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A systematic risk characterization related to the dietary exposure of the population to potentially toxic elements through the ingestion of fruit and vegetables from a potentially contaminated area. A case study: The issue of the "Land of Fires" area in Campania region, Italy☆

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A B S T R A C T

Potentially toxic elements are widespread soil contaminants, whose occurrence could entail a concern for human health upon ingestion of fruit and vegetables harvested in a polluted area. This work set out to evaluate the concentrations of lead and cadmium as well as the levels of thirteen heavy metals for which a limit value is yet to be established by the food safety authorities, in order to perform a risk characterization related to the dietary intake of these metals and to provide a scientific opinion with wider relevance in the light of current worldwide regulatory issues. The sampling consisted of fruit and vegetables grown in a potentially contaminated area of southern Italy due to the illegal dump of hazardous wastes. An evaluation of the dietary exposure through the calculation of the Hazard Index (HI), the Maximum Cumulative Ratio (MCR) and the Target Cancer Risk (TCR) was adopted to this end. The results revealed that about the 30% of samples showed quantifiable levels of chemicals and no significant difference emerged between the potentially polluted area and the nearby cities that were selected as a control landfill site. The overall risk characterization for non-carcinogenic endpoints showed that the HI did not reach unsafe values, except for a small number of samples mainly because of aberrant occurrences and, in any case, the cumulative toxicity was mainly driven by thallium and vanadium. As far as the carcinogenic effects of arsenic are concerned, the distribution of TCR values broadly lay below the safety threshold; a certain percentage of data, however, exceeded this limit and should be taken into account for the enforcement of future regulatory thresholds.

1. Introduction

Potentially Toxic Elements (PTEs) are persistent environmental contaminants, not biodegradable and with a long biological half-life. Crop and vegetables grown in polluted environments could accumulate PTEs by uptake from soil or by atmospheric deposition, consequently the human intake of PTEs through the consumption of cereals, fruit and vegetables may represent a concerning issue (Agrelli et al., 2017; Khan et al., 2008; Li et al., 2006). These chemicals can be soluble in soil water and have the capability to accumulate in various tissues and organs of the individuals such as the heart, brain, kidneys, bone and liver (Alam et al., 2003; Arora et al., 2008; Singh et al., 2011). Besides, some of them (such as Se, Cu and Zn) are essential for maintaining the physiological functions and the biochemical processes of individuals (Radwan and Salama, 2006) and can act as protective factors against many diseases and should be present in the diet because the body is unable to synthesize them; however the excess of some of these metals as well as their deficiency may exert negative effects in individuals (Whitfield

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et al., 2010). Some other PTEs, such as Cd, Co, Cr, Ni, Pb and As, are involved in carcinogenesis, mutagenesis and teratogenesis processes and may increase the prevalence of gastrointestinal cancer and they may also act as endocrine disruptors (Arora et al., 2008; IARC, 1993; Türkdoğan et al., 2003). Besides, the acute effects may affect cardiovascular system, kidney, nervous system and bones (Khan et al., 2008; Naseri et al., 2015). Therefore, their occurrence in the environment and more specifically in the soil can affect the safety of various food matrices constituting a public health concern. The major route of exposure to these substances is diet; their entry into the food chain is mainly due to uptake of plants, which absorb PTEs from the soil and to a lesser extent, through foliar deposition, even though many studies have shown that direct oral ingestion of soil particles plays an important role in exposing humans to heavy metals in soils (Fu et al., 2008; Shahid et al., 2017; Wang et al., 2011; Wu et al., 2015; Zheng et al., 2010). Thus far, the current regulations do not provide any concentration limit for the majority of PTEs and no maximum level in fruit and vegetables has been set so far, with the exception of Pb and Cd (EC, 2006). It is well known that the occurrence of an element in food depends upon a series of factors not only related to the presence of such element in soil but also to the characteristics of the plant species, to the mobility and bioavailability of the element according to soil properties and pollution sources, and to soil management practices (Adamo et al., 2018). This makes it difficult to set limits in soils intended for agricultural production and consequently in foodstuffs intended for human consumption, even though up to now most countries have multiple limits for numerous PTEs in different categories of land uses, including agricultural purposes. For the reasons outlined above, each product whose concentration of PTEs apart from Pb and Cd reaches not negligible levels, may represent a health concern although conforming to current regulations. However, a huge amount of toxicological studies allowed to establish a Reference Dose (RfD) or a Tolerable Daily Intake (TDI) considering the toxicological profile of each xenobiotic as well as their related exposure pathways and which are used by risk assessors as a reference guideline for health risk characterization. The occurrence of PTEs in polluted areas is one of the key issues in terms of public health concern. One of the most important environmental outcomes of the last years has regarded the effects of the worldwide indiscriminate disposal of wastes. A particular case study concerned a specific area known as "Terra dei fuochi", located in the Campania region (Italy). The "Terra dei fuochi" (hereafter identified as "Land of Fires" (LoF)), is located between the provinces of Naples and Caserta, covering a total area of 1076 km^2, which includes 88 municipalities and more than two millions of inhabitants. Currently the LoF is in the spotlight of the international press in relation to the environmental contamination due to the illegal dump of hazardous wastes including industrial mud, hospital and sewage wastes, ground urban wastes and other inert materials as well as an uncontrolled combustion of municipal solid waste (Ferrara et al., 2013). Some studies performed during the last decade have documented an augmented mortality rate in some cities included in this area due to the development of various neoplastic diseases and high prevalence rates of congenital anomalies (Fazzo et al., 2011; Martuzzi et al., 2009). The above-mentioned studies and the growing media interest have raised important issues about the huge amount of pollutants generated by the combustion processes and percolation of liquid wastes through soils, which can contaminate all environmental compartments: air, water and soil, eventually entering the trophic chain and affecting livestock and vegetables. The impact of the consequent negative publicity on public opinion led to a financial crisis of the agricultural sector in the Campania region, compromising the national and international trading of cereals, fruit and vegetables, with serious economic consequences (Ducci et al., 2017).

The purposes of this work, carried out in collaboration with the National Institute of Health (Istituto Superiore di Sanità), were:

1. Assessment of the occurrence of PTEs in plants grown in the area of LoF and in landfill sites not belonging to the LoF area of the Campania region (Italy), in order to establish whether any environmental factor affects the food safety of these products.
2. A comprehensive risk characterization related to the dietary exposure of the adult population to PTEs, through the ingestion of vegetables and fruits harvested in a potentially contaminated environment as the LoF area. Achieving this aim will eventually provide a scientific opinion with wider relevance in the perspective of risk management of the dietary exposure to heavy metals, for which a law limit is yet to be established.

2. Materials and methods

2.1. Study area

The LoF area is included in the "Litorale Domizio-Agro Aversano" area recognized as a National Interest Priority Site (NIPS) as early as in 1998, along the western coast of Italy in the Campania region and includes about 90 municipalities according to the recent Ministerial directions (Ducci et al., 2017; MIPAAF, 2017). In this study, the sampling regarded 45 municipalities in the LoF area and 20 nearby cities not included in this area, in order to provide a suitable control group with similar environmental characteristics of the landfill. The territories of sampling sites are shown in Figure S1 ("S" designates tables and figures in the Supplementary material thereafter).

2.2. Sampling

A total of 350 plant samples were collected according to the following scheme:

- 115 samples in the province of Naples
- 180 samples in the province of Caserta
- 55 samples in the province of Salerno

A total of 190 samples were collected in LoF areas and the remaining 160 in non LoF areas.

The samples were divided into two groups: fruits and vegetables. Each group was further divided into 15 subgroups according to the scheme showed in Table S1.

The collected samples were analyzed for the occurrence of the following PTEs: As, Be, Cd, Co, Cr, Cu, Hg, Ni, Pb, Sb, Se, Sn, Tl, V, Zn. Briefly, the samples were cleaned, washed, and labeled. Each sample was deprived of the non-edible parts and made "ready for consumption", freeze-dried and homogenized. Half a gram of the obtained powder was acid digested with 6 mL of HNO_3 at 65% and 2 mL of hydrogen peroxide at 30% in a microwave oven system with temperature control (Start D, Milestone) and diluted to 25 mL with deionized water (Milli-Q grade, Millipore). PTEs concentrations were determined on the digestion solution through an ICP-MS instrument (Agilent 7700 series - Agilent Technologies, USA). Each sample was analyzed in duplicate. Procedural blanks were below quantification limits, and reference standard materials were used to check accuracy of the analytical procedures. The recovery rate of PTEs content lay in the range 71–92% and the variability between analytical replicates was lower than 10%. The limit of detection (LOD) and the limit of quantification (LOQ) of the applied method were 0.0003 and 0.001 mg kg^{-1}, respectively.

2.3. Data analysis

Data analysis and graph processing were performed through R Software version 3.4.1 (R Core Team, 2017). The mean values were calculated according to a medium bound (MB) and an upper bound (UB) approach, considering the concentrations below the LOQ (left-censored data) equal to LOQ/2 for the MB mean and equal to the LOQ for the UB mean.

2.4. Exposure assessment

A preliminary critical study of the literature was carried out with a focus on the toxicological profiles of the chemicals. The critical analysis of the epidemiological data was aimed at highlighting possible correlations between the occurrence and the concentrations of the concerned toxic compounds and the possible adverse effects resulting from the dietary exposure. Any Tolerable Daily Intake (TDI), Acceptable Daily Intake (ADI) or Reference Dose (RfD) was evaluated, analyzing the data documented by the World Health Organization (WHO), United States Environmental Protection Agency (USEPA), Netherlands National Institute for Public Health and the Environment (RIVM), Food Safety Commission of Japan (FSCJ), U.S. Agency for Toxic Substances and Disease Registry (ATSDR), European Food Safety Authority (EFSA), Food and Drug Administration (FDA), International Agency for Research on Cancer, U.S. Center for Disease Control (CDC) and other food safety authorities.

To assess the exposure of the population to PTEs through the ingestion of fruit and vegetables harvested in the Campania region, the calculation of the daily intake of each metal (DI_m) was carried out according to the following formula:

$$\boldsymbol{DI_m} = \frac{\boldsymbol{C_m} \times \boldsymbol{IR}}{\boldsymbol{BW}}$$

DI_m = Daily intake (dietary exposure) for each PTE (μg kg body weight (bw)$^{-1}$ day^{-1})
C_m= Concentration of each PTE detected in the samples (μg g^{-1})
IR = Intake rate of food (g day^{-1}) of adult population.
BW = Body weight (60 kg body weight (bw))

The data on food consumptions and the IR were retrieved from the cross-sectional study "The National Survey on Food consumption in Italy: INRAN-SCAI 2005-06" (Leclercq et al., 2009). On the basis of this survey, two subpopulations were considered: adult mean consumers and adult consumers at 95th percentile. Hence, four different intake rates were considered for the calculation of the DI showed above, namely: 186 g/day (fruit) and 194 g/day (vegetables) for mean consumers and 499 g/day (fruit) and 409 g/day (vegetables) for consumers at 95th percentile.

For each metal the Target Hazard Quotient (THQ_m) for non-carcinogenic effects of each PTE through a dietary exposure pathway, was calculated adapting the approach suggested by the United States Environmental Protection Agency (USEPA) (USEPA, 2007):

$$\boldsymbol{THQ_m} = \boldsymbol{DI_m} \times \frac{\boldsymbol{EF} \times \boldsymbol{TE}}{\boldsymbol{RfD_m} \times \boldsymbol{AT}}$$

THQ_m = Target Hazard Quotient related to a specific PTE (dimensionless);
DI_m = Daily Intake of a specific PTE (μg kg bw^{-1} day^{-1});
EF = Exposure Frequency to the contaminant (350 day year^{-1});
TE = Total Exposure (70 year);
RfD = Reference Dose: A reference value according to the Table 1 (μg kg bw^{-1} day^{-1});
AT = Average lifetime time for non-carcinogenic risk (TE × 365 day year^{-1}).
A $THQ_m > 1$ is considered of high concern.

However, in the case of multiple exposure to different contaminants, a correct risk characterization should consider the cumulative risk arising from the dietary exposure to all PTEs at once. Thus, the Hazard Index (HI) is calculated as the sum of each individual THQ_m:

$$\boldsymbol{HI} = \sum_{\boldsymbol{m}} \boldsymbol{THQ_m}$$

Even as far as the HI is concerned, a value > 1 entails a high non-carcinogenic risk. In order to help display where values are concentrated over the interval, the evaluation of HI and its effect on the non-carcinogenic risk threshold was performed by plotting a density plot of data distribution of the Hazard Indexes as shown in the forthcoming results section. To partially offset the effect of aberrant values, the data were winsorized by replacing them with the highest non-outlying value.

Since the HI takes into account the contribution of multiple PTEs, it is worth considering whether the exceeding of this threshold is driven by one or more elements. Hence, drawing on an extensive range of sources, some authors suggest to investigate the extent to which a stressor is important when the exposure depends upon a mixture of toxicants, through the Maximum Cumulative Ratio (MCR) approach, thus evaluating the effects of a mixture in the case of non-carcinogenic chemicals (De Brouwere et al., 2014; Price and Han, 2011; Vallotton and Price, 2016). The MCR is expressed as:

$$\boldsymbol{MCR} = \frac{\boldsymbol{HI}}{\boldsymbol{max}(\boldsymbol{THQ_m})}$$

MCR = Maximum Cumulative Ratio (dimensionless)
HI = Hazard Index (dimensionless)
Max (THQ_m) = the highest THQ assessed for each PTE (dimensionless)

Turning now to the carcinogenic effects of As, in the same vein

Table 1
Reference doses used for the calculation of the Target Hazard Quotient (THQ) according to the Tolerable Daily Intakes or Tolerable Weekly Intakes issued by International institutions.

PTEs	Reference Dose (μg/kg bw/day)	Reference
As	1	(Baars et al., 2001)
Be	2	(WHO, 2009)
Co	1.4	(Baars et al., 2001)
Cr	300	(EFSA, 2014)
Cu	140	(Baars et al., 2001)
Hg	0.6	(EFSA, 2012)
Ni	2.8	(EFSA, 2015)
Sb	6	(Tiesjema and Baars, 2009)
Se	4	(FSCJ, 2010)
Sn	200	(Tiesjema and Baars, 2009)
Tl	0.07	(Fard et al., 2017)
V	2	(Tiesjema and Baars, 2009)
Zn	500	(Baars et al., 2001)

was calculated the Target Cancer Risk (TCR) in order to ascertain the carcinogenic risk related to the ingestion of food contaminated by arsenic, according to the following formula (USEPA, 1989):

$$TCR_{As} = DI_{As} \times \frac{EF \times TE}{AT} \times CSF_{As}$$

TCR_{As} = Target Cancer Risk related to the ingestion of Arsenic (dimensionless);
DI_{As} = Daily Intake of Arsenic through consumption of fruit and vegetables (μg kg bw^{-1} day^{-1});
EF = Exposure Frequency to the contaminant (350 day $year^{-1}$);
TE = Total Exposure (70 year);
CSF_{As} = The Cancer Slope Factor related to the ingestion of Arsenic 1.50 (μg kg bw^{-1} $day^{-1})^{-1}$;
AT = Average lifetime time for carcinogenic risk (TE × 365 day $year^{-1}$).

A TCR of 10^{-4} refers to the possibility that 1 person out of a population of 10^4 individuals develops cancer upon exposure to the studied element. Therefore, a value of TCR $<10^{-4}$ can be considered an acceptable risk over a human lifetime.

3. Results and discussion

About 70% of the samples showed concentrations below the LOQ for all the investigated PTEs. The summary statistics of data are shown in Tables 2 and 3: either for fruit or vegetables the median levels of PTEs were greater than LOQ only for elements whose concentration was above the LOQ in more than 50% of analyzed samples (Cu, Ni, and Zn).

Disregarding zinc and copper which were the most abundant PTEs occurred in fruit and vegetables, Ni, Sn, Tl and V showed the highest contamination levels, although a considerable number of outliers was observed among these elements, due to the high percentage of values below the LOQ (Fig. 1). The comparison between the levels of PTEs in the samples harvested in and outside the LoF area showed no statistically significant difference both for fruit and vegetables (Kruskall-Wallis test, $p > 0.05$). Higher levels of Tl and V were detected in Brassicaceae and leafy vegetables (data not shown), reflecting the tendency of these plants to accumulate PTEs (Hou et al., 2013; Xiao et al., 2012).

Table 2
Levels of PTEs in fruit (as consumed) expressed as mg kg^{-1} fresh weight.

Chemical	Mean		*SD*	Median	*Range*		LC (%)
	MB	UB			*Min*	*max*	
As	0.0086	0.0093	*0.0307*	0.0005	*0.0005*	*0.2600*	68%
Be	0.0081	0.0089	*0.0294*	0.0005	*0.0005*	*0.2410*	76%
Cd	0.0163	0.0168	*0.0321*	0.0005	*0.0005*	*0.1890*	56%
Co	0.0315	0.0322	*0.1140*	0.0005	*0.0005*	*0.7550*	68%
Cr (total)	0.0806	0.0812	*0.1767*	0.0005	*0.0005*	*0.8760*	61%
Cu	0.6303	0.6306	*1.4175*	0.2480	*0.0005*	*11.3680*	22%
Hg	0.0031	0.0040	*0.0199*	0.0005	*0.0005*	*0.1500*	98%
Ni	0.1265	0.1270	*0.3364*	0.0090	*0.0005*	*2.8360*	46%
Pb	0.0271	0.0278	*0.0699*	0.0005	*0.0005*	*0.2860*	76%
Sb	0.0060	0.0067	*0.0202*	0.0005	*0.0005*	*0.1460*	79%
Se	0.0114	0.0122	*0.0263*	0.0005	*0.0005*	*0.1060*	75%
Sn	0.0071	0.0079	*0.0324*	0.0005	*0.0005*	*0.2560*	82%
Tl	0.0149	0.0157	*0.0762*	0.0005	*0.0005*	*0.6200*	76%
V	0.0888	0.0894	*0.1804*	0.0005	*0.0005*	*0.8570*	51%
Zn	3.1628	3.1633	*9.5012*	0.1210	*0.0005*	*73.4330*	44%

MB:Medium bound.
UB: Upper bound.
SD: Standard deviation of the upper bound estimate.
LC: Left-censored data (values below the Limit of Quantification).

Table 3
Levels of PTEs in vegetables (as consumed) expressed as mg kg^{-1} fresh weight.

Chemical	Mean		*SD*	Median	*Range*		LC (%)
	MB	UB			*Min*	*max*	
As	0.0281	0.0287	*0.0649*	0.0005	*0.0005*	*0.4590*	65%
Be	0.0236	0.0243	*0.1054*	0.0005	*0.0005*	*1.2300*	75%
Cd	0.0161	0.0166	*0.0305*	0.0005	*0.0005*	*0.2150*	51%
Co	0.1297	0.1303	*0.6259*	0.0005	*0.0005*	*4.4030*	63%
Cr (total)	0.2249	0.2255	*0.7349*	0.0005	*0.0005*	*6.5490*	61%
Cu	1.9203	1.9205	*6.4572*	0.2670	*0.0005*	*77.8690*	18%
Hg	0.0067	0.0077	*0.0935*	0.0005	*0.0005*	*1.4900*	99%
Ni	0.2711	0.2716	*1.6638*	0.0033	*0.0005*	*24.6520*	48%
Pb	0.0431	0.0437	*0.0977*	0.0005	*0.0005*	*0.7630*	64%
Sb	0.0335	0.0342	*0.2166*	0.0005	*0.0005*	*3.3820*	70%
Se	0.0453	0.0460	*0.1221*	0.0005	*0.0005*	*1.2460*	70%
Sn	0.0822	0.0830	*0.6906*	0.0005	*0.0005*	*8.4450*	84%
Tl	0.0813	0.0821	*0.5539*	0.0005	*0.0005*	*7.3440*	75%
V	0.2756	0.2762	*0.6632*	0.0005	*0.0005*	*3.0020*	55%
Zn	3.9788	3.9792	*12.1409*	0.2855	*0.0005*	*162.5650*	35%

MB: Medium bound.
UB: Upper bound.
SD: Standard deviation of the upper bound estimate.
LC: Left-censored data (values below the Limit of Quantification).

4. Comparison of lead and cadmium levels with regulatory limits

Comparing the values found in this study (data not shown) with the limits of 0.10 (concerning not leafy vegetables, roots and fruit), 0.20 (concerning pulses) and 0.30 (concerning leafy brassica and leaf vegetables) mg kg^{-1} set by Reg. (EC) No. 1005/2015, 25 out of 350 samples (7%) showed lead values that exceeded the above-mentioned thresholds. Whereas, as far as the cadmium is concerned, a comparison between our data (data not shown) and the limits of 0.05 (concerning vegetables and fruit, excluding root and tuber vegetables, leaf vegetables, fresh herbs, leafy brassica, stem vegetables), 0.10 (concerning root and tuber vegetables) and 0.20 (concerning leaf vegetables and leafy brassica) mg kg^{-1}, set by the Reg. EC no 488/2014, showed that 20 out of 350 samples (6%) were above the limits as required by Regulation. Either for lead or cadmium the exceeding of the limit values affected both the investigated areas indifferently. Fig. 2 shows a comparison with literature data, regarding the Pb and Cd values occurring in similar products. The levels found in this study are, in some cases, lower than other studies and consistent with a similar work concerning the same landfill site (Esposito et al., 2015).

4.1. Exposure assessment of the adult population

As regards the metals that are not regulated by the current legislation, an exposure assessment was performed considering the concentration of each PTE detected in the samples. As previously mentioned only the 30% of the samples showed values above the LOQ. The data below the LOQ were considered as LOQ/2 (medium bound approach). Fig. 3 shows the distribution of the resulting THQs for each PTE occurred both in LoF and in non-LoF areas, for mean consumers, whereas figures S2 and S3 deals with consumers at 95th percentile. The blue circles accounts for the contribution to the THQ of each sample, whereas the red dots indicate the outliers. It is apparent from these figures that the values of THQ exceeding the safety threshold set at 1 (1e+00 in log_{10} scale) stem mainly from aberrant values, either in fruit or in vegetables. Conversely, the median values of THQ are well below the safety threshold: the large

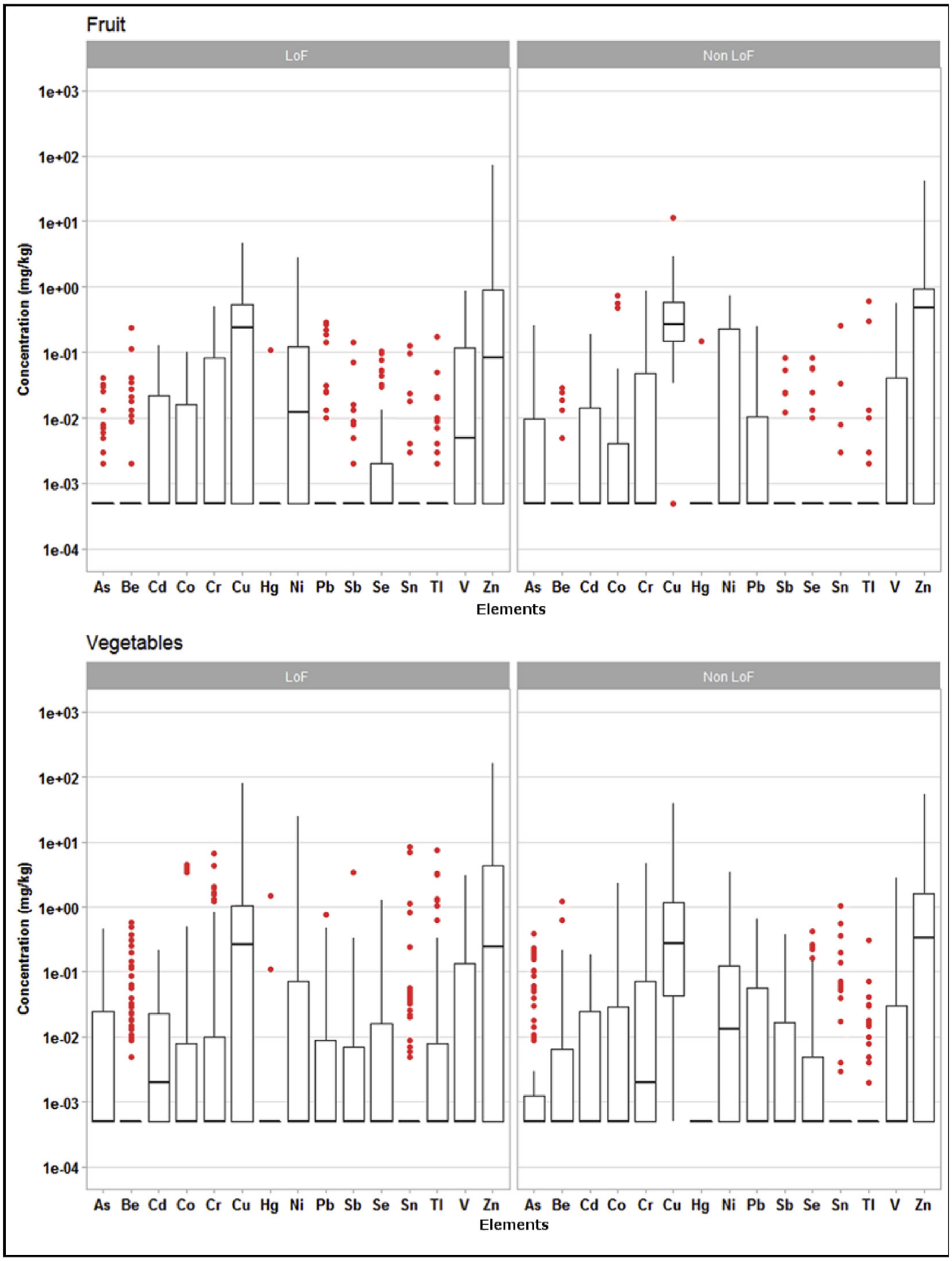

Fig. 1. Summary statistics of occurrence of potentially toxic elements (PTEs) in fruit and vegetables according to the sampling area (LoF = Land of Fires) (Log10 scale at Y-axis). The rectangle shows the interquartile range between the 25th and the 75th percentile, whereas the thicker horizontal line accounts for the value at the 50th percentile (median). The lower and upper whiskers (solid vertical lines) show the lowest and the highest values within 1.5 times the interquartile range and the dots denote the outliers.

number of outliers has been brought about by the high occurrence of left-censored data. The values of THQ >1 denote exposure scenarios that exceed the reference dose by more than 100% and it is apparent from the charts that those values are mainly outliers or in any case a small percentage of samples.

As stated above, the dietary exposure to PTEs should be evaluated in the light of a cumulative effect exerted by the PTEs. Hence, Fig. 4a shows the frequency distribution of the HI obtained on the basis of the individual THQ_m previously calculated. HI values > 1 were observed in less than 30% of samples and mainly because of outliers.

Fig. 4b shows the distribution of HI after replacing the aberrant data with the highest non-outlying value of the distribution. As shown in this figure, the distribution lies beyond the threshold of HI, for mean consumers. Hence, the HI values > 1 could be mainly ascribed to non-recurring concentrations of PTEs (about the 10% of samples). Much the same applies for consumers at 95th percentile (figures S4 and S5).

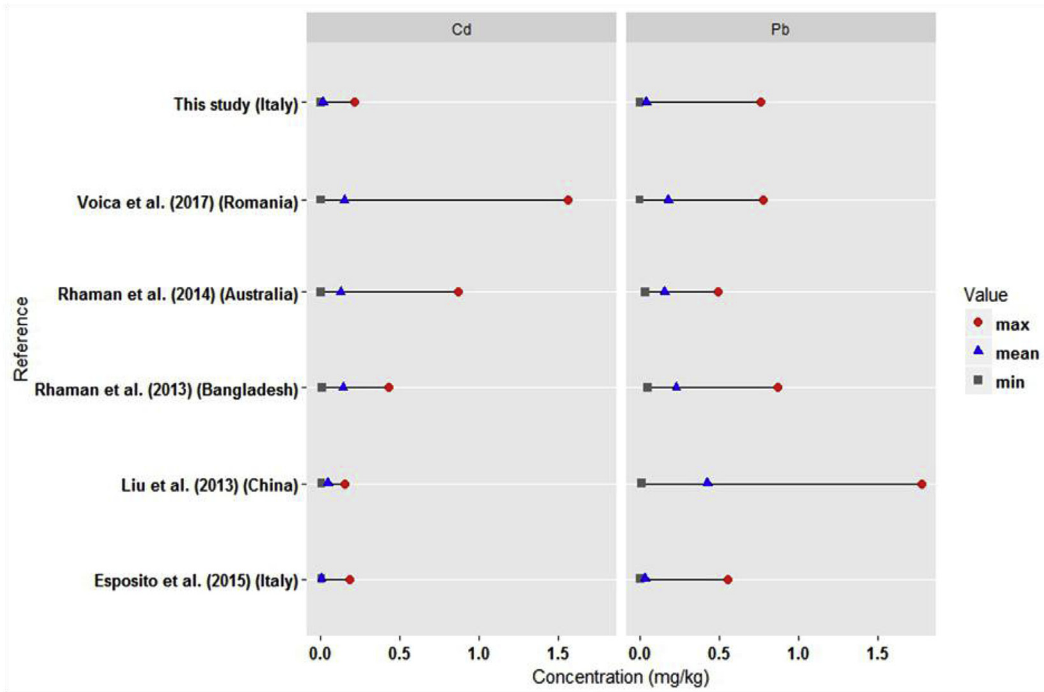

Fig. 2. Comparison of ranges and mean concentrations of cadmium and lead in fruit and/or vegetables as documented by different studies. (Please note: The two studies by Rhaman et al. (2013,2014) reported the results on a dry weight basis; Esposito et al. (2015) reported mean values for each category of fruit and vegetables: in this chart is shown only the median value of the means; as regards Liu et al. (2013), minimum and maximum values were missing: the values at 5th and 95th percentile were used instead) (Voica et al., 2017).

Previous studies provide evidence for the finding that the toxicity of environmental mixtures is frequently dominated by one component (Han and Price, 2011; Kienzler et al., 2016; Mishra et al., 2015). Thus, to better understand the factors that led to an exceeding of the HI threshold, each MCR value was plotted against each respective HI value in order to ascertain the most contributing element in the overall toxicity assessment (Fig. 5).

What stands out in the Fig. 5 is the slight negative correlation between MCR and HI values (Spearman's rank correlation: $\rho = -0.36$, p-value $= 10^{-12}$). The HI values associated to a higher risk ($HI > 1$) are broadly related to lower MCR values (between 1 and 2), revealing that a cumulative exposure is primarily driven by one or two metals together. The major contribution on the highest HI values is mostly due to thallium (9% of samples) and vanadium (10% of samples) as well as to a thallium-vanadium co-occurrence (2% of samples), with no difference between LoF and non LoF areas. This result could be related either to anthropogenic activities (metal smelting, manufacture of cement, alloys production, atmospheric deposition from coal burning and misuse of thallium-based products in rodent control) or to natural sources (thallium naturally occurs in clays and soils) (Blain and Kazantzis, 2015; Evans and Barabash, 2010; Małuszyński, 2009; Turner and Pilsbury, 2013; Xiao et al., 2012; Yang et al., 2005). With respect to vanadium, its occurrence in soils is not uncommon, especially in volcanic sites (Baldantoni et al., 2018) and it is also considered a trace essential element for certain organisms, even though data about its essentiality for humans are limited. Other potential anthropogenic sources of V include the use of phosphate fertilizers and cement production (Evans and Barabash, 2010; Gallo et al., 2014; Garribba and Sanna, 2014; Guagliardi et al., 2016; Imtiaz et al., 2015). A similar study found V levels in fruit and vegetables collected in Sicily region (Italy) ranging from <LOQ to 2.495 mg kg^{-1} fresh weight, mirroring the results of this study (Ferrante et al., 2013).

All things considered, the exposure assessment to PTEs does not seem to bear out the hypothesis of an adverse safety issue.

5. Dietary exposure to inorganic arsenic and related carcinogenic risk

Further attention deserves to be paid to the exposure to inorganic arsenic because, differently from the others PTEs considered in this study, it has well documented carcinogenic endpoints upon dietary exposure. Moreover, arsenic is naturally occurring in soils and rocks, especially in volcanic areas and the main pathways of human exposure are soil, air, water and food (Mirza et al., 2014). The mean and median concentrations of As which were detected in all the samples were 0.0236 (MB) and 0.0005 mg kg^{-1} respectively, whereas the maximum level occurred in a Brassica sample and was 0.4590 mg kg^{-1}. The calculated daily intake ranged from 0.0016 to 1.4918 μg kg bw^{-1} day^{-1} for mean consumers and from 0.0034 to 3.1289 μg kg bw^{-1} day^{-1} for consumers at 95th percentile. This exposure led to a THQ_{As} lying in the range of 0.0015–1.4304 for mean consumers and 0.0033–3.0002 for consumers at 95th percentile. Beccaloni et al. (2013) found that the exposure of Italian population of Sardinia region had a mean value of 0.37 μg kg bw^{-1} day^{-1}. In the same study it is reported that the exposure through the ingestion of food and water in 19 European countries was estimated to range from 0.13 to 0.56 μg kg bw^{-1} day^{-1} for average consumers and from 0.37 to 1.22 μg kg bw^{-1} day^{-1} for 95th percentile consumers (Beccaloni et al., 2013), whereas the dietary intake found in our study showed a larger range. This discrepancy was purely due to eleven samples (five from the LoF area and six from the non LoF landfill sites), showing concentrations of As above 0.200 mg kg^{-1}. Excluding these outlying samples, the range of exposure is in agreement with the data reported by the above-mentioned study. However, the levels of As detected in the samples are likely to be related to the geochemistry of the studied soils

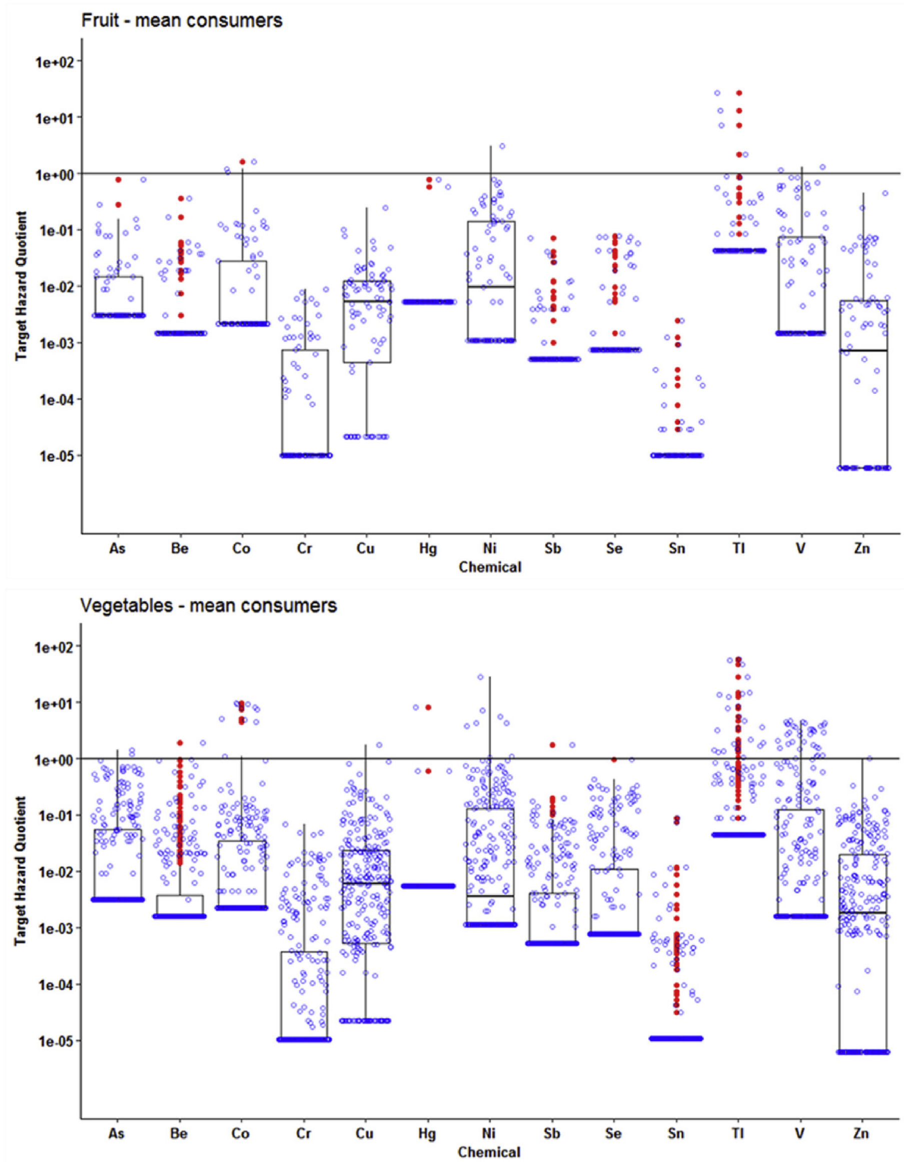

Fig. 3. Tukey boxplot chart of Target Hazard Quotient (THQ) based on mean consumptions of fruit and vegetables (mean consumers) (Log10 scale at Y-axis), and contribution of each sample to the THQ (blue circles) and outliers (red dots). The y-intercept at 1e+00 is a safety threshold, as it accounts for the 100% of effect on the reference dose of each potentially toxic element. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

of volcanic and alluvial origin and this possibility is corroborated by the correlation matrix given in Fig. 6, which shows a positive correlation between As and other PTEs (mainly Sb, Se and V) most commonly occurring in volcanic areas (Aiuppa et al., 2003; Floor and Román-Ross, 2012; Miravet et al., 2007; Varrica et al., 2014).

In conclusion, considering that an acceptable carcinogenic risk should not exceed a TCR value of 10^{-4}, the 19% (mean consumers) and 23% (consumers at 95th percentile) of the samples showed a TCR value above 10^{-4} for carcinogenic risk associated with the intake of arsenic over lifetime. Some studies investigated similar products harvested in different areas and concluded that the TCR value related to dietary exposure to arsenic depends upon either anthropogenic activities or natural sources and could reach unsafe values (beyond 10^{-4}) even among non-high consumers (Antoine et al., 2017; Islam et al., 2018, 2017). However, the median values of TCR occurred in this study are well below the limit of augmented risk as well as the value at 75th percentile, in the case of mean consumers (figures S6 and S7). The data that led to an exceeding of the TCR threshold, even though on a smaller scale, should certainly not be overlooked in terms of safety concern, also bearing in mind that levels of arsenic in vegetables above 0.05 mg kg^{-1}, may lead to a concerning TCR scenario for mean consumers and this certainly represents an important issue for future regulatory challenges.

6. Conclusions

Considering a recent critical environmental issue that caused remarkable detrimental effects to the agricultural production in the so-called Land of Fires landfill area of south Italy, this study set out to highlight any difference between the safety of agro-products grown in and outside the area. No statistically significant difference emerged between the concentrations of PTEs found in fruit and vegetables harvested in the LoF and non-LoF areas with the majority of the samples showing concentrations below the LOQ.

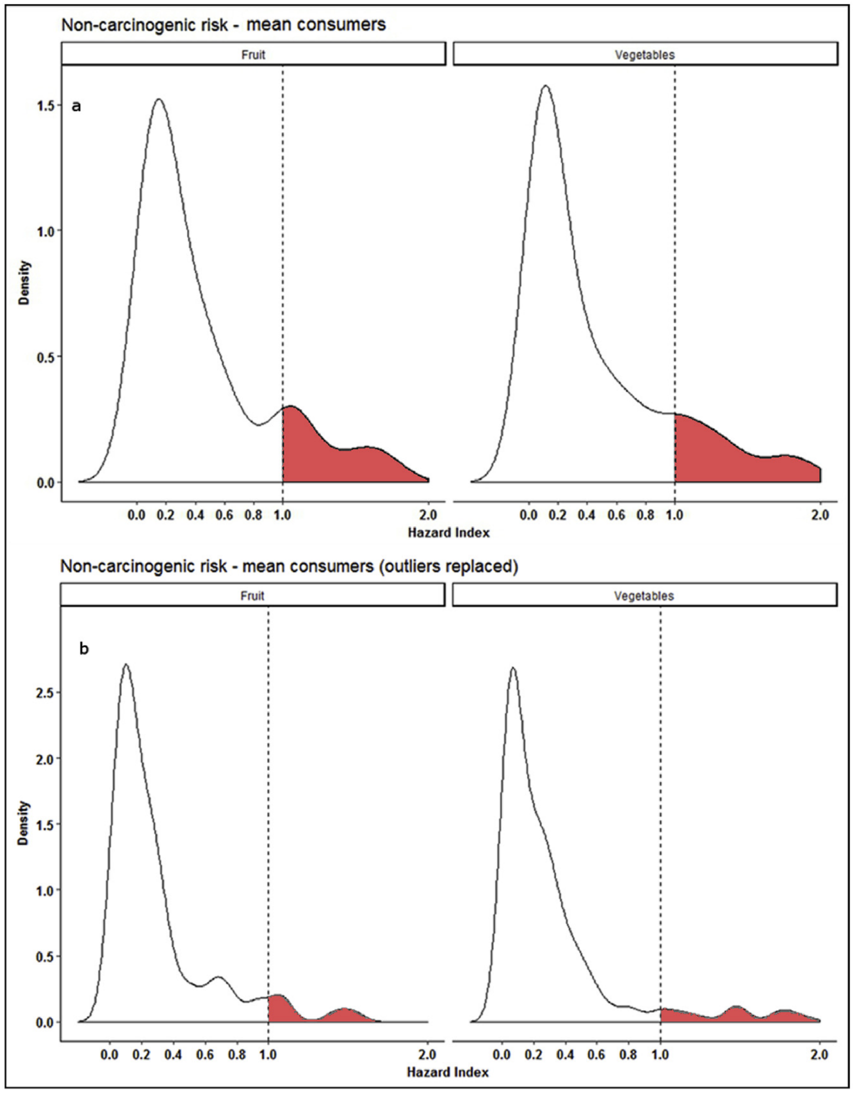

Fig. 4. a) Distribution of the Hazard Indexes calculated as sum of the individual Target Hazard Quotients for mean consumers and effect on the safety threshold (HI > 1); b) The aberrant values were replaced with the highest non-outlying value.

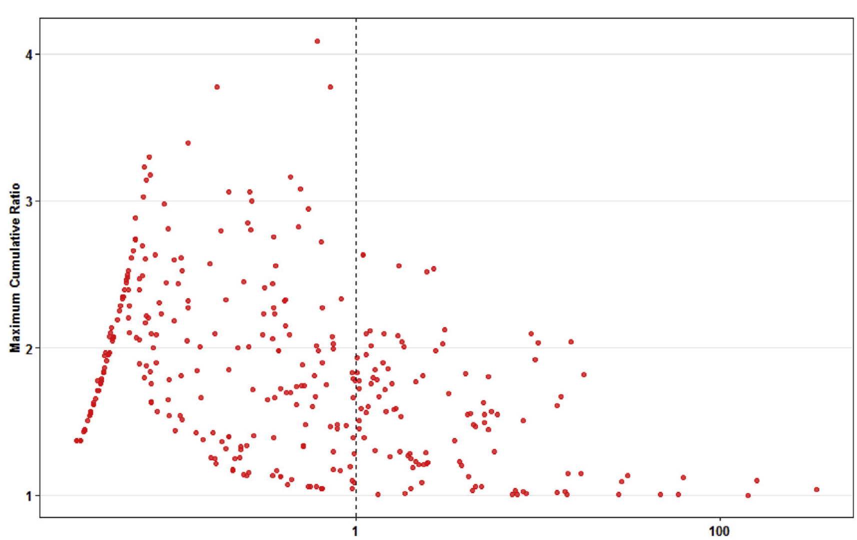

Fig. 5. Maximum Cumulative Ratio distribution according to the Hazard Index values (Log10 scale at X-axis).

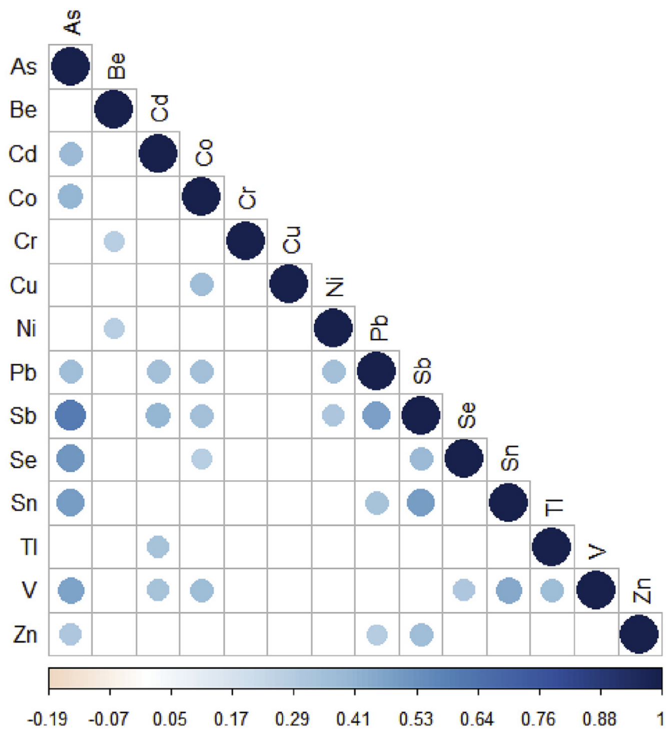

Fig. 6. Plot showing metal-to-metal Spearman's correlation of samples (Spearman's rank correlation with false discovery rate correction, p < 0.001).

Moreover, the levels of the PTEs found in the samples from the LoF were not significantly higher than the levels observed in other potentially polluted areas and in agreement with the data from a previous survey concerning the LoF area. Therefore, the hypothesis that in the LoF landfill area a generalized environmental pollution, brought about by the illegal disposal of urban and industrial wastes, would have made unsafe the fruit and vegetables production, should be ruled out. The negative relation found between the cumulative contribution of PTEs and the overall Hazard Index revealed that the dominating effect, although related to a small percentage of samples, was mainly driven by thallium, vanadium and, on a lesser extent, by arsenic, as regards its carcinogenic endpoint. For this element a concentration threshold in vegetables of 0.03 mg kg^{-1} was calculated above which the mean consumers undergo to a concerning TCR limit value and this might contribute to future implementation of food safety regulations.

The approach used in this case study, tackling a local environmental issue, may well have a bearing on the possibility to ascribe priority to the main toxicity drivers. It might also apply in a wider context in the interests of a tiered approach to the risk characterization of dietary exposure to xenobiotics that are not yet regulated by law.

Conflicts of interest

Authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2018.09.058.

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