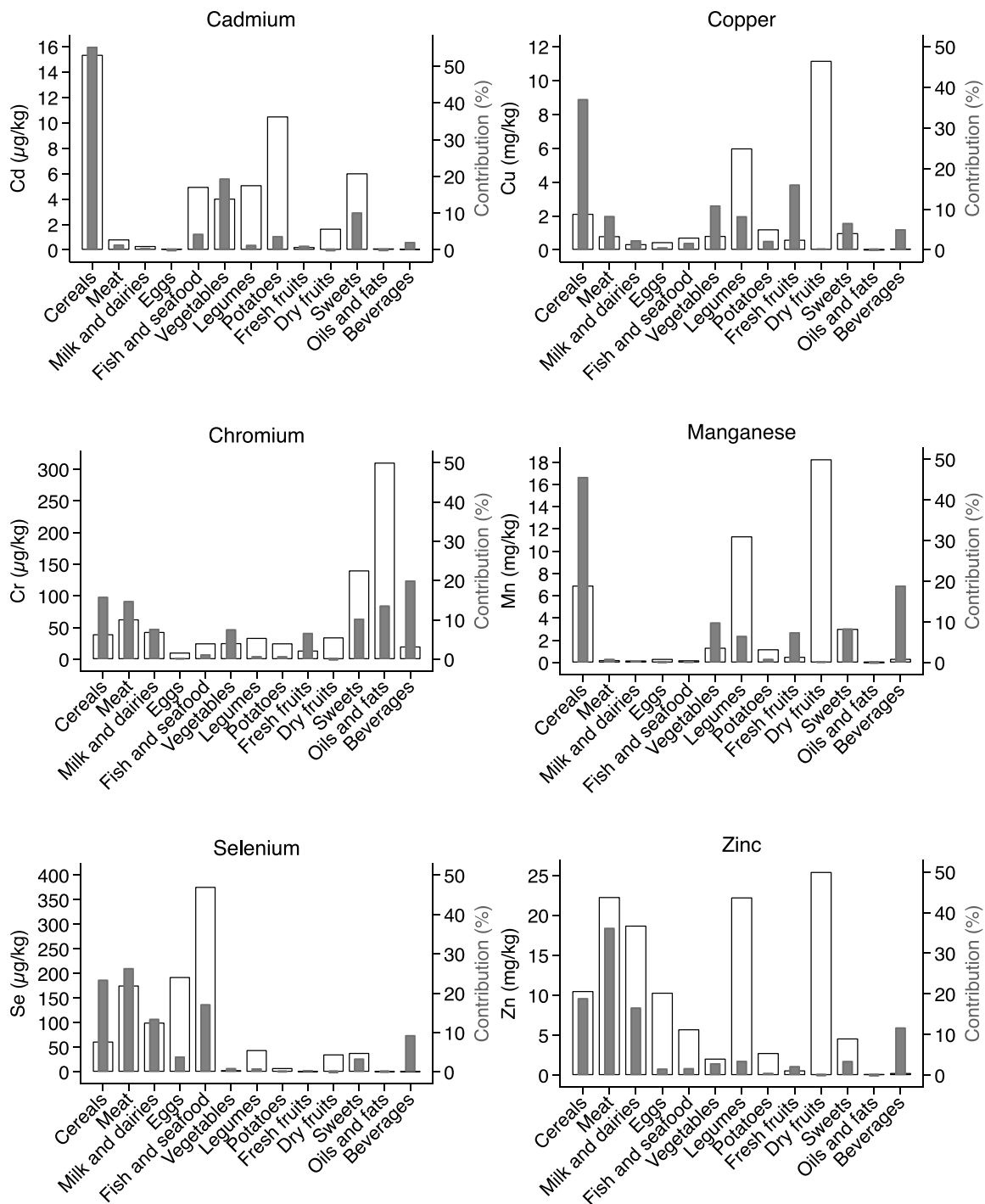
**Table 4.** Comparison of total element intake estimated in the study population with European and International tolerable daily/weekly intakes for adult population.

Element	This study	EFSA <sup>a</sup>			WHO <sup>b</sup>			IOM <sup>c</sup>	
	Dietary intake	Dietary intake	DRV	TDI/TWI	Dietary intake	DRV	TDI/TWI	DRV	TDI/TWI
Cadmium (µg/kg bw/week)	0.50 <sup>d</sup>	1.9-3.0	-	2.5	0.77-1.78 <sup>e</sup>	-	~6 <sup>e</sup>	-	7
Chromium (µg/day)	59.55 M 56.08 F	57.3-83.8	NR	300 <sup>f</sup>	47	NR	250 <sup>g</sup>	30-35 M 20-25 F	NR
Selenium (µg/day)	67.13 M 65.32 F	31.0-65.6	70	300	13-500	33 M 26 F	400	55	400
Copper (mg/day)	1.03 M 0.95 F	1.20-2.07	1.6 M 1.3 F	5	1.0-1.5	1.3 M <sup>h</sup> 1.2 F <sup>h</sup>	10	0.9	10
Manganese (mg/day)	2.49 M 2.25 F	1.39-5.49	3	NR	2.5-3.0	2 to 5	11	2.3 M 1.8 F	11
Zinc (mg/day)	9.09 M 8.03 F	8-14	9.4-16.3 M <sup>i</sup> 7.5-12.7 F <sup>i</sup>	25	14-20	4.2-14 M <sup>j</sup> 3.0-9.8 F <sup>j</sup>	45 M 35 F	11 M 8 F	40

Abbreviations: AI: adequate intake; bw: body weight; DRV: dietary reference value; EFSA: European Food Safety Authority; F: females; IOM: Institute of Medicine; IQR: interquartile range; M: males; NR: not reported; TDI: tolerable daily intake; TWI: tolerable weekly intake; WHO: World Health Organization.

<sup>a</sup>Data of ranges of average dietary intake obtained from EFSA Scientific Opinions [45, 55, 69, 75, 78, 88]; <sup>b</sup>Data of ranges of average dietary intake and for DRV obtained from FAO/WHO [1, 56, 76, 79]; <sup>c</sup>Data from IOM and ATSDR [12, 70]; <sup>d</sup>70 kg of body weight considered for the comparison; <sup>e</sup>The latest updated upper limit for cadmium was 25 PTMI (provisional tolerable monthly intake), corresponding to approximately 6 TWI and to 62 µg/day for a 70 kg person [36]. The estimated dietary exposure on monthly base is 2.2-12 µg/kg bw/month; <sup>f</sup>Value in µg/kg bw/week only for trivalent chromite; <sup>g</sup>Upper limit established especially for chromium supplementation [1]; <sup>h</sup>Values corresponding to nearly (20 µg/kg bw/day); <sup>i</sup>Ranges depending on level of phytate intake; <sup>j</sup>Ranges depending on zinc bioavailability.

**Figure 1.** Trace elements content according to food intake category and % contribution of each food category to trace element daily intake (gray bars) in the Emilia-Romagna Region population



## References

- [1] WHO, Trace elements in human health and nutrition, World Health Organization, Geneva, 1996.
- [2] B. Michalke, K. Fernsebner, New insights into manganese toxicity and speciation, *J Trace Elem Med Biol* 28(2) (2014) 106-16.
- [3] M. Vinceti, B. Burlingame, T. Filippini, A. Naska, A. Bargellini, P. Borella, The epidemiology of selenium and human health, in: D.L. Hatfield, U. Schweizer, P.A. Tsuji, V.N. Gladyshev (Eds.), *Selenium: Its Molecular Biology and Role in Human Health*, Springer International Publishing, Cham, 2016, pp. 365-376.
- [4] M. Bost, S. Houdart, M. Oberli, E. Kalonji, J.F. Huneau, I. Margaritis, Dietary copper and human health: Current evidence and unresolved issues, *J Trace Elem Med Biol* 35 (2016) 107-15.
- [5] L.M. Plum, L. Rink, H. Haase, The essential toxin: impact of zinc on human health, *Int J Environ Res Public Health* 7(4) (2010) 1342-65.
- [6] J. Pan, J.A. Plant, N. Voulvoulis, C.J. Oates, C. Ihlenfeld, Cadmium levels in Europe: implications for human health, *Environ Geochem Health* 32(1) (2010) 1-12.
- [7] A.L. Rowbotham, L.S. Levy, L.K. Shuker, Chromium in the environment: an evaluation of exposure of the UK general population and possible adverse health effects, *J Toxicol Environ Health B Crit Rev* 3(3) (2000) 145-78.
- [8] R.S. Gibson, J.C. King, N. Lowe, A review of dietary zinc recommendations, *Food Nutr Bull* 37(4) (2016) 443-460.
- [9] J.B. Vincent, New evidence against chromium as an essential trace element, *J Nutr* 147(12) (2017) 2212-2219.
- [10] HBM4EU, HBM4EU priority substances, 2017. <https://www.hbm4eu.eu/the-substances/>. (Accessed December 2017).
- [11] IARC, Cadmium and cadmium compounds, IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS 100C (2012) 121-145.
- [12] ATSDR, Toxicological profile for Cadmium, in: P.H.S. U.S. Department of Health and Human Services (Ed.) Agency for Toxic Substances and Disease Registry, Atlanta, GA, 2012.
- [13] IARC, Chromium, nickel and welding, IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS 49 (1990).
- [14] ATSDR, Toxicological profile for Chromium, in: P.H.S. U.S. Department of Health and Human Services (Ed.) Agency for Toxic Substances and Disease Registry, Atlanta, GA, 2012.
- [15] T. Filippini, B. Michalke, C. Malagoli, P. Grill, I. Bottecchi, M. Malavolti, L. Vescovi, S. Sieri, V. Krogh, A. Cherubini, G. Maffei, M. Modenesi, P. Castiglia, M. Vinceti, Determinants of serum cadmium levels in a Northern Italy community: A cross-sectional study, *Environ Res* 150 (2016) 219-26.
- [16] L. Vilavert, M. Nadal, M. Schuhmacher, J.L. Domingo, Concentrations of metals in soils in the neighborhood of a hazardous waste incinerator: assessment of the temporal trends, *Biol Trace Elem Res* 149(3) (2012) 435-42.
- [17] T. Coudon, H. Hourani, C. Nguyen, E. Faure, F.R. Mancini, B. Fervers, P. Salizzoni, Assessment of long-term exposure to airborne dioxin and cadmium concentrations in the Lyon metropolitan area (France), *Environ Int* 111 (2017) 177-190.
- [18] J.E. Heck, A.S. Park, J. Qiu, M. Cockburn, B. Ritz, Risk of leukemia in relation to exposure to ambient air toxics in pregnancy and early childhood, *Int J Hyg Environ Health* 217(6) (2014) 662-8.
- [19] T. Filippini, B. Michalke, P. Grill, C. Malagoli, M. Malavolti, L. Vescovi, S. Sieri, V. Krogh, A. Cherubini, G. Maffei, R. Lucchini, M. Ferrante, M. Vinceti, Determinants of serum manganese levels in an Italian population, *Mol Med Rep* 15(5) (2017) 3340-3349.

- [20] J. Hogervorst, M. Plusquin, J. Vangronsveld, T. Nawrot, A. Cuypers, E. Van Hecke, H.A. Roels, R. Carleer, J.A. Staessen, House dust as possible route of environmental exposure to cadmium and lead in the adult general population, *Environ Res* 103(1) (2007) 30-7.
- [21] C.I. Kim, J. Lee, S. Kwon, H.J. Yoon, Total Diet Study: For a Closer-to-real Estimate of Dietary Exposure to Chemical Substances, *Toxicol Res* 31(3) (2015) 227-40.
- [22] I. Bottecchi, M. Vinceti, [Trace elements in foods. Analysis of diet of Reggio Emilia and Modena], Department of Public Health, University of Modena and Reggio Emilia, 2012, p. 124.
- [23] A. Turrini, A. Saba, D. Perrone, E. Cialfa, A. D'Amicis, Food consumption patterns in Italy: the INN-CA Study 1994-1996, *Eur J Clin Nutr* 55(7) (2001) 571-88.
- [24] T. Filippini, A. Ferrari, B. Michalke, P. Grill, L. Vescovi, C. Salvia, C. Malagoli, M. Malavolti, S. Sieri, V. Krogh, A. Bargellini, A. Martino, M. Ferrante, M. Vinceti, Toenail selenium as an indicator of environmental exposure: A cross-sectional study, *Mol Med Rep* 15(5) (2017) 3405-3412.
- [25] M. Vinceti, C. Malagoli, C. Fiorentini, C. Longo, C.M. Crespi, G. Albertini, C. Ricci, A. Lanzoni, M. Reggiani, A. Virgili, F. Osti, M. Lombardi, M. Santini, P.A. Fanti, E. Dika, S. Sieri, V. Krogh, S. Seidenari, G. Pellacani, Inverse association between dietary vitamin D and risk of cutaneous melanoma in a northern Italy population, *Nutr Cancer* 63(4) (2011) 506-13.
- [26] C. Malagoli, M. Malavolti, C. Agnoli, C.M. Crespi, C. Fiorentini, F. Farnetani, C. Longo, C. Ricci, G. Albertini, A. Lanzoni, L. Veneziano, A. Virgili, C. Pagliarello, M. Santini, P.A. Fanti, E. Dika, S. Sieri, V. Krogh, G. Pellacani, M. Vinceti, Diet quality and risk of melanoma in an Italian population, *J Nutr* 145(8) (2015) 1800-7.
- [27] V. Pala, S. Sieri, D. Palli, S. Salvini, F. Berrino, M. Bellegotti, G. Frasca, R. Tumino, C. Sacerdote, L. Fiorini, E. Celentano, R. Galasso, V. Krogh, Diet in the Italian EPIC cohorts: presentation of data and methodological issues, *Tumori* 89(6) (2003) 594-607.
- [28] P. Pasanisi, F. Berrino, C. Bellati, S. Sieri, V. Krogh, Validity of the Italian EPIC questionnaire to assess past diet, *IARC Sci Publ* 156 (2002) 41-4.
- [29] M. Malavolti, C. Malagoli, C. Fiorentini, C. Longo, F. Farnetani, C. Ricci, G. Albertini, A. Lanzoni, C. Reggiani, A. Virgili, C. Pagliarello, M. Santini, P.A. Fanti, E. Dika, S. Sieri, V. Krogh, G. Pellacani, M. Vinceti, Association between dietary vitamin C and risk of cutaneous melanoma in a population of Northern Italy, *Int J Vitam Nutr Res* 83(5) (2013) 291-8.
- [30] G. Lombardi-Boccia, A. Aguzzi, M. Cappelloni, G. Di Lullo, M. Lucarini, Total-diet study: dietary intakes of macro elements and trace elements in Italy, *Br J Nutr* 90(6) (2003) 1117-21.
- [31] G. Ysart, P. Miller, M. Croasdale, H. Crews, P. Robb, M. Baxter, C. de L'Argy, N. Harrison, 1997 UK Total Diet Study--dietary exposures to aluminium, arsenic, cadmium, chromium, copper, lead, mercury, nickel, selenium, tin and zinc, *Food Addit Contam* 17(9) (2000) 775-86.
- [32] A. Turrini, G. Lombardi-Boccia, The formulation of the market basket of the Italian total diet 1994-96, *Nutr Res* 22(10) (2002) 1151-1162.
- [33] C. Leclercq, D. Arcella, R. Piccinelli, S. Sette, C. Le Donne, A. Turrini, I.-S.S. Group, The Italian National Food Consumption Survey INRAN-SCAI 2005-06: main results in terms of food consumption, *Public Health Nutr* 12(12) (2009) 2504-32.
- [34] A. European Food Safety, Cadmium dietary exposure in the European population, *EFSA Journal* 10(1) (2012) 2551-n/a.
- [35] Z. Marzec, M. Schlegel-Zawadzka, Exposure to cadmium, lead and mercury in the adult population from Eastern Poland, 1990--2002, *Food Addit Contam* 21(10) (2004) 963-70.
- [36] WHO, Safety evaluation of certain contaminants in food prepared by the Seventy-third meeting of the Joint FAO/ WHO Expert Committee on Food Additives (JECFA): Cadmium, WHO, Geneva, 2011.

- [37] E. Jablonska, K. Socha, E. Reszka, E. Wieczorek, J. Skokowski, L. Kalinowski, W. Fendler, B. Seroczynska, M. Wozniak, M.H. Borawska, W. Wasowicz, Cadmium, arsenic, selenium and iron-Implications for tumor progression in breast cancer, *Environ Toxicol Pharmacol* 53 (2017) 151-157.
- [38] G. Van Maele-Fabry, N. Lombaert, D. Lison, Dietary exposure to cadmium and risk of breast cancer in postmenopausal women: A systematic review and meta-analysis, *Environ Int* 86 (2016) 1-13.
- [39] A.A. Tinkov, T. Filippini, O.P. Ajsuvakova, J. Aaseth, Y.G. Gluhcheva, J.M. Ivanova, G. Bjorklund, M.G. Skalnaya, E.R. Gatiatulina, E.V. Popova, O.N. Nemereshina, M. Vinceti, A.V. Skalny, The role of cadmium in obesity and diabetes, *Sci Total Environ* 601-602 (2017) 741-755.
- [40] S. Satarug, D.A. Vesey, G.C. Gobe, Kidney Cadmium Toxicity, Diabetes and High Blood Pressure: The Perfect Storm, *Tohoku J Exp Med* 241(1) (2017) 65-87.
- [41] A.A. Tinkov, T. Filippini, O.P. Ajsuvakova, M.G. Skalnaya, J. Aaseth, G. Bjorklund, E.R. Gatiatulina, E.V. Popova, O.N. Nemereshina, P.T. Huang, M. Vinceti, A.V. Skalny, Cadmium and atherosclerosis: a review of toxicological mechanisms and a meta-analysis of epidemiologic studies, *Environ Res* in press (2018).
- [42] S. Satarug, D.A. Vesey, G.C. Gobe, Health Risk Assessment of Dietary Cadmium Intake: Do Current Guidelines Indicate How Much is Safe?, *Environ Health Perspect* 125(3) (2017) 284-288.
- [43] E.H. Larsen, N.L. Andersen, A. Moller, A. Petersen, G.K. Mortensen, J. Petersen, Monitoring the content and intake of trace elements from food in Denmark, *Food Addit Contam* 19(1) (2002) 33-46.
- [44] C. Cuadrado, J. Kumpulainen, O. Moreiras, Lead, cadmium and mercury contents in average Spanish market basket diets from Galicia, Valencia, Andalucia and Madrid, *Food Addit Contam* 12(1) (1995) 107-18.
- [45] European Food Safety Authority, Cadmium dietary exposure in the European population, *EFSA Journal* 10(1) (2012) 2551-n/a.
- [46] C.M. Iwegbue, Concentrations of selected metals in candies and chocolates consumed in southern Nigeria, *Food Addit Contam Part B Surveill* 4(1) (2011) 22-7.
- [47] R.L. Yanus, H. Sela, E.J. Borojovich, Y. Zakon, M. Saphier, A. Nikolski, E. Gutflais, A. Lorber, Z. Karpas, Trace elements in cocoa solids and chocolate: an ICPMS study, *Talanta* 119 (2014) 1-4.
- [48] G. Turconi, C. Minoia, A. Ronchi, C. Roggi, Dietary exposure estimates of twenty-one trace elements from a Total Diet Study carried out in Pavia, Northern Italy, *Br J Nutr* 101(8) (2009) 1200-8.
- [49] B. Michalke, Review about the manganese speciation project related to neurodegeneration: An analytical chemistry approach to increase the knowledge about manganese related parkinsonian symptoms, *J Trace Elem Med Biol* 37 (2016) 50-61.
- [50] N. Solovyev, M. Vinceti, P. Grill, J. Mandrioli, B. Michalke, Redox speciation of iron, manganese, and copper in cerebrospinal fluid by strong cation exchange chromatography - sector field inductively coupled plasma mass spectrometry, *Anal Chim Acta* 973 (2017) 25-33.
- [51] A. Takeda, Movement of zinc and its functional significance in the brain, *Brain Res Brain Res Rev* 34(3) (2000) 137-48.
- [52] R. Squitti, R. Ghidoni, I. Simonelli, I.D. Ivanova, N.A. Colabufo, M. Zuin, L. Benussi, G. Binetti, E. Cassetta, M. Rongioletti, M. Siotto, Copper dyshomeostasis in Wilson disease and Alzheimer's disease as shown by serum and urine copper indicators, *J Trace Elem Med Biol* 45 (2018) 181-188.
- [53] M. Vinceti, T. Filippini, S. Cilloni, A. Bargellini, A.V. Vergoni, A. Tsatsakis, M. Ferrante, Health risk assessment of environmental selenium: Emerging evidence and challenges (Review), *Mol Med Rep* 15(5) (2017) 3323-3335.

- [54] N. Waegeneers, C. Thiry, L. De Temmerman, A. Ruttens, Predicted dietary intake of selenium by the general adult population in Belgium, *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* 30(2) (2013) 278-85.
- [55] European Food Safety Authority, Scientific Opinion on Dietary Reference Values for selenium, *EFSA Journal* 12(10) (2014) 3846-n/a.
- [56] WHO/FAO, Vitamin and mineral requirements in human nutrition: report of a joint FAO/WHO expert consultation. Bangkok, Thailand, 21–30 September 1998., Joint FAO/WHO Expert Consultation on Human Vitamin and Mineral Requirements, 2004, p. 341 pp.
- [57] M.N.I. Barclay, A. MacPherson, J. Dixon, Selenium Content of a Range of UK Foods, *J Food Compos Anal* 8(4) (1995) 307-318.
- [58] M.G. Ventura, M. do Carmo Freitas, A.M.G. Pacheco, T. van Meerten, H.T. Wolterbeek, Selenium content in selected Portuguese foodstuffs, *Eur Food Res Technol* 224(3) (2007) 403-403.
- [59] J.P. Diaz-Alarcon, M. Navarro-Alarcon, H. Lopez-Garcia de la Serrana, M.C. Lopez-Martinez, Determination of Selenium Levels in Vegetables and Fruits by Hydride Generation Atomic Absorption Spectrometry, *J Agric Food Chem* 42(12) (1994) 2848-2851.
- [60] J.P. Diaz-Alarcon, M. Navarro-Alarcon, H. Lopez-Garcia de la Serrana, M.C. Lopez-Martinez, Determination of selenium in cereals, legumes and dry fruits from southeastern Spain for calculation of daily dietary intake, *Sci Total Environ* 184(3) (1996) 183-9.
- [61] J.P. Diaz, M. Navarro, H. Lopez, M.C. Lopez, Determination of selenium levels in dairy products and drinks by hydride generation atomic absorption spectrometry: correlation with daily dietary intake, *Food Addit Contam* 14(2) (1997) 109-14.
- [62] J.P. Díaz-Alarcón, M. Navarro-Alarcón, H. López-García de la Serrana, M.C. López-Martínez, Determination of Selenium in Meat Products by Hydride Generation Atomic Absorption Spectrometry Selenium Levels in Meat, Organ Meats, and Sausages in Spain, *J Agric Food Chem* 44(6) (1996) 1494-1497.
- [63] J.P. Diaz-Alarcon, M. Navarro-Alarcon, M.C. Lopez-Martinez, H. Lopez-Garcia de la Serrana, Determination of selenium in fresh fish from southeastern Spain for calculation of daily dietary intake, *J Agric Food Chem* 42(2) (1994) 334-337.
- [64] J. Murphy, K.D. Cashman, Selenium content of a range of Irish foods, *Food Chem* 74(4) (2001) 493-498.
- [65] P. Smrkolj, L. Pograjc, C. Hlastan-Ribič, V. Stibilj, Selenium content in selected Slovenian foodstuffs and estimated daily intakes of selenium, *Food Chem* 90(4) (2005) 691-697.
- [66] R. Amodio-Cocchieri, A. Arnese, A. Roncioni, G. Silvestri, Evaluation of the selenium content of the traditional Italian diet, *Int J Food Sci Nutr* 46(2) (1995) 149-54.
- [67] J.B. Vincent, Is chromium pharmacologically relevant?, *J Trace Elem Med Biol* 28(4) (2014) 397-405.
- [68] A. Levina, P.A. Lay, Chemical properties and toxicity of chromium(III) nutritional supplements, *Chem Res Toxicol* 21(3) (2008) 563-71.
- [69] European Food Safety Authority, Scientific Opinion on Dietary Reference Values for chromium, *EFSA Journal* 12(10) (2014) 3845-n/a.
- [70] Institute of Medicine, Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc, National Academy Press, Washington, DC, 2001.
- [71] L. Noel, R. Chekri, S. Millour, C. Vastel, A. Kadar, V. Sirot, J.C. Leblanc, T. Guerin, Li, Cr, Mn, Co, Ni, Cu, Zn, Se and Mo levels in foodstuffs from the Second French TDS, *Food Chem* 132(3) (2012) 1502-1513.
- [72] R.A. Anderson, N.A. Bryden, M.M. Polansky, Dietary chromium intake. Freely chosen diets, institutional diet, and individual foods, *Biol Trace Elem Res* 32 (1992) 117-21.

- [73] H.S. Sharma, V.K. Kutala, P. Kuppusamy, Special issue on oxidative stress in health and disease, *Cell Biochem Biophys* 67(2) (2013) 215-8.
- [74] R. Squitti, A.J. Mendez, I. Simonelli, C. Ricordi, Diabetes and Alzheimer's Disease: Can Elevated Free Copper Predict the Risk of the Disease?, *J Alzheimers Dis* 56(3) (2017) 1055-1064.
- [75] European Food Safety Authority, Scientific Opinion on Dietary Reference Values for copper, *EFSA Journal* 13(10) (2015) 4253-n/a.
- [76] WHO, Copper in Drinking-water: Background document for development of WHO Guidelines for Drinking-water Quality, WHO Press, Geneva, 2004.
- [77] A.C. Pfalzer, A.B. Bowman, Relationships Between Essential Manganese Biology and Manganese Toxicity in Neurological Disease, *Curr Environ Health Rep* 4(2) (2017) 223-228.
- [78] European Food Safety Authority, Scientific Opinion on Dietary Reference Values for manganese, *EFSA Journal* 11(11) (2013) 3419-n/a.
- [79] WHO, Manganese in Drinking-water: background document for development of WHO Guidelines for Drinking-water Quality, World Health Organization, WHO Press, 2011.
- [80] J.C. Leblanc, T. Guerin, L. Noel, G. Calamassi-Tran, J.L. Volatier, P. Verger, Dietary exposure estimates of 18 elements from the 1st French Total Diet Study, *Food Addit Contam* 22(7) (2005) 624-41.
- [81] ATSDR, Toxicological profile for Manganese, in: P.H.S. U.S. Department of Health and Human Services (Ed.) Agency for Toxic Substances and Disease Registry, Atlanta, GA, 2012.
- [82] W. Podwika, K. Kleszcz, M. Krosniak, P. Zagrodzki, Copper, Manganese, Zinc, and Cadmium in Tea Leaves of Different Types and Origin, *Biol Trace Elem Res* (2017).
- [83] S. Hope, K. Daniel, K.L. Gleason, S. Comber, M. Nelson, J.J. Powell, Influence of tea drinking on manganese intake, manganese status and leucocyte expression of MnSOD and cytosolic aminopeptidase P, *Eur J Clin Nutr* 60(1) (2006) 1-8.
- [84] L. Marger, C.R. Schubert, D. Bertrand, Zinc: an underappreciated modulatory factor of brain function, *Biochem Pharmacol* 91(4) (2014) 426-35.
- [85] J.C. King, Zinc: an essential but elusive nutrient, *Am J Clin Nutr* 94(2) (2011) 679S-84S.
- [86] D.R. Morris, C.W. Levenson, Neurotoxicity of Zinc, *Adv Neurobiol* 18 (2017) 303-312.
- [87] S.D. Portbury, P.A. Adlard, Zinc Signal in Brain Diseases, *Int J Mol Sci* 18(12) (2017).
- [88] European Food Safety Authority, Scientific Opinion on Dietary Reference Values for zinc, *EFSA Journal* 12(10) (2014) 3844-n/a.
- [89] R.K. Gupta, S.S. Gangoliya, N.K. Singh, Reduction of phytic acid and enhancement of bioavailable micronutrients in food grains, *J Food Sci Technol* 52(2) (2015) 676-84.
- [90] S. Sette, C. Le Donne, R. Piccinelli, L. Mistura, M. Ferrari, C. Leclercq, I.-S.s. group, The third National Food Consumption Survey, INRAN-SCAI 2005-06: major dietary sources of nutrients in Italy, *Int J Food Sci Nutr* 64(8) (2013) 1014-21.
- [91] A. Turrini, G. Lombardi-Boccia, F. Aureli, F. Cubadda, L. D'Addezio, M. D'Amato, L. D'Evoli, P. Darnerud, N. Devlin, M.G. Dias, M. Jurkovic, C. Kelleher, C. Le Donne, M. Lopez Esteban, M. Lucarini, M.A. Martinez Burgos, E. Martinez-Victoria, B. McNulty, L. Mistura, A. Nugent, H.I. Oktay Basegmez, L. Oliveira, H. Ozer, G. Perello, M. Pite, K. Presser, D. Sokolic, E. Vasco, J.L. Volatier, A conceptual framework for the collection of food products in a Total Diet Study, *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* (2017) 1-20.
- [92] D. Gonzalez-Weller, C. Rubio, A.J. Gutierrez, G.L. Gonzalez, J.M. Caballero Mesa, C. Revert Girones, A. Burgos Ojeda, A. Hardisson, Dietary intake of barium, bismuth, chromium, lithium, and strontium in a Spanish population (Canary Islands, Spain), *Food Chem Toxicol* 62 (2013) 856-8.
- [93] H.T. Shacklette, J.G. Boerngen, Element concentrations in soils and other surficial materials of the conterminous United States, Washington, 2013.

- [94] F. Conte, C. Copat, S. Longo, G.O. Conti, A. Grasso, G. Arena, M.V. Brundo, M. Ferrante, First data on trace elements in *Haliotis tuberculata* (Linnaeus, 1758) from southern Italy: Safety issues, *Food Chem Toxicol* 81 (2015) 143-50.
- [95] M. Ferrante, S.S. Signorelli, S.L. Ferlito, A. Grasso, A. Dimartino, C. Copat, Groundwater-based water wells characterization from Guinea Bissau (Western Africa): A risk evaluation for the local population, *Sci Total Environ* 619-620 (2018) 916-926.
- [96] J.M. Llobet, G. Falco, C. Casas, A. Teixido, J.L. Domingo, Concentrations of arsenic, cadmium, mercury, and lead in common foods and estimated daily intake by children, adolescents, adults, and seniors of Catalonia, Spain, *J Agric Food Chem* 51(3) (2003) 838-42.
- [97] AFSSA, Étude Individuelle Nationale des Consommations Alimentaires 2 (INCA 2) (2006-2007), 2009.
- [98] Z. Vincevica-Gaile, M. Klavins, Concentration of Elements in Food: How Can It Reflect Impact of Environmental and Other Influencing Factors?, *Environmental and Climate Technologies* 12(1) (2013) 15-19.
- [99] C.J. Bates, C.W. Thane, A. Prentice, H.T. Delves, Selenium status and its correlates in a British national diet and nutrition survey: people aged 65 years and over, *J Trace Elem Med Biol* 16(1) (2002) 1-8.
- [100] C. Copat, M.V. Brundo, G. Arena, A. Grasso, G. Oliveri Conti, C. Ledda, R. Fallico, S. Sciacca, M. Ferrante, Seasonal variation of bioaccumulation in *Engraulis encrasicolus* (Linnaeus, 1758) and related biomarkers of exposure, *Ecotoxicol Environ Saf* 86 (2012) 31-7.
- [101] C.A. Swanson, M.P. Longnecker, C. Veillon, M. Howe, O.A. Levander, P.R. Taylor, P.A. McAdam, C.C. Brown, M.J. Stampfer, W.C. Willett, Selenium intake, age, gender, and smoking in relation to indices of selenium status of adults residing in a seleniferous area, *Am J Clin Nutr* 52(5) (1990) 858-62.
- [102] B. Emmanuelle, M. Virginie, S. Fabienne, I. Isabelle, P.G. Martine, L. Bernard, R. Sylvie, Selenium exposure in subjects living in areas with high selenium concentrated drinking water: results of a French integrated exposure assessment survey, *Environ Int* 40 (2012) 155-61.
- [103] A. Agudo, N. Slimani, M.C. Ocke, A. Naska, A.B. Miller, A. Kroke, C. Bamia, D. Karalis, P. Vineis, D. Palli, H.B. Bueno-de-Mesquita, P.H. Peeters, D. Engeset, A. Hjartaker, C. Navarro, C. Martinez Garcia, P. Wallstrom, J.X. Zhang, A.A. Welch, E. Spencer, C. Stripp, K. Overvad, F. Clavel-Chapelon, C. Casagrande, E. Riboli, Consumption of vegetables, fruit and other plant foods in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts from 10 European countries, *Public Health Nutr* 5(6B) (2002) 1179-96.
- [104] J. Halkjaer, A. Olsen, L.J. Bjerregaard, G. Deharveng, A. Tjonneland, A.A. Welch, F.L. Crowe, E. Wirfalt, V. Hellstrom, M. Niravong, M. Touvier, J. Linseisen, A. Steffen, M.C. Ocke, P.H. Peeters, M.D. Chirlaque, N. Larranaga, P. Ferrari, P. Contiero, G. Frasca, D. Engeset, E. Lund, G. Misirli, M. Kostis, E. Riboli, N. Slimani, S. Bingham, Intake of total, animal and plant proteins, and their food sources in 10 countries in the European Prospective Investigation into Cancer and Nutrition, *Eur J Clin Nutr* 63 Suppl 4 (2009) S16-36.
- [105] A. Olsen, J. Halkjaer, C.H. van Gils, B. Buijsse, H. Verhagen, M. Jenab, M.C. Boutron-Ruault, U. Ericson, M.C. Ocke, P.H. Peeters, M. Touvier, M. Niravong, M. Waaseth, G. Skeie, K.T. Khaw, R. Travis, P. Ferrari, M.J. Sanchez, A. Agudo, K. Overvad, J. Linseisen, C. Weikert, C. Sacerdote, A. Evangelista, D. Zylis, K. Tsiotas, J. Manjer, B. van Guelpen, E. Riboli, N. Slimani, S. Bingham, Dietary intake of the water-soluble vitamins B1, B2, B6, B12 and C in 10 countries in the European Prospective Investigation into Cancer and Nutrition, *Eur J Clin Nutr* 63 Suppl 4 (2009) S122-49.
- [106] A.A. Welch, H. Fransen, M. Jenab, M.C. Boutron-Ruault, R. Tumino, C. Agnoli, U. Ericson, I. Johansson, P. Ferrari, D. Engeset, E. Lund, M. Lentjes, T. Key, M. Touvier, M. Niravong, N. Larranaga, L. Rodriguez, M.C. Ocke, P.H. Peeters, A. Tjonneland, L. Bjerregaard, E. Vasilopoulou, V.



- Dilis, J. Linseisen, U. Nothlings, E. Riboli, N. Slimani, S. Bingham, Variation in intakes of calcium, phosphorus, magnesium, iron and potassium in 10 countries in the European Prospective Investigation into Cancer and Nutrition study, *Eur J Clin Nutr* 63 Suppl 4 (2009) S101-21.
- [107] M. Vinceti, A. Chiari, M. Eichmuller, K.J. Rothman, T. Filippini, C. Malagoli, J. Weuve, M. Tondelli, G. Zamboni, P.F. Nichelli, B. Michalke, A selenium species in cerebrospinal fluid predicts conversion to Alzheimer's dementia in persons with mild cognitive impairment, *Alzheimers Res Ther* 9(1) (2017) 100.
- [108] C.M. Weekley, H.H. Harris, Which form is that? The importance of selenium speciation and metabolism in the prevention and treatment of disease, *Chem Soc Rev* 42(23) (2013) 8870-94.
- [109] A. Castro Grijalba, E.F. Fiorentini, R.G. Wuilloud, Ionic liquid-assisted separation and determination of selenium species in food and beverage samples by liquid chromatography coupled to hydride generation atomic fluorescence spectrometry, *J Chromatogr A* 1491 (2017) 117-125.
- [110] M. Ruiz-de-Cenzano, A. Rochina-Marco, M.L. Cervera, M. de la Guardia, Evaluation of the content of antimony, arsenic, bismuth, selenium, tellurium and their inorganic forms in commercially baby foods, *Biol Trace Elem Res* 180(2) (2017) 355-365.
- [111] L. Ruzik, Speciation of challenging elements in food by atomic spectrometry, *Talanta* 93 (2012) 18-31.
- [112] B. Michalke, S. Halbach, V. Nischwitz, JEM spotlight: metal speciation related to neurotoxicity in humans, *J Environ Monit* 11(5) (2009) 939-54.
- [113] T. Eagling, A.L. Neal, S.P. McGrath, S. Fairweather-Tait, P.R. Shewry, F.J. Zhao, Distribution and speciation of iron and zinc in grain of two wheat genotypes, *J Agric Food Chem* 62(3) (2014) 708-16.
- [114] D. Citak, M. Tuzen, M. Soylak, Speciation of Mn(II), Mn(VII) and total manganese in water and food samples by coprecipitation-atomic absorption spectrometry combination, *J Hazard Mater* 173(1-3) (2010) 773-7.
- [115] EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), Scientific Opinion on the risks to public health related to the presence of chromium in food and drinking water, *EFSA Journal* 12(3) (2014) 3595 [261 pp.].
- [116] E. Sazakli, C.M. Villanueva, M. Kogevinas, K. Maltezis, A. Mouzaki, M. Leotsinidis, Chromium in drinking water: association with biomarkers of exposure and effect, *Int J Environ Res Public Health* 11(10) (2014) 10125-45.
- [117] M.E. Soares, E. Vieira, L. Bastos Mde, Chromium speciation analysis in bread samples, *J Agric Food Chem* 58(2) (2010) 1366-70.
- [118] M.W. Mathebula, K. Mandiwana, N. Panichev, Speciation of chromium in bread and breakfast cereals, *Food Chem* 217 (2017) 655-659.
- [119] B. Novotnik, T. Zuliani, J. Scancar, R. Milacic, Chromate in food samples: an artefact of wrongly applied analytical methodology?, *J Anal At Spectrom* 28(4) (2013) 558-566.
- [120] V. Vacchina, I. de la Calle, F. Seby, Cr(VI) speciation in foods by HPLC-ICP-MS: investigation of Cr(VI)/food interactions by size exclusion and Cr(VI) determination and stability by ion-exchange on-line separations, *Anal Bioanal Chem* 407(13) (2015) 3831-9.
- [121] F. Hernandez, F. Seby, S. Millour, L. Noel, T. Guerin, Optimisation of selective alkaline extraction for Cr(VI) determination in dairy and cereal products by HPIC-ICPMS using an experimental design, *Food Chem* 214 (2017) 339-346.
- [122] V.M. Labunskyy, D.L. Hatfield, V.N. Gladyshev, Selenoproteins: molecular pathways and physiological roles, *Physiol Rev* 94(3) (2014) 739-77.
- [123] C.W. Nogueira, J.B. Rocha, Toxicology and pharmacology of selenium: emphasis on synthetic organoselenium compounds, *Arch Toxicol* 85(11) (2011) 1313-59.

- [124] T.A. Marschall, J. Bornhorst, D. Kuehnelt, T. Schwerdtle, Differing cytotoxicity and bioavailability of selenite, methylselenocysteine, selenomethionine, selenosugar 1 and trimethylselenonium ion and their underlying metabolic transformations in human cells, *Mol Nutr Food Res* 60(12) (2016) 2622-2632.
- [125] J. Mandrioli, B. Michalke, N. Solovyev, P. Grill, F. Violi, C. Lunetta, A. Conte, V.A. Sansone, M. Sabatelli, M. Vinceti, Elevated levels of selenium species in cerebrospinal fluid of amyotrophic lateral sclerosis patients with disease-associated gene mutations, *Neurodegener Dis* 17(4-5) (2017) 171-180.
- [126] S.J. Fairweather-Tait, R. Collings, R. Hurst, Selenium bioavailability: current knowledge and future research requirements, *Am J Clin Nutr* 91(5) (2010) 1484S-1491S.
- [127] W.R. Wolf, R.J. Goldschmidt, Updated estimates of the selenomethionine content of NIST wheat reference materials by GC-IDMS, *Anal Bioanal Chem* 387(7) (2007) 2449-52.
- [128] S.J. Fairweather-Tait, Y. Bao, M.R. Broadley, R. Collings, D. Ford, J.E. Hesketh, R. Hurst, Selenium in human health and disease, *Antioxid Redox Signal* 14(7) (2011) 1337-83.
- [129] J.W. Finley, Selenium accumulation in plant foods, *Nutr Rev* 63(6 Pt 1) (2005) 196-202.
- [130] C.J. Cappon, J.C. Smith, Chemical form and distribution of mercury and selenium in edible seafood, *J Anal Toxicol* 6(1) (1982) 10-21.
- [131] C.J. Cappon, J.C. Smith, Chemical form and distribution of mercury and selenium in canned tuna, *J Appl Toxicol* 2(4) (1982) 181-9.
- [132] J. Moreda-Pineiro, A. Moreda-Pineiro, V. Romaris-Hortas, R. Dominguez-Gonzalez, E. Alonso-Rodriguez, P. Lopez-Mahia, S. Muniategui-Lorenzo, D. Prada-Rodriguez, P. Bermejo-Barrera, In vitro bioavailability of total selenium and selenium species from seafood, *Food Chem* 139(1-4) (2013) 872-7.
- [133] WHO, Zinc in Drinking-water: Background document for development of WHO Guidelines for Drinking-water Quality, WHO Press, Geneva, 2003.
- [134] WHO, Cadmium in Drinking-water: background document for development of WHO Guidelines for Drinking-water Quality, World Health Organization, WHO Press, 2011.
- [135] WHO, Chromium in Drinking-water: Background document for development of WHO Guidelines for Drinking-water Quality, WHO Press, Geneva, 2003.
- [136] WHO, Selenium in Drinking-water: background document for development of WHO Guidelines for Drinking-water Quality, World Health Organization, WHO Press, 2011.
- [137] M. Vinceti, C.M. Crespi, F. Bonvicini, C. Malagoli, M. Ferrante, S. Marmiroli, S. Stranges, The need for a reassessment of the safe upper limit of selenium in drinking water, *Sci Total Environ* 443 (2013) 633-42.
- [138] R.B. Jain, Factors affecting the variability in the observed levels of urinary cadmium among children and nonsmoker adolescents, *Environ Sci Pollut Res Int* 24(3) (2017) 2515-2526.