Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the risk associated with the presence of nickel in food for the population sensitised to this metal

Reference number: AESAN-2021-015

Report approved by the Scientific Committee in its plenary session on 24 November 2021

Working group

María José González Muñoz (Coordinator), Houda Berrada Ramdani, Álvaro Daschner*, Ángel Gil Izquierdo and Silvia Pichardo Sánchez

Abstract

Nickel (Ni) is a toxic metal whose most prevalent effect in the general population is allergic contact dermatitis. There is concern that Ni-sensitised individuals may develop eczematous skin reactions after dietary exposure, as their main source of non-occupational exposure is food. Therefore, it is essential to assess the risk associated with the presence of Ni in food for this population.

Once analysing the problem of sensitisation to Ni and knowing the kinetics and toxicity of this metal, the sources and causes of the presence of Ni in different foods and the contribution of the different food groups to the total diet have been studied.

In conclusion, a careful selection of foods with relatively low Ni levels can result in a reduction of

Translated from the original published in the journal: Revista del Comité Científico de la AESAN, 35, pp: 53-90.

the total daily intake of Ni in the diet and may help in some cases to control systemic contact dermatitis in Ni-sensitised patients. Therefore, professionals who consider it are offered a diet proposal for patients who present hypersensitivity with systemic affection to Ni, by following a low Ni-diet, not consuming the first jet of water in the tap and reducing the consumption of black chocolate of high purity.

Key words

Nickel, food, hypersensitivity, allergic dermatitis, diet, systemic contact dermatitis.

Suggested citation

AESAN Scientific Committee. (Working group) González, M.J., Berrada, H., Daschner, Á., Gil, Á. y Pichardo, S. Informe del Comité Científico de la Agencia Española de Seguridad Alimentaria y Nutrición (AESAN) sobre el riesgo asociado a la presencia de níquel en alimentos para población sensibilizada a este metal. *Revista del Comité Científico*, 2022, 35, pp: 53-90.

1. Introduction

Nickel (Ni) forms part of different minerals in the Earth's crust: chalcopyrite, pentlandite, garnierite, niccolite and millerite. The average concentration of Ni in soil varies between 20 and 30 mg/kg, and can reach up to 10 000 mg/kg in certain soil types. Therefore, Ni can come from the environment and be transferred through the soil to the plant by root or foliar absorption, being a first source of this element in plant food, and from there, be transferred to the whole food chain either by direct human consumption or indirectly through other animals included in the food chain (AFSSA, 2007). It must also be noted that Ni is included on the list of processing aids to catalyse the hydrogenation of food fats and oils (with the exception of butter) with a maximum content of 0.2 mg Ni/kg of final product. Thus, processing can include Ni in an authorised external manner, in principle without any health risk to the general population, except for Ni-sensitised groups of people (ANSES, 2019). Ni may also be passively present in water pipes and other fluids in the food industry by transfer. The presence of this element is therefore quite widespread and can come from different sources within the diet and, despite the fact that it is not essential for humans, its intake varies between 74 and 231 µg/day for adults.

In 2015, the European Food Safety Authority (EFSA) published a scientific opinion on Ni in food and drinking water and considered systemic contact dermatitis in sensitive humans as the critical effect for the assessment of acute effects. It set a 95 % lower confidence limit for a baseline response, with an additional 10 % risk (BMDL10) of 1.1 µg Ni/kg body weight (b.w.) and used the Margin of Exposure (MOE) approach, noting that a value of less than 10 would be indicative of low health concern. The calculated MOEs for both the mean and 95th percentile acute exposure levels for all age groups were significantly below 10. EFSA concluded that, despite this, acute dietary exposure is of concern in nickel-sensitised individuals, as eczematous skin reactions may develop. In 2020, the EFSA published an update of the risk assessment of Ni in food and drinking water in which it continues to consider systemic contact dermatitis to be the critical effect for acute oral exposure risk characterisation. Both EFSA opinions (2015a, 2020) warn that oral exposure to Ni triggers systemic symptoms in previously sensitised patients. Acute oral exposure may cause skin reactions after consumption of foods with high levels of Ni, such as cereals (rice), legumes, cocoa, tea and green leafy vegetables.

Therefore, this report reviews the presence of Ni in food in order to assess the risk to the Ni-sensitised population diagnosed with systemic contact dermatitis.

2. Toxicokinetics

Pharmacokinetic studies in humans indicate that Ni is absorbed through the lungs, skin and gastrointestinal tract. Oral absorption varies greatly depending on different factors, one of the most important of which is the fasting state.

The variability of the toxic effect of Ni species lies partly in how different forms of Ni are endocytosed by the cell, while others are not. Soluble Ni species are rapidly excreted by tissues, so their ability to enter cells via divalent metal transporters is limited; evidence suggests that their route of entry is via calcium channels. Nickel carbonyl, a highly toxic species, is lipid-soluble, allowing it to pass through the cell membrane and allowing significant absorption by inhalation and skin con-

tact. On the other hand, there are species that are poorly soluble in aqueous media, such as nickel sulphide (Ni_3S_2), which enter via the endocytic pathway, and which are among the most toxic and carcinogenic forms. Other species, also poorly soluble in aqueous media, such as the amorphous form of NiS, do not penetrate the cell and are therefore of little or no toxicological significance (Muñoz and Costa, 2012).

Once it has entered the body it is well distributed throughout, largely bound to plasma proteins (Sarkar, 1984) (Sunderman et al., 1986). The body burden of Ni in a 70 kg adult varies between 0.5 and 10 mg (Olivares et al., 2015). Importantly, Ni is capable of crossing the placental barrier and reaching the foetus, which is particularly sensitive to the metal (Hou et al., 2011).

Finally, absorbed Ni is excreted in urine while unabsorbed Ni is excreted in faeces (Sunderman et al., 1989) (Patriarca et al., 1997) (ATSDR, 2005). The elimination half-life is 28 ± 9 hours (Sunderman et al., 1989). Ni has also been detected in breast milk at concentrations ranging from 0.79 to 43.9 µg/l.

3. Bioavailability and bioaccessibility

According to the EFSA's opinion, the bioavailability and bioaccessibility of Ni should be considered in order to perform a correct dietary exposure assessment (EFSA, 2015a). However, the vast majority of articles available on Ni content in food do not take both parameters into account when assessing exposure, resulting in an overestimation of exposure (Babaahmadifooladi et al., 2020).

Bioaccessibility is defined as the soluble fraction of total Ni that has left the food matrix and is found in the digestive fluids at the time of digestion, which is the maximum fraction that can be absorbed (Junli et al., 2013). It is highly dependent on the nature of the Ni, so that there is great variability in the bioaccessibility of the metal depending on the compound it forms (Dutton et al., 2021). The most soluble forms are nickel chloride, nickel acetate, nickel fluoride and nickel hydroxycarbonate, with a bioaccessibility rate of 82-91 %. Ni metal, nickel (II) oxide and nickel alloys have very low bioaccessibility levels 0.09-23.6 %, 0.03-0.3 % and 0.008-2.8 %, respectively (Henderson et al., 2012) (Heim et al., 2020).

Regarding the influence of food on Ni absorption, higher bioaccessibility has generally been observed in foods of animal origin (83.11 % in mussels, followed by 59.93 % in fish and cephalopods) (Gedik, 2018) (Gu et al., 2018), and lower in certain plant foods (<LOD for *Sarcocornia ambigua* and 27-40 % for *Ipomoea aquatica*) (Lam and Lai, 2018). For other vegetables, as well as cereals, the bioavailability ranged from approximately 30-60 % (Junli et al., 2013) (Liu et al., 2017). However, very high bioaccessibilities have recently been reported for wheat-based cereals (99.6 %) (Babaahmadifooladi et al., 2021).

Once the fraction is bioaccessible in the gastrointestinal tract, it must be absorbed. We define bioavailability, therefore, as the fraction of Ni that passes through the intestinal epithelium into the blood (Wei et al., 2012). Early studies reported Ni bioavailability values after water consumption of 25 % and 1 % when consumed with food (Sunderman, 1989). Subsequently, the importance of fasting on Ni bioavailability was shown to be 1-5 % in exposure with food and 12-27 % under fasting conditions (Nielsen et al., 1999). Similar data have been found after consumption of water with 30 % bioavailability (ECB, 2008) and in processed foods and fast food with 4.5-7.8 % (Cabrera-Vique et

al., 2011). The presence of other essential elements (such as zinc or copper) significantly decreases the bioavailability of Ni (Cempel and Janicka, 2002). Thus, low iron content in rice has been shown to increase the bioavailability of Ni in rice (Li et al., 2020).

4. Health effects

Ni is not essential for humans although it plays an essential role in methionine metabolism in other animal species (WHO, 2005). The toxic effects of Ni in the body depend on multiple factors such as chemical species, physical form, concentration or source of exposure (Ahmad and Ashraf, 2011) (Schaumlöffel, 2012).

4.1 Toxicity

Acute Ni poisoning is exceptional in humans. In the few published cases, the ingested doses associated with toxic effects were very high, above 7 mg/kg b.w. (Sunderman, 1989).

Human and animal studies suggest that chronic exposure to soluble Ni salts leads to systemic kidney effects, neonatal mortality and effects on the immune system. The kidney is the main target organ in both exposures. It should be noted that there are no human studies on the chronic reproductive and developmental effects of orally administered Ni (WHO, 1996) (ATSDR, 1999). Chronic exposure may be responsible for a variety of adverse health effects in humans, such as pulmonary fibrosis, kidney and cardiovascular diseases and respiratory tract cancer (Das et al., 2018) (Genchi et al., 2020) (Guo et al., 2020).

Several studies underline the genotoxicity of Ni (Costa et al., 2002) (Chen et al., 2003). The mechanisms of this genotoxicity are multiple:

- Single and double stranded DNA breaks for concentrations of 0.1-10 µM with activation of Poly ADP-ribose polymerase which is normally induced in the presence of DNA lesions (Lei et al., 2001).
- Production of reactive oxygen species such as hydroxyl radical (Costa et al., 2002) (Chen et al., 2003).
- Inhibition (at non-cytotoxic Ni 2+ concentrations) of DNA damage repair processes caused by UV and B(a)P, among others (Wozniak and Blasiak, 2004) (Hu et al., 2004).

According to the International Agency for Research on Cancer (IARC), Ni and Ni compounds were classified as carcinogenic to humans after inhalation and may cause cancers of the lungs, nasal cavity and paranasal sinuses and are included in Group 1 "potential human carcinogen" (IARC, 1990). Outside an occupational context, the main source of human exposure is food and, to a lesser extent, drinking water. So far, there are few experimental studies available to judge the carcinogenicity of orally administered Ni (Haber et al., 2000) (WHO, 2005). However, the most prevalent effect in the general population is allergic contact dermatitis.

4.2 Toxicological reference values

According to the EFSA opinion of 25 January 2005, the lack of adequate data does not allow the

establishment of a safe limit for dietary intake of Ni, although the World Health Organization (WHO) establishes a Tolerable Daily Intake (TDI) of 0.022 mg/kg b.w./day in 2005, based on a study of two generations of rats by Springborn Laboratories, Inc. (SLI, 2000). A No Observable Adverse Effect Level (NOAEL) of 2.2 mg/kg b.w./day Ni is also proposed for all critical effects studied. A safety factor of 100 (for interspecies and intraspecies variations) is applied.

EFSA established, in its scientific opinion on Ni in food and water, reference values for both acute and chronic risk, with a BMDL10 reference value equal to 1.1 µg/kg b.w./day and a TDI of 2.8 µg/kg b.w., setting a MOE for acute effects of 1 and 10 for chronic effects (EFSA, 2020).

The WHO emphasises, however, that this toxicological reference value is not sufficient to protect people sensitised to Ni and for whom oral exposure to Ni may induce eczema. Therefore, based on the study by Nielsen et al. (1999), which shows an effect (eczema) in Ni-sensitised individuals receiving on an empty stomach (12 hours before and 4 hours after ingestion) a single dose of 12 µg/kg b.w. via drinking water, the WHO retains a TDI of 12 µg/kg b.w./day without applying a safety factor as this study is conducted on fasting Ni-sensitised individuals and therefore under very unfavourable conditions. According to WHO (2008), this is the worst-case scenario, as the absorption of Ni from food is almost 10 to 40 times lower than the absorption of water ingested on an empty stomach (EFSA, 2015a).

WHO reports that the value found is close to the dose presented in the publication of Hindsén et al. (2001) of 17 µg/kg b.w.

5. The problem of nickel sensitisation

Ni belongs to one of many molecular substances capable of sensitising the skin in the role of a contact allergen. Due to their small size, these allergens are able to penetrate the skin barrier and in certain situations the effector immune response (cellular hypersensitivity reaction, type IV) predominates over the suppressor one, producing contact dermatitis in affected areas. It is important to note that the possibility of oral sensitisation has not been established, but several cases of systemic contact dermatitis have been described that are inducible via the oral route. Food safety agencies have a special interest in sensitisation to Ni. This is because the risk assessment related to the presence of Ni in drinking water or food selects systemic Ni-induced contact dermatitis in sensitised humans following oral exposure as the critical effect indicated for the assessment of acute effects of Ni (EFSA, 2015a, 2020).

Different names have been given to the various systemic pictures that have been attributed to oral exposure to Ni.

5.1 Systemic contact dermatitis

Systemic Contact Dermatitis (SCD) is the most accepted clinical picture. These are usually outbreaks of dermatitis associated with oral exposure to Ni. There are different presentations, the most frequent and typical being eczema/dermatitis of variable extension with erythematous, vesicular and later scaly lesions. Other distinct pictures affect the hands (in some cases: dyshidrotic eczema), generalised maculopapular rash, isolated flexural dermatitis, and baboon syndrome, which manifests as

a pink to violet rash on the buttocks, genitalia and inner thighs (occasionally in the armpits). If in a diagnostic provocation (with Ni) the outbreak affects the area, which in the previous study with patch tests had been positive, this reaction is considered the most specific, being also the most accepted in the scientific community, while it also usually affects previous eczema sites (flare-up) as in the case of vesicular eczema of the hands (Hindsén et al., 2001). Another study describes chronic pruritus, vasculitis-like urticaria, flexural dermatitis, papuloerythematous eruptions, chronic urticaria, baboon syndrome, etc. as variants within the spectrum of Ni exposure-induced SCD, resulting in an improvement of these lesions after administration of a low-Ni diet (Antico and Soana, 2015). It should be noted that in our environment the diagnosis of SCD (due to sensitisation to Ni) is extremely rare in routine clinical practice (allergology/dermatology), partly due to the existing controversies in terms of diagnostic methodology and attribution of causality.

5.2 Systemic allergy syndrome

Systemic Ni allergy syndrome (SNAS) is described as an alternative entity to systemic contact dermatitis and has been proposed for those patients presenting with symptoms that do not belong to typical SCD pictures. It refers to skin symptoms other than dermatitis and includes urticaria, pruritus (itching), angioedema, but also atypical pustulosis, but especially to those extra-cutaneous symptoms affecting other systems, such as digestive, pulmonary or neurological symptoms (Braga et al., 2013). Some authors report that, of these patients with Ni hypersensitivity, up to 20 % also have systemic symptoms such as urticaria, angioedema, cough, headache or gastrointestinal symptoms (Braga et al., 2013). This nosological entity is even more controversial than Ni-CSD and requires studies and postulates that explain or hypothesise pathogenetic and immunological mechanisms different from contact dermatitis, in which (at least in the occurrence of direct contact lesions) the mechanism of delayed hypersensitivity type IV is well documented. On the other hand, a high incidence of recurrent cold sores, urinary tract infections, genital candidiasis and other infections has also been associated in patients with Ni hypersensitivity (EFSA, 2015a).

5.3 Allergic contact mucositis

Allergic contact mucosistis has been proposed as a distinct entity, in which an oral mucosal patch test would be able to demonstrate Ni sensitisation, with the novel method intended as a tool to demonstrate the link between Ni sensitisation and the occurrence of intestinal symptoms (Picarelli et al., 2011). If independent studies were able to reproduce these results, it could shed light on many epidemiological studies associating various digestive symptoms with Ni sensitisation and, if confirmed, lead to useful dietary advice. Thus, the association between exposure to Ni and gastro-oesophageal reflux has already been proposed in isolation, with a doubling of the prevalence of sensitisation in this group of patients compared to non-sensitised patients (Stanghellini et al., 2016) (Aslan et al., 2017), irritable bowel syndrome (Rizzi et al., 2017) or the recurrence of digestive symptoms in coeliac patients on a correct gluten-free diet (Borghini et al., 2020). In fact, chronic gastrointestinal symptoms are very frequent at the population level, and it would be interesting to have more evidence on

the possibility that Ni levels in oral intake may play a causative role in these symptoms. SNAS has been proposed, which would include gastrointestinal symptoms as an emerging allergic condition (Lombardi et al., 2020).

5.4 Diagnosis

In clinical practice, the diagnosis of contact dermatitis can sometimes be suspected because of the location of the eczematous lesions and the possible triggering or causative agents. Thus, contact dermatitis due to sensitisation to Ni, although relatively frequent at population level, also has its typical local manifestations, often associated with the use of costume jewellery or clothing containing metals. Definitive diagnosis is established by patch tests, in which a certain amount and concentration is applied to the skin surface for 24-48 hours and read at 72-96 hours, typically with very localised lesions appearing in the area of allergen application. Ni contact dermatitis, diagnosed by skin testing with Ni sulphate, affects up to 10-20 % of the world's population (Braga et al., 2013).

Clinical suspicion of SNAS (which also applies to SCD) is defined by a positive skin test and clinical improvement after 1 month of a low-Ni diet. For diagnostic confirmation, oral provocation with nickel sulphate capsules is proposed (in these patients on a low-Ni diet) (Ricciardi et al., 2014). This author describes this picture in 6.4 % of patients seen in an allergy unit in Italy. Thus, SNAS can manifest as recurrent conditions that are attributed to high levels of Ni in the diet or a chronic condition that improves after dieting. In both cases, Ni provocation triggers or exacerbates previous symptoms. Gastrointestinal and neurological symptoms are the most frequent symptoms attributed to acute exposure to Ni (EFSA, 2015a).

There is some dispute related to the diagnoses of SCD, but especially SNAS. It is difficult to establish causality of chronic processes with natural exposure (as in the case of food) to multiple agents in the absence of hard evidence, which in the case of food agents are: 1) disappearance of symptoms after avoidance of the causative or suspected agent, and 2) reappearance after reintroduction or provocation and a proposed mechanistic explanation is also desirable.

This, however, causes a number of problems. The disputes are even evident in two successive EFSA opinions published in recent years on the public health risk of Ni in food and drinking water, the latter being considered an update (EFSA, 2015a, 2020). Regarding the SCD, this latest EFSA document (2020) highlights information uncertainties that arise in relation to the occurrence of adverse reactions following ingestion of Ni in humans. The assessment in the first report is based on three individual studies with a limited number of Ni-sensitised individuals. The update criticises the lack of information on the level of sensitisation among these individuals. Moreover, the results were expressed in different ways and therefore the studies are not comparable with each other.

Controversies related to the pictures of SCD and SNAS also arise in the diagnostic methods. Specific sensitisation demonstrated by patch testing only demonstrates sensitisation and does not in itself define the symptoms or the picture. Therefore, the next steps are avoidance and subsequent re-exposure. However, the diagnostic application of a low-Ni diet always automatically includes the reduction of other dietary factors. A different estimation of Ni content in food has an influence on the prescription of the low-Ni diet (Antico and Soana, 2015).

Regarding the common method in the studies, the fact that individuals have fasted prior to the provocation tests attracts criticism because this considerably increases Ni absorption. However, the updated opinion panel still maintains the DCS view that it is the critical effect for the risk characterisation of acute exposure to Ni. The final recommendation includes further studies involving large numbers of Ni-sensitised individuals as a basis for a more accurate risk assessment of systemic skin reactions to Ni through food and drinking water (EFSA, 2020).

On the other hand, re-exposure with provocation has been criticised because most studies use high doses of Ni from a physiological point of view (Gawkrodger et al., 1986) (Jensen et al., 2006). On the other hand, a tendency to associate the severity of reaction after exposure with increasing doses of Ni in sensitised patients has often been established (Jensen et al., 2006).

6. Nickel in food

Ni is a ubiquitous trace element in the biosphere as it is a general component of the Earth's crust (0.008 %) (Dara, 2006a).

This metal can reach the environment from a variety of sources, both natural and anthropological (Table 1). The Ni released is adsorbed on the sediments, immobilised and can be captured by plants that will later be consumed by humans. Furthermore, in the case of acidic soils, it may filter into groundwater as its mobility increases (González et al., 2009) (Ahmad and Ashraf, 2011). The level of contamination can be determined through the use of "biomarkers", which in the case of Ni are organisms that have the ability to accumulate it such as certain molluscs and crustaceans like the red crab, lichens, fungi and other plants (Fındık and Çiçek, 2011).

Table 1. Sources of nickel in the environment

Primary anthropogenic sources	Secondary anthropogenic sources	Natural sources	Additional sources
Smelting and refining operations Sewage sludge disposal or use of sludge as fertiliser Combustion of coal, oil, and other fossil fuels Nickel alloy (steel) production Electroplating processes, waste incineration and wastewater (Ahmad and Ashraf, 2011)	Emissions from motor vehicles and electric power utilities	Meteorisation and erosion of geological materials	Food and drinking water Migration of food contact material (EFSA, 2020)

Dietary intake estimates range from 74 to 231 µg/day for adults. In addition to raw food, Ni levels in food can be increased by migration from cooking materials and containers. The specific migration of Ni should not exceed 0.1 mg/kg according to the Council of Europe guidelines for metals and metal alloy materials in contact with food (Reilly, 2002).

Food is the main source of Ni exposure for the general population. It is therefore essential to

know the content of this metal in different food groups and its contribution to the diet. In this regard, Babaahmadifooladi et al. (2020) reviewed the scientific literature for Ni occurrence data, including the EFSA opinion of 2015, to determine the amounts and sources of Ni in different foods, water and drinks, dietary exposure to Ni, bioavailability and bioaccessibility of Ni in different foods, either through *in vivo* or *in vitro* studies (Tables 2, 3 and 4).

Table 2. Nickel content in animal-based food products (with product type, sample size and origin). All data are based on the fresh (wet) weight (w.w.) of the edible portion

Food category	Product type	Sample size	Origin	Ni content: mean, mean ± SD or range (µg/g w.w.)	Reference
Sea products	Sea food	N= 159	France	Mean: 0.299	(Guérin et al., 2011)
	Fish	-	-	Mean: 0.074	(Guérin et al., 2011)
	Fresh water fish	N= 9	Poland	Mean: 0.040	(Skibniewskaa et al., 2009)
	Sardina *pilchardus* fish	N= 68	France	Mean: 0.023	(Bouchoucha et al., 2019)
	Scyliorhinus canicula fish	N= 82	France	Mean: 0.013	(Bouchoucha et al., 2019)
	Fish	N= 282	China	6.63-20.03	(Gu et al., 2018)
	Fish-based infant formula	N= 8	Malta	Mean: 0.81	(Vella and Attard, 2019)
Meat products	Chicken meat	N= 3	Turkey	Mean: 2.08	(Uluozlu et al., 2009)
	Poultry	N= 38	France	UB[a]: 0.027-0.148	(Noël et al., 2012)
	Lamb	N= 80	-	UB[a]: 0.027-0.316	(Noël et al., 2012)
	Offal	N= 16	-	UB[a]: 0.027-0.255	(Noël et al., 2012)
	Poultry-based infant formula	N= 4	Malta	Mean: 1.07	(Vella and Attard, 2019)
	Chicken breast	N= 36	Selangor (Malaysia)	Mean: 0.119	(Abduljaleel et al., 2012)
	Quail breast	N= 36	Selangor (Malaysia)	Mean: 0.330	(Abduljaleel et al., 2012)
Eggs	Eggs and egg products	N= 30	France	0.027-0.328	(Noël et al., 2012)
	Chicken eggs	N= 24	Greece	0.077-0.280 yolk: 0.059 ± 0.005 egg white: 0.074 ± 0.007	(Nisianakis et al., 2009)
	Duck eggs	N= 24	Greece	yolk: 0.058 ± 0.006 egg white: 0.050 ± 0.006	(Nisianakis et al., 2009)
Dishes and meals	Prepared dishes	N= 68	France	0.027-0.554	(Noël et al., 2012)

Table 2. Nickel content in animal-based food products (with product type, sample size and origin). All data are based on the fresh (wet) weight (w.w.) of the edible portion

Food category	Product type	Sample size	Origin	Ni content: mean, mean ± SD or range (µg/g w.w.)	Reference
	Ready meals and fast food	N= 170	Granada (Spain)	0.018-0.095	(Cabrera-Vique et al., 2011)
	Ready-to-eat meal for babies	-	-	Mean[b]: 0.033-0.165 (LB-UB[c])	(EFSA, 2015a)
		-	-	Mean[b]: 0.036-0.091 (LB-UB[c])	(EFSA, 2015a)
Dairy products	Milk	N= 38	France	0.027-0.086	(Noël et al., 2012)
		N= 72	Croatia	0.072-0.097	(Vahčić et al., 2010)
		N= 12	Romania	0.005-0.039	(Ghimpeteanu, 2009)
		N= 30	Slovakia	0.25-1.65	(Lukáčová et al., 2012)
		N= 360	Spain	0.015-0.014	(Rey-Crespo et al., 2013)
		-	United Kingdom	Below the detection limit of 0.007-0.04	(Rose et al., 2010)
		N= 3	Turkey	Mean: 1.38	(Güler, 2007)
	Butter	N= 6	France	0.001-0.233	(Noël et al., 2012)
	Milk based products	N= 42	France, Germany, Italy, Portugal, Sweden and United Kingdom	<0.05	(Pandelova et al., 2012)
	Cheese	N= 16	France	0.112-0.409	(Noël et al., 2012)
		N= 10	Romania	0.002-0.010	(Gogoasa et al., 2006)
		N= 57	Spain	0.050-1.10	(Moreno-Rojas et al., 2010)
		N= 145	-	Mean[b] : 0.09-0.11 (LB-UB[c])	(EFSA, 2015a)
	Fermented milk products	N= 58	-	Mean[b]: 0.007-0.076 (LB-UB[c])	(EFSA, 2015a)
	Cow's milk	N= 21	Turkey	Mean: 0.038	(Saribal, 2019)
Honey and beeswax	Honey	N= 32	Israel	Mean: 1.24	(Bommuraj et al., 2019)
	Beeswax	N= 32	Israel	Mean: 4.15	(Bommuraj et al., 2019)

Table 2. Nickel content in animal-based food products (with product type, sample size and origin). All data are based on the fresh (wet) weight (w.w.) of the edible portion

Food category	Product type	Sample size	Origin	Ni content: mean, mean ± SD or range (µg/g w.w.)	Reference
	Honey	N= 183	-	Mean[b] : 0.14-0.16 (LB-UB[c])	(EFSA, 2015a)
	Honey	N= 30	Poland	0.023-1.33	(Madejczyk and Baralkiewicz, 2008)
	Honey	N= 6	Poland	0.42-1.83	(Nowak et al., 2011)
	Honey	N= 8	Pakistan	0.06-0.33	(Lanjwani and Channa, 2019)

[a]UB= upper bound scenario at which results below which the limit of detection (LOD) were replaced with the value reported as LOD. [b]Refers to the occurrence values used for the assessment of exposure to Ni through food consumption. [c]LB-UB= lower bound-upper bound scenarios. LB= lower bound scenario where results below LOD/LOQ were replaced by zero.

Table 3. Nickel content in plant-based food products (with product type, sample size and origin). All data are based on the fresh (wet) weight (w.w.) of the edible portion

Food category	Product type	Sample size	Origin	Ni content: mean, mean ± SD or range (µg/g w.w.)	Reference
Vegetables	Edible vegetables	N= 60	Hong Kong	0.26-1.1	(Junli et al., 2013)
	Green beans	N= 30	Zambia	Mean: 44.1	(Nakaona et al., 2019)
	Carrots	N= 20	Zambia	Mean: 31.9	(Nakaona et al., 2019)
	Rapeseed	N= 30	Zambia	Mean: 25.8	(Nakaona et al., 2019)
	Cabbage	N= 30	Zambia	Mean: 39.4	(Nakaona et al., 2019)
Cereals and cereal based products	Breakfast cereals	N= 6	France	0.077-0.280	(Noël et al., 2012)
		N= 313	-	Mean[a]: 0.63-0.71 (LB-UB[b])	(EFSA, 2015a)
	Pasta	N= 4	France	0.053-0.121	(Noël et al., 2012)
		N= 150	-	Mean[a]: 0.12-0.160 (LB-UB[b])	(EFSA, 2010)
	Rice	N= 5[c]	France	0.053-0.066	(Noël et al., 2012)
		N= 110	Italy	0.15-0.48	(Sommella et al., 2013)
Coffee and coffee drinks	Coffee	N= 30	France	0.024-0.214	(Noël et al., 2012)
		N= 83	-	Mean[a]: 1.2-1.2 (LB-UB[b])	(EFSA, 2010)

Table 3. Nickel content in plant-based food products (with product type, sample size and origin). All data are based on the fresh (wet) weight (w.w.) of the edible portion

Food category	Product type	Sample size	Origin	Ni content: mean, mean ± SD or range (µg/g w.w.)	Reference
Fats and oils	Edible vegetable oils	N= 10	France	0.027-0.087	(Noël et al., 2012)
		N= 151	-	Mean[a]: 0.305-0.36 (LB-UB[b])	(EFSA, 2010)
	Margarines	N= 4	France	0.027-0.077	(Noël et al., 2012)
		N= 10	Poland	0.11-1.76	(Lodyga-Chruścińska et al., 2012)
Seasonings	Herbs and spices	N= 12	France	0.024-0.533	(Noël et al., 2012)
Sugar and sugar based products	Sugar	N= 8	France	0.026-0.186	(Noël et al., 2012)
		N= 95	-	Mean[a]: 0.011-0.15 (LB-UB[b])	(EFSA, 2010)
	Sugar and confectioneries	N= 1170	-	Mean[a]: 1.5-1.6 (LB-UB[b])	(EFSA, 2015a)
	Sugar plants	N= 30	-	Mean[a]: 0.064-0.084 (LB-UB[b])	(EFSA, 2015a)
	Biscuits	N= 24[c]	France	0.027-0.639	(Noël et al., 2012)
Soy and soya based products	Soybean	N= 42[c]	France, Germany, Italy, Portugal, Sweden and United Kingdom	<0.05	(Pandelova et al., 2012)
	Tofu	N= 2	France	0.309-0.392	(Noël et al., 2012)
	Tofu (soybean)	N= 3	Slovenia	Mean: 2.130	(Ščančar et al., 2013)
	Fermented soy milk	N= 3	Slovenia	Mean: 5.950	(Ščančar et al., 2013)
Legumes	Dried beans	-	-	Mean: 3.1	(EFSA, 2010)
Nuts	Almonds	N= 3	Slovenia	Mean: 0.830	(Ščančar et al., 2013)
	Hazelnut	N= 48	-	Mean: 2.2	(EFSA, 2010)
Cocoa based products	Chocolate	N= 10	France	0.422-3.26	(Noël et al., 2012)
		N= 490	-	Mean[a]: 3.231-3.236 (LB-UB[b])	(EFSA, 2010)
Fruits	Grape	N= 9	Egypt	Mean: 0.805	(Amer et al., 2019)
	Orange	N= 9	Egypt	Mean: 0.228	(Amer et al., 2019)
	Apple	N= 9	Egypt	Mean: 0.25	(Amer et al., 2019)
	Prune-based baby formula	N= 4	Malta	Mean: 0.86	(Vella and Attard, 2019)

Table 3. Nickel content in plant-based food products (with product type, sample size and origin). All data are based on the fresh (wet) weight (w.w.) of the edible portion

Food category	Product type	Sample size	Origin	Ni content: mean, mean ± SD or range (µg/g w.w.)	Reference
	Apple-based baby formula	N= 6	Malta	Mean: 0.63	(Vella and Attard, 2019)
	Pear-based baby formula	N= 6	Malta	Mean: 0.85	(Vella and Attard, 2019)
Dishes	*Kimchi*[d]	N= 75	South Korea	0.056-0.263	(Hwang et al., 2019)
Tubers	Wild yam (*Dioscorea* spp.)	N= 8	India	0.03-0.089	(Padhan et al., 2018)
Edible wild mushroom	Ectomycorrhizal fungi (*Boletaceae*)	N= 74	China	0.1-1.2	(Zhang et al., 2019)

[a]Refers to the occurrence values used for the assessment of Ni exposure through food consumption. [b]LB = lower bound scenario at which results below LOD/LOQ were replaced by zero, UB= upper bound scenario at which results below LOD were replaced with the value reported as the LOD and those lower than LOQ were replaced with the LOQ value. [c]Reported values are based on dry weight. [d]Traditional Korean dish made mainly from nepa cabbage.

Table 4. Reported nickel content for water and drinks (with product type, sample size and origin)

Category	Type	Sample size	Origin	Ni content in water (µg/l) and drinks (µg/kg)	Reference
Water	Fresh water	-	United States	Mean: 0.3	(Barceloux, 1999)
		N= 59	Sweden	0.11-0.54	(Borg, 1987)
		N= 116	Finland	0.25[a]	(Mannio et al., 1995)
Water	Drinking water	N= 2503	United States	<20	(IARC, 1990)
		-	European countries	2-13	(OMS, 2000)
		N= 18	Norway, Sweden, Finland, Iceland	0.045-1.59	(Frengstad et al., 2010)
		N= 20	Pakistan	Mean: 1306	(Hussain and Habib-Ur-Rehman, 2019)
		N= 150	Zambia	20-2580	(Nakaona et al., 2019)
Drinks	Soft drinks	N= 26	France	27-457	(Noël et al., 2012)
		N= 35	-	Mean[b]: 37-41 (LB-UB[c])	(EFSA, 2015a)

Table 4. Reported nickel content for water and drinks (with product type, sample size and origin)					
Category	**Type**	**Sample size**	**Origin**	**Ni content in water (µg/l) and drinks (µg/kg)**	**Reference**
	Alcoholic beverages	N= 10	France	25-271	(Noël et al., 2012)
		N= 110	-	Mean[b]: 2-16 (LB-UB[c])	(EFSA, 2015a)
		N= 30	Brazil	Mean[d]: 160	(Gama et al., 2017)

[a]Expressed as median. [b]Refers to the occurrence values used for the assessment of Ni exposure through beverage consumption. [c]LB= lower bound scenario at which results below LOD/LOQ were replaced by zero, UB= upper bound scenario at which results below LOD were replaced with the value reported as the LOD and those below than LOQ were replaced with the value of the LOQ. [d]Only obtained for the beers.

6.1 Fish and seafood

The main sources of Ni contamination in aquatic systems are:

- Domestic wastewater effluents.
- Non-ferrous metal foundries (Cempel and Nikel, 2006).
- Industrial processes (e.g. use of dyes).
- Rainfall, biological cycles, rock and soil erosion (Sadeghi et al., 2011).
- Refinery wastes.
- Ship waste and anti-corrosion paints from ships (Dhaneesh et al., 2012).
- Waste from agriculture (e.g. pesticides and fertilisers) (Maceda-Veiga et al., 2012).
- Plastics: act as a vector to transport trace elements to aquatic organisms, including Ni from the aquatic environment (Bradney et al., 2019).
- Surface run-off, air deposition and release of municipal and industrial wastewater (surface water).

Under anaerobic conditions, typical of deep water, Ni can be released from the environment as insoluble sulphide. Although total Ni may be present in surface waters at levels above a few µg/l, the element is generally detected at average concentrations in the order of 3 µg/l or lower, with rivers being more polluted than lakes and seawater (EFSA, 2020).

It is important to note that it is often not easy to assess the effect of human activities on the contamination of shellfish with trace elements (Bouchoucha et al., 2013).

In the absence of contamination, normal levels of Ni found in fish range from 0.2-2 µg/g on a dry matter basis. Logically, these values are significantly higher in the case of polluted areas.

Blue fish accumulate more Ni than white or semi-fatty fish. Within shellfish, high levels of Ni have been found in oysters, clams or mussels (Demirezen and Uruç, 2006) (Mutlu et al., 2011). Algae also accumulate amounts that exceed up to 10 times the normal levels, showing an accumulation factor of even x 200 (Sadeghi et al., 2011) (Dhaneesh et al., 2012).

It is important to know the influence that technological and culinary treatments can have on the

final concentration of Ni in food. In this regard, Kalogeropoulos et al. (2012) studied the effects of three different heat treatments such as frying, baking and grilling. These authors observed an increase in trace element levels in all fish due to water loss. Fried fish were the most affected, although the levels of Ni contained were not of concern from a health point of view. Furthermore, it should be noted that Ni is included in the list of processing aids to catalyse the hydrogenation of food fats and oils (with the exception of butter) with a maximum content of 0.2 mg Ni/kg of final product (ANSES, 2019).

6.2 Meat and meat products

The levels of trace elements and their distribution in animal tissues depend primarily on the animal species (Uluozlu et al., 2009) (Abduljaleel et al., 2012).

As poultry and poultry meats are the most consumed, they have also been the most studied (Uluozlu et al., 2009) (Noël et al., 2012). Ni levels in these meats have been found to be influenced by various factors such as diet, growth, moulting and reproduction, with breast meat showing the lowest levels (Nisianakis et al., 2009) (Abduljaleel et al., 2012).

6.3 Eggs

Eggs of different avian species have different levels of minerals, including Ni, depending on their diet, their geographical origin and their ability to eat and digest soil. Also, the Ni concentration in the yolk is slightly higher than in the white. In any case, the low values found do not pose a danger to the population (Nisianakis et al., 2009).

6.4 Dairy products

The high consumption of dairy products by some population subgroups (young people and young children) gives milk and dairy products a prominent role in the dietary intake of Ni (EFSA, 2015a), as the average Ni concentration in 631 milk samples was 0.071 µg/g. Factors such as cattle diet, genetic variation between cattle breeds, herbicide used in the grazing area, geographical origin of cattle and seasonality contribute to the trace element content of cattle milk (Pechová et al., 2008).

Cheese shows significantly higher levels than milk (0.112-0.400 mg/kg fresh weight vs. 0.027-0.086 mg/kg). Several causes can explain this: water loss during manufacture, possible leaching from machinery (Noël et al., 2012), or Ni absorption from caseins and fats in the flocculation stage of the cheese making process, or other contamination (Ziarati et al., 2018).

6.5 Honey and beeswax

Bommuraj et al. (2019) found that trace element levels in honey were much lower than in beeswax.

6.6 Other products

Food processing significantly affects the final Ni content (Cabrera-Vique et al., 2011). Some additional ingredients can reduce the Ni content of ready-to-eat food by diluting the initial Ni content. While Noël et al. (2012) indicate that sauces and spices can be an important source of this element in the

diet. These authors, who determined the Ni content of a wide variety of food products, showed that cooked dishes had an intermediate level of Ni contamination.

6.7 Food products of vegetable origin

Food products of vegetable origin are the main source of dietary Ni (Noël et al., 2012). Plants absorb metals through the soil and therefore the physical nature of the soil and the absorption capacity of each species will determine the final levels. Furthermore, irrigation with wastewater and industrial effluents will increase them (Lemos et al., 2007) (Li et al., 2012) (Amin et al., 2013). Pollution from industries such as electronics, metallurgy and mining in close proximity to crops will raise levels (Li et al., 2012).

In the case of tea leaves, it has been observed that their final Ni content is influenced by environmental conditions during growth: total Ni/bioavailable Ni ratio in the soil, use of fertilisers or use of Ni-containing plant protection agents (Ščančar et al., 2013).

Also, soil composition, the presence of environmental contaminants during the extraction/packing process, etc. (Zhu et al., 2011), determine the trace element content of edible oils.

Apart from the anthropogenic source, the Ni content in some species such as legumes comes from natural processes, as this metal is essential for the functioning of plant enzymes such as urease and hydrogenase, which are involved in nitrogen metabolism (Lavres et al., 2016).

Among cereals, rice often has high amounts (2.34 ± 0.27 µg Ni/g) when in direct contact with water, especially if the water is contaminated (Li et al., 2012) (Rahman et al., 2018). The grain milling process could also contribute to pollution by metal migration from machinery. Cabrera et al. (2003) find Ni values in legumes and nuts produced in Spain in the order of 0.02-0.35 and 0.10-0.64 µg/g, respectively.

Plant-based food products (chocolate, soya, nuts, oats, cabbage, spinach tea and coffee) also have high levels of Ni.

Zhang et al. (2019) warn about the high Ni content of wild mushrooms of the genus *Boletus*, which is widely consumed worldwide.

In conclusion, some crops contain naturally high concentrations of Ni, as Ni is essential for enzymes involved in nitrogen metabolism. However, anthropogenic activities can also have a drastic impact on the final concentrations of trace elements (including Ni) in food products of vegetable origin.

6.8 Chocolate

Following the EFSA report (2015a) which found that the sugar and confectionery food group accounted for the highest exposure in several population groups, and that this was due to the major contribution of cocoa and chocolate products, a prospective study focusing on cocoa and chocolate products was proposed.

The main conclusions reached were that dark or pure chocolate contributes most to Ni content and thus exposure, with a correlation between the amount of cocoa in the product and the amount of Ni in the product (EFSA, 2015b).

High levels of Ni in final cocoa products can be attributed to natural environmental occurrence in cocoa growing soils, as well as to the use of pesticides and possible migrations from the materials used in the harvesting processes (Ščančar et al., 2013).

As Ni currently has no maximum limit in food in Regulation (EC) No. 1881/2006 (EU, 2006), the sampled products were in compliance with the current food legislation.

Furthermore, and according to the study performed by the Spanish Agency for Food Safety and Nutrition (AESAN), ENALIA (National Dietary Survey on the Child and Adolescent Population) and ENALIA2 (National Dietary Survey on the Adults, Elderly and Pregnant Population), it is possible to identify the populations (consumers only) with the highest average and extreme consumption of dark chocolate and derived products by age group. However, ANSES (*Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail*) is concerned about Ni exposure in toddlers among whom chocolate appears to be the main contributor of this element and recommends acute exposure studies in this population segment to prevent the risk of early sensitisation to Ni (ANSES, 2016).

Based on the estimated exposure, considering an average concentration and consumption of Ni in chocolate (50 g/day and 3.89 mg/kg) any risk for consumers can be ruled out, although for those consumers who are hypersensitive to Ni it is recommended to reduce the consumption of high purity dark chocolate.

Finally, and given that Ni concentration depends to a large extent on Ni fixation by the plant (leaves and/or fruit), the application of good agricultural practices both in cultivation (soil type, environmental pollution, use of fertilisers and pesticides) and good manufacturing practices in chocolate production (materials intended for food contact) would be necessary to avoid high Ni concentrations (EFSA, 2015b).

6.9 Water and drinks

Ni is present in water in the form of soluble salts: chlorides, nitrates, sulphates and to a lesser extent, carbonates ($NiCO_3$) and hydroxides ($Ni(OH)_2$) (AFSSA, 2007). Several factors affect the Ni content in drinking water: the origin of the water, the pipes/materials at the tap and the stagnation time (EFSA, 2015a). Ni enters surface waters from degraded bedrock and by precipitation in soil (WHO/IPCS, 1991).

In addition, mining activity, corrosion and pipe material, pH, presence of chloride and sulphates, temperature and residence time of water in water distribution pipes (Tuzen et al., 2009) (Karim, 2011) determine the levels of metals in drinking water (Khan et al., 2019).

The concentration of Ni in unpolluted freshwater in Europe, according to Barceloux (1999), is 0.3 µg/l.

Nakaona et al. (2019) found that drinking water obtained from wells is highly contaminated. This is of particular concern in poor and developing countries such as Pakistan and Zambia that use these waters for drinking, which calls for stricter regulation. According to EFSA, sediment is a very important deposit of Ni in water, so that Ni concentrations in both matrices are similar.

The average levels of Ni in drinking water calculated by EFSA in 2020 were twice as high as those

reported in the previous assessment (EFSA, 2015a), which is attributed to changes in the detection limit of the determination technique.

In European Council Directive 98/83/EC and European Commission Directive 2003/40/EC (EU, 1998, 2003), the maximum level for Ni in drinking water was set at 20 µg/l in the European Union. The reported level of Ni in drinking water in European countries, from 2 to 13 µg/l (IARC, 1990) (WHO, 2000), is below this limit. The World Health Organisation (WHO, 2008) assigned a maximum level of 70 µg/l Ni in drinking water in its guidelines. There are methods for reducing the Ni content in water such as decarbonation (co-precipitation of Ni hydroxide needs a pH greater than or equal to 9) and selective adsorption using iron oxyhydroxide or manganese dioxide coated sand; the pH of the water must be above 7. However, each of the methods must be studied on a case-by-case basis to ensure that they are authorised (AFSSA, 2007).

The US Environmental Protection Agency (EPA) set a maximum level of 100 µg/l for Ni in drinking water, estimating a Ni concentration <20 µg/l (N= 2503) (IARC, 1990).

Given that some people are particularly sensitive to Ni and that the ingestion of water with a high concentration of Ni can aggravate these allergic phenomena, EFSA (2005) recommends, especially for these people, not to consume first jet of tap water and to let the tap run because of its high content of metallic elements (Ni, copper and lead).

On the other hand, non-alcoholic beverages have higher Ni levels than alcoholic beverages (0.027-0.45 and 0.027-0.396 mg/kg, respectively) and both are much higher than those in drinking water (0.014-0.067 mg/kg) (Noël et al., 2012). The cause could be contamination from the production and storage process. In the case of beers, their Ni concentration derives from their plant origin and the quality of the water used for irrigation and production (Gama et al., 2017).

6.10 Food supplements

Such products are widely consumed, either to alleviate dietary deficiencies (multiminerals and multivitamins) or as an aid for diseases such as obesity. As they are not free of Ni and there is no strict regulation in certain countries, it is necessary to develop a monitoring and regulatory system to ensure the safety of the population (Schwalfenberg et al., 2018) (Adolfo et al., 2019).

6.11 Occurrence data in food submitted to EFSA

EFSA collected Ni occurrence data in 43 915 food samples, 39 381 drinking water samples and 3372 non-food samples from 26 European countries. Analytical results were obtained between 2000 and 2019 (Table 5) (EFSA, 2020).

The category "Legumes, nuts and oilseeds", in particular for soya beans, soya flour, chestnuts and cashews had the highest mean Ni concentrations, followed by the food category "Products for special nutritional use", in particular for plant extract formula and mineral supplements.

High average Ni concentration levels were also measured for food products belonging to the food categories "Sugar and confectionery" (mainly driven by chocolate (cocoa) products), "Herbs, spices and condiments" (mainly driven by different spices) and "Vegetables and vegetable products" (mainly driven by cocoa beans/cocoa products, tea leaves and seaweed).

Therefore, foods high in Ni are mostly of plant origin, e.g., legumes, soy-based products and nuts, compared to foods of animal origin such as meat, fish and honey, which have lower Ni concentrations.

Table 5. Summary of occurrence data for nickel by food category (µg/kg)

Food Category FoodEx Levels 1	N	% LCD	Mean		Medium		P95	
			LB	UB	LB	UB	LB	UB
Grains and grain-based products	5221	23	311	331	160	160	1250	1250
Vegetables and vegetable products	6476	25	731	741	50	54	5100	5100
Starchy roots and tubers	887	16	100	106	42	46	500	500
Legumes, nuts and oilseeds	2368	4	2236	2250	1342	1342	7490	7490
Fruit and fruit products	2130	34	81	107	29	50	274	440
Meat and meat products	2322	70	105	144	0	50	202	500
Fish and other seafood	1655	51	128	160	0	50	420	500
Milk and dairy products	1067	55	82	100	0	25	500	515
Eggs and egg products	153	61	19	28	0	10	70	70
Sugar and confectionery	772	38	1392	1462	305	503	5330	5330
Animal and vegetable fats and oils	1343	85	100	213	0	60	180	1000
Fruit and vegetable juices	1246	46	25	52	11	24	78	110
Non-alcoholic beverages	88	30	49	58	12	20	180	180
Alcoholic beverages	1512	68	12	40	0	20	36	100
Drinking water	17 831	81	2	3	0	1	7	7
Herbs, spices and condiments	982	20	1176	1201	361	460	4640	4640
Food for infants and small children	995	37	127	193	40	78	630	740
Products for special nutritional use	690	29	1637	1748	443	500	6500	6720
Composite food	160	19	117	141	60	64	340	500
Snacks, desserts and other foods	109	48	133	168	40	100	630	630
Total	48 007	53	-	-	-	-	-	-

Source: (EFSA, 2020). N= number of analytical results. % LCD= proportion of left-censored data. P95= 95th percentile. LB= lower bound; UB= upper bound. Due to the high proportion of left-censored data (>50 %), the distribution of LB concentrations is skewed to the right. Therefore, the median result of LB is 0.

7. Dietary intake of nickel

To understand the average dietary intake of Ni, several research studies have been conducted, which have evaluated exposure from different perspectives: chronic *versus* acute exposure, deterministic *versus* probabilistic exposure and type of diet applied in the studies to give a complete picture (Table 6) (Larsen et al., 2002) (Marzec, 2004) (Rose et al., 2010) (Hwang et al., 2019).

As can be seen, the data obtained are similar, except for the one carried out in 2009, in Italy by Turconi et al. (2009), where the values are three times higher than the other data collected (361.1 µg/day). In this study, milk and dairy products contributed the most to the total daily exposure to Ni.

Studies on dietary intakes of Ni in Spain are few and far between, although *a priori*, no significant differences according to geographical location have been detected. A study conducted by Fernández et al. (2007) in young people from Alcarria found that dietary intake of Ni accounted for almost 50 % of the TDI, with a consequent health risk. Also, Ni intake levels in young Germans exceeded the maximum level of 25-30 µg Ni/day set by the German Nutrition Society (Wittsiepe et al., 2009). These researchers highlight the significant influence of intake derived from drinking water, as well as food processing and cooking.

Ovo-lacto-vegetarians have been found to ingest significantly higher daily levels of Ni than people on a mixed diet (Anke et al., 2000).

As detailed above, the dietary intake of Ni depends on different factors such as differences in the Ni content of foods attributable to geographical variation, the type of diet (especially the proportion of foods of animal or plant origin and dietary habits), environmental contamination, degree and contamination of foods, how foods have been processed and stored, and possible migration from different sources (Leblanc et al., 2005) (Aung et al., 2006) (Rose et al., 2010). According to EFSA, the extent of Ni migration into food and drinking water due to the use of good quality stainless steel cookware, tableware and, in general, food contact materials is likely to be of little or no relevance compared to dietary exposure as determined by the intrinsic presence of Ni in dietary components (EFSA, 2020).

Table 6. Dietary intake/exposure of Ni (mg/person/day) through various foods and water in different countries, with description of method used, type of exposure and type of exposure assessment, type of food/diet involved and type of study (single- or multi-element); studies are classified chronologically according to year of publication

Country	Year	Method used	Average Ni exposure (mg/person/day)[a]	Type of exposure assessment	Acute *versus* chronic exposure	Type of food/diet	Multi-element study/Ni alone	Reference
United Kingdom	1999	Food analysis and food consumption	0.120	Deterministic	Chronic (daily)	Total diet	Multi-element	(Ysart et al., 1999)
Germany	2000	Food analysis and food consumption	0.025-0.035	-	Chronic (daily)	Multi-foods	Ni alone	(Anke et al., 2000)
Denmark	2002	Food analysis and food consumption	0.167	Deterministic	Chronic (daily)	Multi-foods	Multi-element	(Larsen et al., 2002)
Poland	2004	Food analysis and food consumption	0.124-0.166	-	Chronic (daily)	Total diet	Multi-element	(Marzec, 2004)
Spain (Tarragona)	2005	Food analysis and food consumption	0.138	Deterministic	-	Multi-foods	Multi-element	(Bocio et al., 2005)
Japan	2005	Food analysis and food consumption	0.172	Deterministic	Chronic (daily)	Market basket study	Multi-element	(Shiraishi, 2005)
France	2005	Food analysis and surveys Frequency of food consumption	0.0924	Deterministic	Chronic	Total diet	Multi-element	(Leblanc et al., 2005)

Table 6. Dietary intake/exposure of Ni (mg/person/day) through various foods and water in different countries, with description of method used, type of exposure and type of exposure assessment, type of food/diet involved and type of study (single- or multi-element); studies are classified chronologically according to year of publication

Country	Year	Method used	Average Ni exposure (mg/person/day)[a]	Type of exposure assessment	Acute *versus* chronic exposure	Type of food/diet	Multi-element study/Ni alone	Reference
Japan	2006	Duplicate diet analysis	<0.198	Deterministic	Chronic (daily)	Drinking water, snacks and drinks	Multi-element	(Aung et al., 2006)
Italy	2008	Food analysis and food consumption frequency tables	0.361	Deterministic	Chronic (daily)	Total diet	Multi-element	(Turconi et al., 2009)
Germany	2009	Record food consumption and food composition tables of the food	0.030-1.050	Deterministic	Chronic (daily)	Total diet	Ni and Zn	(Wittsiepe et al., 2009)
Germany	2009	Portion analysis and duplicate tables with Ni levels in foodstuffs	0.012-0.560	Deterministic	Chronic (daily)	Total diet	Ni and Zn	(Wittsiepe et al., 2009)
United Kingdom	2010	Data collected in the British National Diet and Nutrition Survey	0.130	Deterministic	Chronic (daily)	Total diet	Multi-element	(Rose et al., 2010)
Spain (Canary Islands)	2010	Food analysis and food frequency questionnaires	0.093	-	-	Most consumed foods and drinks	Ni alone	(González-Weller et al., 2010)
Lebanon	2010	Food analysis and surveys food consumption	0.126	Deterministic	Chronic (daily)	Total diet	Multi-element	(Nasreddine et al., 2010)

Table 6. Dietary intake/exposure of Ni (mg/person/day) through various foods and water in different countries, with description of method used, type of exposure and type of exposure assessment, type of food/diet involved and type of study (single- or multi-element); studies are classified chronologically according to year of publication

Country	Year	Method used	Average Ni exposure (mg/person/day)[a]	Type of exposure assessment	Acute *versus* chronic exposure	Type of food/diet	Multi-element study/Ni alone	Reference
Spain (Peninsula)	2012	Food analysis and surveys food consumption	0.109	-	-	Duplicate diet study	Multi-element	(Domingo et al., 2012)
Hong Kong	2013	Population-based food consumption survey	0.099 0.036[b]	-	-	Vegetables	Multi-element	(Junli et al., 2013)
Canada	2018	-	0.005	-	-	Prenatal supplement	-	(Schwalfenberg et al., 2018)
Zambia	2019	Face-to-face interview and level of Ni in drinking water	4.64 8.94	-	-	Drinking water	Multi-element	(Nakaona et al., 2019)
South Korea	2019	Korean *kimchi* consumption survey 2016	Male	0.009	-	Unique food	Multi-element	(Hwang et al., 2019)

[a]Reported values are based on the total concentration of Ni in food, unless otherwise specified. [b]Estimated bioaccessible daily intake.

8. Human dietary exposure assessment

8.1 Contributions of different food groups to chronic dietary exposure

EFSA estimated (%) the contribution of each food category to the total average Ni exposure, considering different age ranges, using dietary surveys (Table 7) (EFSA, 2020).

The results obtained showed that the average chronic dietary exposure to Ni ranged from 2.0 to 13.1 µg/kg b.w./day (minimum LB-maximum UB). The 95th percentile dietary exposure ranged from 3.6 to 20.1 µg/kg b.w./day (minimum LB-maximum UB). The group of toddlers (1-3 years) had the highest chronic dietary exposure to Ni, with a maximum exposure of 12.5-14.6 µg/kg b.w./day. The highest 95th percentile LB-UB exposure was observed in infants (<12 months) with estimates of 28.1-29.9 µg/kg b.w./day. Dietary exposure in specific population groups, namely pregnant and lactating women, was within the range of exposure estimates for the adult population.

The category "Cereals and cereal products'' was found to be the largest contributor to the mean chronic dietary exposure of LB to Ni in all age groups, reaching up to 49 % in infants (<12 months) and toddlers (1-3 years). Within this category, the subcategory bread and rolls are the highest contributors, not because they contain high levels of Ni, but because their consumption is very high. Fine bakery wares also contributed significantly to the LB average chronic dietary exposure to Ni, particularly in the category of other children (3-9 years).

It is followed in order of contribution by the food category "Non-alcoholic beverages" except for the young age groups, with a contribution of up to 47 % for the very elderly.

Other food categories contributing significant amounts of Ni chronically are the group "Legumes, nuts and oilseeds", contributing up to 36 % in toddlers (1-3 years) and within this category in particular beans; "Vegetables and vegetable products" with a contribution of up to 34 % in infants and "Sugar and confectionery" with 31 % in adolescents (9-18 years). Within this food group, the contribution of chocolate (cocoa) products stands out, especially among young age groups.

Within composite food, dietary surveys show a high consumption of ready-to-eat soups, which significantly increases Ni consumption on a chronic basis.

The contribution of "Drinking water" was rather low (up to 3 % in infants). Comparing the contribution of bottled water and the other water types (i.e., tap water, water ice, well water, unspecified drinking water), the contribution to the mean chronic dietary exposure of LB to Ni from bottled water is slightly higher.

Other food groups contain considerable levels of Ni, such as "Herbs, spices and condiments" and "Products for special nutritional use". However, their contribution to exposure to these foods was small due to the low consumption reported in the dietary surveys.

Table 7. Summary statistics on chronic dietary exposure to nickel (µg/kg b.w./day) in European countries

Class/age	Minimum		Median		Maximum	
	LB	UB	LB	UB	LB	UB
Infants (<12 months)	3.05	4.25	4.40	6.14	8.31	9.71
Toddlers (1-3 years)	6.23	7.77	8.53	10.1	12.5	14.6
Other children (3-9 years)	4.69	5.42	7.05	8.16	8.97	10.1
Adolescents (9-18 years)	2.40	2.80	3.58	4.27	5.56	6.44
Adults	1.83	2.20	2.90	3.41	3.65	4.19
Elderly	1.57	1.89	2.51	2.99	3.65	4.28
Very elderly	1.91	2.31	3.05	3.55	3.77	4.29
95th percentile dietary exposure in the total population (µg/kg b.w./day)						
Infants (<12 months)	6.19	7.91	9.81	12.8	28.1	29.9
Toddlers (1-3 years)	10.7	12.5	16.1	17.9	23.2	24.8
Other children (3-9 years)	10.3	11.5	13.3	14.6	18.8	20.5
Adolescents (9-18 years)	5.59	6.13	7.47	8.27	11.3	12.8
Adults	3.83	4.29	5.66	6.30	7.43	8.05
Elderly	3.55	4.12	4.98	5.56	6.83	7.69
Very elderly	3.35	3.93	5.58	6.31	6.81	7.60

Source: (EFSA, 2020).

8.2 Contributions of different food groups to acute dietary exposure

The mean acute dietary exposure in young populations (infants, toddlers, other children and adolescents) ranged from 3.4 (95 % CI: 3.1-3.7) µg/kg b.w. in an adolescent (9-18 years) survey at 14.3 (95 % CI: 13.2-15.5) µg/kg b.w. in a survey for toddlers (1-3 years). The 95th percentile ranged from 8.6 (95 % CI: 8.0 to 9.1) µg/kg b.w. in an adolescent survey at 35.0 (95 % CI: 26.8 to 47.2) µg/kg b.w. in a survey of toddlers.

In adult populations, the mean acute dietary exposure ranged from 2.5 (95 % CI: 2.2-2.9) µg/kg b.w. in an elderly survey to 4.9 (95 % CI: 4.6-5.5) µg/kg b.w. in an adult survey. The 95th percentile ranged from 5.5 (95% CI: 5.1-6.0) µg/kg b.w. in an elderly survey to 11.8 (95 % CI: 10.6-13.8) µg/kg b.w. in an adult survey (EFSA, 2020).

The most relevant food categories varied considerably between surveys and age groups, due to differences in specific food consumption patterns in individual European countries and age ranges.

So, for infants (<12 months), the most relevant foods implicated in acute exposure to Ni were

cereal-based products (in particular breakfast cereals, oat milling products and cereal flakes), ready-to-eat meals and in some surveys also infant formula.

For toddlers (1-3 years), the most relevant foods involved in acute Ni exposure were also highly variable: beans, ready-to-eat soups, chocolate, breakfast cereals and cereal flakes.

For other children (3-9 years) and adolescents (9-18 years), the consumption pattern was more homogeneous with beans and chocolate and, in one survey, also fruit and vegetable juices the foods contributing the most Ni to acute exposure.

Finally, among the adult population groups (adults, elderly and very elderly), the most relevant foods involved in acute exposure to Ni were beans, coffee, ready-to-eat soups, chocolate, breakfast cereals and, in one particular survey, also pickled vegetables (EFSA, 2020).

8.3 Acute exposure from drinking water

EFSA (2020) estimated the dietary exposure to Ni from a small bottle of water (500 ml) with a high concentration of Ni under fasting conditions, since, as discussed above, the bioavailability of Ni is higher during fasting and when Ni is ingested without food. In this specific scenario, the acute exposure from tap water was 0.04 µg/kg b.w. and 0.08 µg/kg b.w. from bottled water. It was concluded that exposure from drinking a small bottle of water is low.

9. The concept of a low nickel diet

Since Ni is a ubiquitous trace metal, it is impossible to avoid it completely in the diet. What can be attempted is to achieve a relatively low-Ni diet, and this would be possible by careful selection of foods with a relatively low Ni concentration to reduce the total daily intake of Ni in the diet. This is relevant in the case of Ni-sensitised individuals who are at risk of endogenous activation of immunocompetent cells. It has also been shown that this low-Ni diet may, according to some authors, influence the outcome of systemic Ni contact dermatitis. However, it should be understood that dermatitis will not necessarily disappear completely during the diet period; however, it is likely to cause fewer and milder outbreaks. When planning a low-Ni diet, the dietary habits of patients should be considered to promote the acceptability of the diet.

When designing a low-Ni diet, several practical difficulties can be encountered (Sharma, 2013):

1. The difference in Ni content of the same foods, depending on where they come from and even between the same batch (Dara, 2006b).
2. The influence of seasons on Ni concentration in plant-derived human food, as plant tissue contains more Ni in spring and autumn, but is low in midsummer (Jeffrey, 1987).
3. Differences in Ni concentration of different parts of the same plant: leaves contain more Ni than stem and root, and old leaves contain more Ni than young leaves (Boyd et al., 1999).

Thus, the benefits of this diet for patients with Ni systemic contact dermatitis will vary according to place of residence, season and the patient.

The low-Ni diet should avoid foods with a high Ni content (cocoa, chocolate, legumes) and canned foods, due to "migration" problems. Consumption of coffee and tea, fatty fish and green leafy vegeta-

bles would also be limited in favour of meat, poultry, eggs and dairy products. It would therefore be a diet that differs from the traditional Mediterranean diet, which has so many general health benefits. Therefore, the cost/benefit ratio should be carefully analysed when recommending it.

Other useful tips would be to replace nickel-plated utensils and not to cook acidic foods using stainless steel utensils, as acids can cause Ni dissociation from the utensils and increase the Ni content of the food. Finally, the initial flow of water from the tap in the morning should not be drunk or used for cooking, as Ni can flow from the tap during the night.

Conclusions of the Scientific Committee

In general, it can be concluded that foods with high Ni content are mostly of plant origin such as cereals (rice), legumes, cocoa, tea and green leafy vegetables, compared to foods of animal origin such as meat, poultry, eggs, dairy products and honey, which have lower Ni concentrations.

Ni causes more cases of allergic contact dermatitis than all other metals combined. Once sensitised, sensitisation tends to persist throughout life. However, the possibility of sensitisation through diet has not been documented. Some patients, once sensitised, develop systemic symptoms that have been associated with oral exposure to Ni in food. Thus, by reducing the continuous supply of Ni, an improvement is achieved in some patients. Careful selection of foods with a relatively low Ni concentration can result in a reduction of the total daily intake of Ni in the diet. Therefore, a good knowledge of the presence of Ni in food is useful for the treatment of Ni allergy.

Professionals treating patients with Ni hypersensitivity with manifestation of systemic contact dermatitis are therefore offered a proposal for a low-Ni diet, including the selection of foods with low Ni levels. In addition, it is recommended not to consume the initial flow tap water because it has the highest values of metallic elements, and to reduce the consumption of high purity dark chocolate as well as canned food.

It should be noted that the low-Ni diet differs from the traditional Mediterranean diet, which has so many general health benefits. Practitioners should therefore consider the benefits of recommending it on a case-by-case basis.

References

Abduljaleel, S.A., Shuhaimi-Othman, M. and Babji, A. (2012). Assessment of trace metals contents in chicken (*Gallus gallus domesticus*) and quail (*Coturnix coturnix japonica*) tissues from Selangor (Malaysia). *Journal of Environmental Science and Technology*, 5, pp: 441-451.

Adolfo, F.R., do Nascimento, P.C., Leal, G.C., Bohrer, D., Viana, C., de Carvalho, L.M. and Colim, A.N. (2019). Simultaneous determination of iron and nickel as contaminants in multimineral and multivitamin supplements by solid sampling HR-CS GF AAS. *Talanta*, 195, pp: 745-751.

AFSSA (2007). Agence Française de Sécurité Sanitaire des Aliments. Évaluation des risques sanitaires liés aux situations de dépassement des limites et références de qualité des eaux destinées à la consommation humaine. Juin 2004-Avril 2007. Tome I, pp: 144.

Ahmad, M.S. and Ashraf, M. (2011). Essential roles and hazardous effects of nickel in plants. *Review of Environmental Contamination and Toxicology*, 214, pp: 125-167.

Anke, M., Trüpschuch, A., Dorn, W., Seifert, M., Pilz, K., Vormann, J. and Schäfer, U. (2000). Intake of nickel in Germany: Risk or normality? *Journal of Trace and Microprobe Techniques*, 18 (4), pp: 549-556.

Amer, M.M., Sabry, B.A., Marrez, D.A., Hathout, A.S. and Fouzy, A.S.M. (2019). Exposure assessment of heavy metal residues in some Egyptian fruits. *Toxicology Reports*, 6, pp: 538-543.

Amin, N.U., Hussain, A., Alamzeb, S. and Begum, S. (2013). Accumulation of heavy metals in edible parts of vegetables irrigated with waste water and their daily intake to adults and children, District Mardan, Pakistan. *Food Chemistry*, 136, pp: 1515-1523.

ANSES (2016). Étude sur les expositions alimentaires aux substances chimiques des enfants de moins de trois ans.

ANSES (2019). Avis Anses Saisine n° 2019-SA-0031. Autorisation d'emploi de nickel, en tant qu'auxiliaire technologique, comme catalyseur dans le procédé d'hydrogénation des huiles alimentaires.

Antico, A. and Soana, R. (2015). Nickel sensitization and dietary nickel are a substantial cause of symptoms provocation in patients with chronic allergic-like dermatitis syndromes. *Allergy and Rhinology (Providence),* 6 (1), pp: 56-63.

Aslan, N., Sezikli, M. and Erdal, E. (2017). Nickel sensitivity in patients with gastroesophageal reflux disease. *Cutaneous and Ocular Toxicology*, 36 (4), pp: 347-350.

ATSDR (1999). Agency for Toxic Substances and Disease Registry. Toxicological Profile Information Sheet, Nickel. Barceloux D.G. Nickel. *Journal of Toxicology: Clinical Toxicology*, 37 (2), pp: 239-258.

ATSDR (2005). Agency for Toxic Substances and Disease Registry. Toxicological Profile for Nickel. Agency for Toxic Substances and Disease Registry, US Department of Health and Human Services. Available at: http://www.atsdr.cdc.gov/toxprofiles/tp15.pdf [accessed: 8-10-21].

Aung, N.N., Yoshinaga, J. and Takahashi, J.I. (2006). Dietary intake of toxic and essential trace elements by the children and parents living in Tokyo Metropolitan Area, Japan. *Food Additives and Contaminants*, 23, pp: 883-894.

Babaahmadifooladi, M., Jacxsens, L., Van de Wiele, T. and Du Laing, G. (2020). Gap analysis of nickel bioaccessibility and bioavailability in different food matrices and its impact on the nickel exposure assessment. *Food Research International*, 129, pp: 108866.

Babaahmadifooladi, M., Jacxsens, L., Van de Wiele, T., da Silva Junior, E.C. and Du Laing, G. (2021). Assessment of bioaccessible and dialyzable fractions of nickel in food products and their impact on the chronic exposure of Belgian population to nickel. *Food Chemistry*, 342, pp: 128210.

Barceloux, D.G. (1999). Nickel. *Journal of Toxicology: Clinical Toxicology*, 37, pp: 239-258.

Bocio, A., Nadal, M. and Domingo, J.L. (2005). Human exposure to metals through the diet in Tarragona, Spain: Temporal tren. *Biological Trace Element Research*, 104 (3), pp: 193-201.

Bommuraj, V., Chen, Y., Klein, H., Sperling, R., Barel, S. and Shimshoni, J.A. (2019). Pesticide and trace element residues in honey and beeswax combs from Israel in association with human risk assessment and honey adulteration. *Food Chemistry*, 299 (30), pp: 125123.

Borg, H. (1987). Trace-metals and water chemistry of forest lakes in Northern Sweden. *Water Research*, 21, pp: 65-72.

Borghini, R., De Amicis, N., Bella, A., Greco, N., Donato, G. and Picarelli, A. (2020). Beneficial Effects of a Low-Nickel Diet on Relapsing IBS-Like and Extraintestinal Symptoms of Celiac Patients during a Proper Gluten-Free Diet: Nickel Allergic Contact Mucositis in Suspected Non-Responsive Celiac Disease. *Nutrients*, 12 (8), pp: 2277.

Bouchoucha, A., Terbouche, A., Zaouani, M., Derridj, F. and Djebbar, S. (2013). Iron and nickel complexes with heterocyclic ligands: Stability, synthesis, spectral characterization, antimicrobial activity, acute and subacute toxicity. *Journal of Trace Elements in Medicine and Biology*, 27, pp: 191-202.

Bouchoucha, M., Chekri, R., Leufroy, A., Jitaru, P., Millour, S., Marchond, N. and Guerin, T. (2019). Trace element contamination in fish impacted by bauxite red mud disposal in the Cassidaigne canyon (NW French Mediterranean). *Science of the Total Environment*, 690, pp: 16-26.

Boyd, R.S., Jaffre, T. and Odom, J.W. (1999). Variation in nickel content in the hyperaccumulating nickel shrub Psychotria douarrei (Rubiaceae). *Nueva Caledonia: Biotropica*, 31, pp: 403-410.

Bradney, L., Wijesekara, H., Palansooriya, K.N., Obadamudalige, N., Bolan, N.S., Ok, Y.S., Rinklebe, J., Kim, K.H. and Kirkham, M.B. (2019). Particulate plastics as a vector for toxic trace-element uptake by aquatic and terrestrial organisms and human health risk. *Environment International*, 131, pp: 104937.

Braga, M., Quecchia, C., Perotta, C., Timpini, A., Maccarinelli, K., Di Tommaso, L. and Di Gioacchino, M. (2013). Systemic nickel allergy syndrome: nosologic framework and usefulness of diet regimen for diagnosis. *International Journal of Immunopathology and Pharmacology*, 26 (3), pp: 707-716.

Cabrera, C., Lloris, F., Giménez, R., Olalla, M. and López, M.C. (2003). Mineral content in legumes and nuts: Contribution to the Spanish dietary intake. *Science of the Total Environment*, 308, pp: 1-14.

Cabrera-Vique, C., Mesías, M. and Bouzas, P.R. (2011). Nickel levels in convenience and fast foods*: In vitro* study of the dialyzable fraction. *Science of the Total Environment*, 409 (8), pp: 1584-1588.

Cempel, M. and Nikel. G. (2006). Nickel: A Review of Its Sources and Environmental Toxicology. *Polish Journal of Environmental Studies*, 15, pp: 375-338.

Cempel, M. and Janicka, K. (2002). Distribution of nickel, zinc, and copper in rat organs after oral administration of nickel (II) chloride. *Biological Trace Element Research*, 90 (1), pp: 215.

Chen, C.Y., Wang, Y.F., Huang, W.R. and Huang, Y.T. (2003). Nickel induces oxidative stress and genotoxicity in human lymphocytes. *Toxicology and Applied Pharmacology*, 189, pp: 153-159.

Costa, M., Salnikow, K., Sutherland, J.E., Broday, L., Peng, W., Zhang, Q. and Kluz, T. (2002). The role of oxidative stress in nickel and chromate genotoxicity. *Molecular and Cellular Biochemistry*, 234-235, pp: 265-275.

Dara, S.S. (2006a). Soil Pollution. In book: *A textbook of environmental chemistry and pollution control*. 8th revised ed. Dara SS, editor. New Delhi: S. Chand and Company Ltd, pp: 274-287.

Dara, S.S. (2006b). Trace elements: Pollution and control. In book: *A textbook of environmental chemistry and pollution control*. 8th revised ed. Dara SS, editor. New Delhi: S. Chand and Company Ltd, pp: 177-216.

Das, K.K., Reddy, R.C., Bagoji, I.B., Das, S., Bagali, S., Mullur, L., Khodnapur, J.P. and Biradar, M.S. (2018). Primary concept of nickel toxicity - an overview. *Journal of Basic and Clinical Physiology and Pharmacology*, 30, pp: 141-152.

Demirezen, D. and Uruç, K. (2006). Comparative study of trace elements in certain fish, meat and meat products. *Meat Science*, 74, pp: 255-260.

Dhaneesh, K.V., Gopi, M., Ganeshamurthy, R., Kumar, T.T. and Balasubramanian, T. (2012). Bioaccumulation of metals on reef associated organisms of lakshadweep archipelago. *Food Chemistry*, 131, pp: 985-991.

Domingo, J.L., Perelló, G. and Bordonaba, J.G. (2012). Dietary intake of metals by the population of Tarragona County (Catalonia, Spain): Results from a duplicate diet study. *Biological Trace Element Research*, 146, pp: 420-425.

Dutton, M.D., Thorn, R., Lau, W., Vasiluk, L. and Hale, B. (2021). Gastric bioaccessibility is a conservative measure of nickel bioavailability after oral exposure: Evidence from Ni-contaminated soil, pure Ni substances and Ni alloys. *Environmental Pollution*, 268, pp: 115830.

ECB (2008). European Chemicals Bureau. European Union Risk Assessment Reports on Nickel and Nickel Compounds. ECB. Available at: http://esis.jrc.ec.europa.eu/doc/existing-hemicals/riskassessment/REPORT/nickelreport311.pdf [accessed: 8-10-21].

EFSA (2005). European Food Safety Authority. Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Nickel (Request N° EFSA-Q-2003-018) 25 January 2005. *EFSA Journal*, 146, pp: 1-21.

EFSA (2010). European Food Safety Authority. Management of left-censored data in dietary exposure assessment of chemical substances. *EFSA Journal*, 8 (3): 1557, pp: 1-96.

EFSA (2015a). European Food Safety Authority. Scientific Opinion on the risks to public health related to the presence of nickel in food and drinking water. *EFSA Journal*, 13 (2): 4002, pp: 1-202.

EFSA (2015b). European Food Safety Authority. Report on the results of the prospective study for the determination of nickel in chocolate (EP 05 18).

EFSA (2020). European Food Safety Authority. Update of the risk assessment of nickel in food and drinking water. *EFSA Journal*, 18 (11), pp: 6268-6369.

EU (1998). Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption. OJ L 330 of 05 December 1998, pp: 32- 54.

EU (2003). Commission Directive 2003/40/EC of 16 May 2003 establishing the list, concentration limits and labelling requirements for the constituents of natural mineral waters and the conditions for using ozone-enriched air for the treatment of natural mineral waters and spring waters. OJ L 126 of 22 May 2003, pp: 34-39.

EU (2006). Commission Regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. OJ L 364 of 20 December 2006, pp: 5-24.

Fernández, I., Mateos, C.J., Aguilar, M.V. and Martínez, M.C. (2007). Ingesta diaria de níquel entre jóvenes españoles. Valoración del riesgo toxicológico. *Revista de Toxicología*, 24, pp: 10-13.

Frengstad, B., Lax, K., Tarvainen, T., Jaeger, Ø. and Wigum, B.J. (2010). The chemistry of bottled mineral and spring waters from Norway, Sweden, Finland and Iceland. *Journal of Geochemical Exploration*, 107, pp: 350-361.

Fındık, Ö. and Çiçek, E. (2011). Metal concentrations in two bioindicator fish species, Merlangius merlangus and Mullus barbatus, captured from the West Black sea coasts (Bartin) of Turkey. *Bulletin of Environmental Contamination and Toxicology*, 87, pp: 399-403.

Gama, E.M., Nascentes, C.C., Matos, R.P., Rodrigues, G.C. and Rodrigues, G.D. (2017). A simple method for the multi-elemental analysis of beer using total reflection X-ray fluorescence. *Talanta*, 174, pp: 274-278.

Gawkrodger, D.J., Cook, S.W., Fell, G.S. and Hunter, J.A. (1986). Nickel dermatitis: the reaction to oral nickel challenge. *British Journal of Dermatology*, 115 (1), pp: 33-38.

Gedik, K. (2018). Bioaccessibility of Cd, Cr, Cu, Mn, Ni, Pb, and Zn in Mediterranean mussel (*Mytilus galloprovincialis* Lamarck, 1819) along the southeastern Black Sea coast. *Human & Ecological Risk Assessment*, 24, pp: 754-766.

Genchi, G., Carocci, A., Lauria, G., Sinicropi, M.S. and Catalano, A. (2020). Nickel: human health and environmental toxicology. *International Journal of Environmental Research and Public Health*, 17, pp: 679.

Ghimpeteanu, O.M. (2009). Researches concerning heavy metals in milk. *Scientific Works, C series*, 3, pp: 126-132.

Gogoasa, I., Gergen, I., Rada, M., Parvu, D., Ciuobanu, C., Bordean, D., MăruŃoiu, C. and Moigrădean, D. (2006). AAS detection of heavy metal in sheep cheese (the Banat area, Romania). *Buletinul USAMV-CN*, 62, pp: 240-245.

González, M.J., Messeguer, I. and Mateos, C.J. (2009). Elementos ultratrazas ¿Nutrientes o tóxicos? *Revista de Toxicología*, 26, pp: 93-103.

González-Weller, D., Gutiérrez, Á.J., de la Torre, A., Armendáriz, C. and Arméndariz, A. (2010). Dietary nickel intake in the Canary Islands (Spain): A total diet study. *Toxicology*, 278, pp: 377-377.

Gu, Y.G., Ning, J.J., Ke, C.L. and Huang, H.H. (2018). Bioaccessibility and human health implications of heavy metals in different trophic level marine organisms: A case study of the South China Sea. *Ecotoxicology and Environment Safety*, 163, pp: 551-557.

Guérin, T., Chekri, R., Vastel, C., Sirot, V., Volatier, J.L., Leblanc, J.C. and Noël, L. (2011). Determination of 20 trace elements in fish and other seafood from the French market. *Food Chemistry*, 127 (3), pp: 934-942.

Guo, H., Liu, H., Jian, Z., Cui, H., Fang, J., Zuo, Z., Deng, J., Li, Y., Wang, X., Zhao, L., He, R. and Tang, H. (2020). Immunotoxicity of nickel: pathological and toxicological effects. *Ecotoxicology and Environmental Safety*, 203, pp: 111006.

Güler, Z. (2007). Levels of 24 minerals in local goat milk, its strained yoghurt and salted yoghurt (tuzluyogurt). *Small Ruminant Research*, 71, pp: 130-137.

Haber, L.T., Diamond, G.L., Zhao, Q., Erdreich, L. and Dourson, M.L. (2000). Hazard identification and dose response of ingested nickel-soluble salts. *Regulatory Toxicology and Pharmacology*, 31 (2-1), pp: 231-241.

Heim, K.E., Danzeisen, R., Verougstraete, V., Gaidou, F., Brouwers, T. and Oller, A.R. (2020). Bioaccessibility of nickel and cobalt in synthetic gastric and lung fluids and its potential use in alloy classification. *Regulatory Toxicology and Pharmacology*, 110, pp: 104549.

Henderson, R.G., Cappellini, D., Seilkop, S.K., Bates, H.K. and Oller, A.R. (2012). Oral bioaccessibility testing and read-across hazard assessment of nickel compounds. *Regulatory Toxicology and Pharmacology*, 63, pp: 20-e28.

Hindsén, M., Bruze, M. and Christensen, O.B. (2001). Flare-up reactions after oral challenge with nickel in relation to challenge dose and intensity and time of previous patch test reactions. *Journal of the American Academy of Dermatology*, 44 (4), pp: 616-623.

Hou, Y.P., Gu, J.Y., Shao, Y.F., Song, Y.F., Jing, Y.H., Wu, W.S. and Pu, S. (2011). The characteristics of placental transfer and tissue concentrations of nickel in late gestational rats and fetuses. *Placenta*, 32, pp: 277-282.

Hu, W., Feng, Z. and Tang, M.S. (2004). Nickel (II) enhances benzo[a]pyrene diol epoxide-induced mutagenesis through inhibition of nucleotide excision repair in human cells: a possible mechanism for nickel (II)-induced carcinogenesis. *Carcinogenesis*, 25, pp: 455-462.

Hussain, S. and Habib-Ur-Rehman, M. (2019). Health risk assessment of different heavy metals dissolved in drinking water. *International Journal of Environmental Research and Public Health*, 16 (10).

Hwang, I.M., Yang, J.S., Jung, J.H., Lee, H.W., Lee, H.M., Seo, H.Y. and Khan, N. (2019). Dietary intake assessment of macro, trace and toxic elements via consumption of kimchi in South Korea. *Journal of the Science of Food and Agriculture*, 99, pp: 6474-6481.

IARC (1990). International Agency for Research on Cancer IARC. Monographs on the Evaluation of Carcinogenic Risks to Humans. Chromium, nickel, and welding. World Health Organization: Lyon, pp: 257-445.

Jeffrey, D.W. (1987). Portland Oregon, USA: Timber Press; 1987. Soil-Plant Relationships: An ecological approach. First published in the USA, pp: 19.

Jensen, C.S., Menné. T. and Johansen, J.D. (2006). Systemic contact dermatitis after oral exposure to nickel: a review with a modified meta-analysis. *Contact Dermatitis*, 54 (2), pp: 79-86.

Junli, H., Fuyong, W., Shengchun, W., Zhihong, C., Xiangui, L. y Ming, H.W. (2013). Bioaccessibility, dietary exposure and human risk assessment of heavy metals from market vegetables in Hong Kong revealed with an *in vitro* gastrointestinal model. *Chemosphere*, 91, pp: 455-461.

Kalogeropoulos, N., Karavoltsos, S., Sakellari, A., Avramidou, S., Dassenakis, M. and Scoullos, M. (2012). Heavy metals in raw, fried and grilled Mediterranean finfish and shellfish. *Food and Chemical Toxicology*, 50, pp: 3702-3708.

Khan, U.A., Kujala, K., Nieminen, S.P., Raisanen, M.L. and Ronkanen, A.K. (2019). Arsenic, antimony, and nickel leaching from northern peatlands treating mining influenced water in cold climate. *Science of the Total Environment*, 657, pp: 1161-1172.

Karim, Z. (2011). Risk assessment of dissolved trace metals in drinking water of Karachi, Pakistan. *Bulletin of Environmental Contamination and Toxicology*, 86, pp: 676-678.

Lam, C.M. and Lai, H.Y. (2018). Effect of inoculation with arbuscular mycorrhizal fungi and blanching on the bioaccessibility of heavy metals in water spinach (*Ipomoea aquatica* Forsk). *Ecotoxicology and Environment Safety*, 162, pp: 563-570.

Lanjwani, M.F. and Channa, F.A. (2019). Minerals content in different types of local and branded honey in Sindh, Pakistan. *Heliyon*, 5 (7), pp: e02042.

Larsen, E.H., Andersen, N.L., Møller, A., Petersen, A., Mortensen, G.K. and Petersen, J. (2002). Monitoring the content and intake of trace elements from food in Denmark. *Food Additives and Contaminants*, 19, pp: 33-46.

Lavres, J., Castro Franco, G. and de Sousa Câmara, G.M. (2016). Soybean seed treatment with nickel improves biological nitrogen fixation and urease activity. *Frontiers in Environmental Science*, 4 (37), pp: 1-11.

Leblanc, J.C., Guérin, T., Noël, L., Calamassi-Tran, G., Volatier, J.L. and Verger, P. (2005). Dietary exposure estimates of 18 elements from the 1st French total diet study. *Food Additives and Contaminants*, 22, pp: 624-641.

Lei, Y.X., Chen, J.K. and Wu, Z.L. (2001). Detection of DNA strand breaks, DNA-protein crosslinks, and telomerase activity in nickel-transformed BALB/c-3T3 cells. *Teratogenesis, Carcinogenesis, and Mutagenesis*, 21, pp: 463-471.

Lemos, V.A., Dos Passos, A.S., Dos Santos Novaes, G., De Andrade Santana, D., De Carvalho, A.L. and Da Silva, D.G. (2007). Determination of cobalt, copper and nickel in food samples after pre-concentration on a new pyrocatechol-functionalized polyurethane foam sorbent. *Reactive Functional Polymers*, 67, pp: 573-581.

Li, Q., Chen, Y., Fu, H., Cui, Z., Shi, L., Wang, L. and Liu, Z. (2012). Health risk of heavy metals in food crops grown on reclaimed tidal flat soil in the Pearl River Estuary, China. *Journal of Hazardous Materials*, 227-228, pp: 148-154.

Li, H.B., Wang, J.Y., Chen, X.Q., Li, Y.P., Fan, J., Ren, J.H., Luo, X.S., Juhasz, A.L. and Ma, L.Q. (2020). Geogenic nickel exposure from food consumption and soil ingestion: A bioavailability based assessment. *Environmental Pollution*, 265, pp: 114873.

Lodyga-Chruścińska, E., Sykuła-Zając, A. and Olejnik, D. (2012). Determination of nickel in Polish brands of margarines. *Food Additives and Contaminants*: Part B, 5, pp: 25-254.

Lombardi, F., Fiasca, F., Minelli, M., Maio, D., Mattei, A., Vergallo, I., Cifone, M.G. and Cinque, B. (2020). The Effects of Low-Nickel Diet Combined with Oral Administration of Selected Probiotics on Patients with Systemic Nickel Allergy Syndrome (SNAS) and Gut Dysbiosis. *Nutrients*, 12 (4), pp: 1040.

Liu, B., Ai, S., Zhang, W., Huang, D. and Zhang, Y. (2017). Assessment of the bioavailability, bioaccessibility and transfer of heavy metals in the soil-grain-human systems near a mining and smelting area in NW China. *Science of the Total Environment*, 609, pp: 822-829.

Lukáčová, A., Massányi, P., Greń, A. and Golian, J. (2012). Concentration of selected elements in raw and Ultra-heat treated cow milk. *Journal of Microbiology and Biotechnology*, 2, pp: 795-802.

Maceda-Veiga, A., Monroy, M. and De Sostoa, A. (2012). Metal bioaccumulation in the Mediterranean barbel (*Barbus meridionalis*) in a Mediterranean river receiving effluents from urban and industrial wastewater treatment plants. *Ecotoxicology and Environmental Safety*, 76, pp: 93-101.

Madejczyk, M. and Baralkiewicz, D. (2008). Characterization of Polish rape and honeydew honeyaccording to their mineral contents using ICP-MS and F-AAS/AES. *Analytica Chimica Acta*, 617, pp: 11-17.

Mannio, J., Jarvinen, O., Tuominen, R. and Verta, M. (1995). Survey of trace-elements in lake waters of Finnish Lapland using the ICP-MS technique. *Science of the Total Environment*, 160-161, pp: 433-439.

Marzec, Z. (2004). Alimentary chromium, nickel, and selenium intake of adults in Poland estimated by analysis and calculations using the duplicate portion technique. *Nahrung*, 48 (1), pp: 47-52.

Moreno-Rojas, R., Sánchez-Segarra, P.J., Cámara-Martos, F. and Amaro-López, M.A. (2010). Heavy metal levels in Spanish cheeses: Influence of manufacturing conditions. *Food Additives and Contaminants*, Part B, 3, pp: 90-100.

Muñoz, A. and Costa, M. (2012). Elucidating the mechanisms of nickel compound uptake: A review of particulate and nano-nickel endocytosis and toxicity. *Toxicology Applied and Pharmacology*, 260, pp: 1-6.

Mutlu, C., Türkmen, M., Türkmen, A. and Tepe, Y. (2011). Comparison of metal concentrations in tissues of blue crab, *Callinectes sapidus* from Mediterranean lagoons. *Bulletin of Environmental Contamination and Toxicology*, 87, pp: 282-286.

Nakaona, L., Maseka, K.K., Hamilton, E.M. and Watts, M.J. (2019). Using human hair and nails as biomarkers to assess exposure of potentially harmful elements to populations living near mine waste dumps. *Environmental Geochemistry and Health*, 42, pp: 1197-1209.

Nasreddine, L., Nashalian, O., Naja, F., Itani, L., Parent, D., Nabhani, M. and Hwalla, N. (2010). Dietary exposure to essential and toxic trace elements from a total diet study in an adult Lebanese urban population. *Food and Chemical Toxicology*, 48, pp: 1262-1269.

Nielsen, G.D., Soderberg, U., Jorgensen, P.J., Templeton, D.M., Rasmussen, S.N., Andersen, K.E. and Grandjean, P. (1999). Absorption and retention of nickel from drinking water in relation to food intake and nickel sensitivity. *Toxicology and Applied Pharmacology*, 154, pp: 67-75.

Nisianakis, P., Giannenas, I., Gavriil, A., Kontopidis, G. and Kyriazakis, I. (2009). Variation in trace element contents among chicken, Turkey, duck, goose, and pigeon eggs analyzed by inductively coupled plasma mass spectrometry (ICP-MS). *Biological Trace Element Research*, 128, pp: 62-71.

Noël, L., Chekri, R., Millour, S., Vastel, C., Kadar, A., Sirot, V., Leblanc, J.C. and Guérin, T. (2012). Li, Cr, Mn, Co, Ni, Cu, Zn, Se and Mo levels in foodstuffs from the second French TDS. *Food Chemistry*, 132, pp: 1502-1513.

Nowak, L., Dziezyc, H. and Piotrowski, M. (2011). Content of bioelements and toxic metals in honey of various botanical origin from lower Silesia. *Journal of Elementology*, pp: 437-444.

Olivares, V., Valverde, L., Quiros, V., García, R., Muñoz, N., Navarro, M. and Cabrera, C. (2015). Níquel en alimentos y factores influyentes en sus niveles, ingesta, biodisponibilidad y toxicidad: una revisión. *CyTA - Journal of Food,* 13 (1), pp: 87-101.

Padhan, B., Biswas, M., Dhal, N.K. and Panda, D. (2018). Evaluation of mineral bioavailability and heavy metal content in indigenous food plant wild yams. *Journal of Food Science and Technology*, 55 (11), 4681-4686.

Pandelova, M., Lopez, W.L., Michalke, B. and Schramm, K.W. (2012). Ca, Cd, Cu, Fe, Hg, Mn, Ni, Pb, Se, and Zn contents in baby foods from the EU market: Comparison of assessed infant intakes with the present safety limits for minerals and trace elements. *Journal of Food Composition and Analysis*, 27, pp: 120-127.

Patriarca, M., Lyon, T.D. y Fell, GS. (1997). Nickel metabolism in humans investigated with an oral stable isotope. *The American Journal of Clinical Nutrition*, 66, pp: 616-621.

Pechová, A., Pavlata, I., Dvořák, R. and Lokajová, E. (2008). Contents of Zn, Cu, Mn and Se in milk in relation to their concentrations in blood, milk yield and stage of lactation in dairy cattle. *Acta Veterinaria Brno*, 77, pp: 523-531.

Picarelli, A., Di Tola, M., Vallecoccia, A., Libanori, V., Magrelli, M., Carlesimo, M. and Rossi, A. (2011). Oral mucosa patch test: a new tool to recognize and study the adverse effects of dietary nickel exposure. *Biological Trace Element Research,* 139 (2), pp: 151-159.

Rahman, M.S., Biswas, P.K., Al Hasan, S.M., Rahman, M.M., Lee, S.H., Kim, K.H., Rahman, S.M. and Islam, M.R. (2018). The occurrences of heavy metals in farmland soils and their propagation into paddy plants. *Environmental Monitoring and Assessment*, 190, pp: 201.

Reilly, C. (2002). Metal contamination of food: its signifcance for food quality and human health. Blackwell, Oxford. Available at: https://doi. org/10.1002/9780470995105 [accessed: 8-10-21].

Rey-Crespo, F., Miranda, M. and López-Alonso, M. (2013). Essential trace and toxic element concentrations in organic and conventional milk in NW Spain. *Food and Chemical Toxicology*, 55, pp: 513-518.

Ricciardi, L., Arena, A., Arena, E., Zambito, M., Ingrassia, A., Valenti, G., Loschiavo, G., D'Angelo, A. and Saitta, S. (2014). Systemic nickel allergy syndrome: epidemiological data from four Italian allergy units. *International Journal of Immunopathology and Pharmacology*, 27 (1), pp: 131-136.

Rizzi, A., Nucera, E., Laterza, L., Gaetani, E., Valenza, V., Corbo, G.M., Inchingolo, R., Buonomo, A., Schiavino, D. and Gasbarrini, A. (2017). Irritable Bowel Syndrome and Nickel Allergy: What Is the Role of the Low Nickel Diet? *Journal of Neurogastroenterology and Motility*, 23 (1), pp: 101-108.

Rose, M., Baxter, M., Brereton, N. and Baskaran, C. (2010). Dietary exposure to metals and other elements in the 2006 UK total diet study and some trends over the last 30 years. *Food Additives & Contaminants*: Part A, 27, pp: 1380-1404.

Sadeghi, O., Tavassoli, N., Amini, M.M., Ebrahimzadeh, H. and Daei, N. (2011). Pyridine-functionalized mesoporous silica as an adsorbent material for the determination of nickel and lead in vegetables grown in close proximity by electrothermal atomic adsorption spectroscopy. *Food Chemistry*, 127, pp: 364-368.

Saribal, D. (2019). ICP-MS analysis of trace element concentrations in Cow's milk samples from supermarkets in Istanbul, Turkey. *Biological Trace Element Research*, 193, pp: 166-173.

Sarkar, B. (1984). Nikel metabolism. *IARC Scientific Publications*, pp: 367-384.

Ščančar, J., Zuliani, T., Žigon, D. and Milačič, R. (2013). Ni speciation in tea infusions by monolithic chromatography-ICP-MS and Q-TOFMS. *Analytical and Bioanalytical Chemistry*, 405, pp: 2041-2051.

Schaumlöffel, D. (2012). Nickel species: Analysis and toxic effects. *Journal of Trace Elements in Medicine and Biology*, 26, pp: 1-6.

Schwalfenberg, G., Rodushkin, I. and Genuis, S.J. (2018). Heavy metal contamination of prenatal vitamins. *Toxicology Reports*, 5, pp: 390-395.

Sharma, A.D. (2013). Low nickel diet in dermatology. *Indian Journal of Dermatology*, 58 (3), pp: 240.

SLI (2000). An oral (gavage) two-generation reproduction toxicity study in Sprague-Dawley rats with nickel sulphate hexahydrate. Prepared by Springborn Laboratories, Inc., Spencerville, OH, for Nickel Producers Environmental Research Association, Durham, NC (Study No. 3472.2).

Skibniewskaa, K.A., Guziurb, J., Marecc, Z., Zarębac, S., Grybowskib, M. and Szarek, J. (2009). Nickel in the muscle tissues of freshwater fish from north eastern Poland should not cause human health concerns. *Toxicological & Environmental Chemistry*, 91, pp: 773-778.

Sommella, A., Deacon, C., Norton, G., Pigna, M., Violante, A. and Meharg, A.A. (2013). Total arsenic, inorganic arsenic, and other elements concentrations in Italian rice grain varies with origin and type. *Environmental Pollution*, 181, pp: 38-43.

Stanghellini, V., Tosetti, C., Benedetto, E., Condoluci, M., De Bastiani, R., Cogliandro, R., Mastronuzzi, T., De Polo, M., Di Mita, F., Napoli, L. and cols. (2016). Nickel sensitization in patients with gastro-esophageal reflux disease. *United European Gastroenterology Journal*, 4 (2), pp: 184-190.

Sunderman, F.W.Jr., Aitio, A., Morgan, L.G. and Norseth, T. (1986). Biological monitoring of nickel. *Toxicology & Industrial Health*, 2, pp: 17-78.

Sunderman, F.W.Jr. (1989). Mechanisms of nickel carcinogenesis. *Scandinavian Journal of Work Environment and Health*, 15, pp: 1-12.

Sunderman, Jr F.W., Hopfer, S.M., Sweeney, K.R., Marcus, A.H., Most, B.M. and Creason, J. (1989). Nickel absorption and kinetics in human volunteers. *The Society for Experimental Biology and Medicine*, 191, pp: 5-11.

Turconi, G., Minoia, C., Ronchi, A. and Roggi, C. (2009). Dietary exposure estimates of twenty-one trace elements from a total diet study carried out in Pavia, Northern Italy. *British Journal of Nutrition*, 101, pp: 1200-1208.

Tuzen, M., Soylak, M., Citak, D., Ferreira, H.S., Korn, M.G. and Bezerra, M.A. (2009). A preconcentration system for determination of copper and nickel in water and food samples employing flame atomic absorption spectrometry. *Journal of Hazardous Materials*, 162, pp: 1041-1045.

Uluozlu, O.D., Tuzen, M., Mendil, D. and Soylak, M. (2009). Assessment of trace element contents of chicken products from Turkey. *Journal of Hazardous Materials*, 163, pp: 982-987.

Vahčić, N., Hruškar, M., Marković, K., Banović, M. and Colić Barić, I. (2010). Essential minerals in milk and their daily intake through milk consumption. *Mljekarstvo*, 60, pp: 77-85.

Vella, C. and Attard, E. (2019). Consumption of minerals, toxic metals and hydroxymethylfurfural: Analysis of infant and formulae. *Toxics*, 7 (2), pp: 33.

Wei, Y., Shohag, M.J.I. and Yang, X. (2012). Biofortification and bioavailability of rice grain zinc as affected by different forms of foliar zinc fertilization. *PLoS ONE*, 7 (9), pp: e45428.

WHO/IPCS (1991). World Health Organization/International Programme on Chemical Safety. Environmental Health Criteria no. 108: nickel. Available at: http://www.inchem.org/documents/ehc/ehc/ehc108.htm [accessed: 8-10-21].

WHO (1996). World Health Organization. Nickel in: Guidelines for drinking-water quality, 2nd ed. Vol. 2. Health criteria and other supporting information. Geneva.

WHO (2000). World Health Organization. WHO air quality guidelines for Europe, 2nd edition. Available at: http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/pre2009/who-air-quality-guidelines-for-europe [accessed: 8-10-21].

WHO (2005). World Health Organization. Nickel in Drinking-water WHO/SDE/WSH/05.08/55. Available at: http://www.who.int/water_sanitation_health/dwq/chemicals/rrnickel/en/ [accessed: 8-10-21].

WHO (2008). World Health Organization. Uncertainty and data quality in exposure assessment. Available at: http://www.who.int/iris/handle/10665/44017 [accessed: 8-10-21].

Wittsiepe, J., Schnell, K., Hilbig, A., Schrey, P., Kersting, M. and Wilhelm, M. (2009). Dietary intake of nickel and zinc by young children-Results from food duplicate portion measurements in comparison to data calculated from dietary records and available data on levels in food groups. *Journal of Trace Elements in Medicine and Biology*, 23, pp: 183-194.

Wozniak, K. and Blasiak, J. (2004). Nickel impairs the repair of UV- and MNNG-damaged DNA. *Cellular & Molecular Biology Letters*, 9, pp: 83-94.

Ysart, G., Miller, P., Crews, H., Robb, P., Baxter, M., De L'Argy, C., Lofthouse, S., Sargent, C. and Harrison, N. (1999). Dietary exposure estimates of 30 elements from the UK Total Diet Study. *Food Additives and Contaminants*, 16 (9), pp: 391-403.

Zhang, N., Chen, M., Li, J., Deng, Y., Li, S.L., Guo, Y.X., Li, N., Lin, Y., Yu, P., Liu, Z. and Zhu, J. (2019). Metal nickel exposure increase the risk of congenital heart defects occurrence in offspring: a case-control study in China. *Medicine (Baltimore),* 98, pp: e15352.

Zhu, F., Fan, W., Wang, X., Qu, L.I. and Yao, S. (2011). Health risk assessment of eight heavy metals in nine varieties of edible vegetable oils consumed in China. *Food and Chemical Toxicology*, 49, pp: 3081-3085.

Ziarati, P., Shirkhan, P., Mostafidi, M. and Tamaskani Zahedi, M. (2018). An overview of the heavy metal contamination in milk and dairy products. *Acta Pharmaceutica Sciencia*, 2 (7), pp: 8-21.