Environmental Research 224 (2023) 115478

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Environmental exposure to manganese and health risk assessment from personal sampling near an industrial source of airborne manganese

B. Markiv [a,*], A. Expósito [a], L. Ruiz-Azcona [b], M. Santibáñez [b,c], I. Fernández-Olmo [a]

[a] Dpto. de Ingenierías Química y Biomolecular, Universidad de Cantabria, Avda. Los Castros s/n, 39005, Santander, Cantabria, Spain
[b] Global Health Research Group. Dpto Enfermería, Universidad de Cantabria, Avda. Valdecilla, s/n, 39008, Santander, Cantabria, Spain
[c] Nursing Research Group, IDIVAL, Calle Cardenal Herrera Oria s/n, 39011, Santander, Cantabria, Spain

ARTICLE INFO

Handling Editor: Jose L Domingo

Keywords:
Non-carcinogenic risk
Metal exposure
Personal health risk assessment
Inhaled manganese

ABSTRACT

Manganese (Mn), despite being a trace element necessary in small quantities for the correct functioning of the organism, at higher concentrations can induce health disorders, mainly in motor and cognitive functions, even at levels found in non-occupational environments. For this reason, US EPA guidelines define safe reference doses/concentrations (RfD/RfC) for health.

In this study, the individualised health risk of exposure to Mn through different media (air, diet, soil) and routes of entry into the organism (inhalation, ingestion and dermal absorption) was assessed according to the procedure defined by the US EPA. Calculations related to Mn present in ambient air were made on the basis of data obtained from size-segregated particulate matter (PM) personal samplers carried by volunteers recruited in a cross-sectional study conducted in the Santander Bay (northern Spain), where an industrial source of airborne Mn is located.

Individuals residing in the vicinity of the main Mn source (within 1.5 km) were found to have a hazard index (HI) higher than 1, indicating that there is a potential risk for these subjects to develop health alterations. Also, people living in Santander, the capital of the region, located 7–10 km from the Mn source, may have some risk (HI > 1) under some wind conditions (SW). In addition, a preliminary study of media and routes of entry into the body confirmed that inhalation of $PM_{2.5}$-bound Mn is the most important route contributing to the overall non-carcinogenic health risk related to environmental Mn.

1. Introduction

Human exposure to trace metals is of concern because of their potential health effects. In fact, toxicity associated with particulate matter (PM) is sometimes linked to the metal content in PM (Bates et al., 2019; Mukherjee and Agrawal, 2017). Thus, global public health concerns associated with metal pollution are increasing, which has led to the establishment of air quality guideline and/or limit values for some metal (loid)s (European Parliament and Council of the European Union, 2008; 2005; WHO, 2000). It is well-known that such exposure depends on several factors, including the environments where they are present, such as outdoor and indoor air, water and sediments, soil and dust, food, aquatic biota, and consumer products (US EPA, 2021). Metals present in these media can reach humans mainly through three routes of exposure: dermal contact, ingestion and inhalation. Exposure can be estimated using one or more of the described media and routes according to three possible approaches: (i) direct measurement of exposure; (ii) estimation of exposure based on different scenarios (i.e. considering the characteristics of the exposed population and the frequency/duration of contact between pollutants and the exposed group) and stationary measurements and/or modelling; and (iii) reconstruction of exposure from biomonitoring data with biomarkers of exposure (US EPA, 2021).

Exposure to EU-regulated PM-bound metal(loid)s such as As, Cd and Pb has been widely studied in the literature (Stojsavljević et al., 2019; Zubero et al., 2010). Other metals not regulated in the EU have also been included in the WHO air quality guidelines, such as V and Mn. In particular, Mn may cause neurobehavioral and neuromotor disorders, not only in occupational environments (Mergler et al., 1994; Roels et al., 1992), but also in non-occupational ones (Bowler et al., 2015; Ruiz-Azcona et al., 2022; Santos-Burgoa et al., 2001). In contrast, Mn is also a trace element, so a minimal amount in the diet is necessary.

Epidemiological studies suggest that although environmental

* Corresponding author.
E-mail address: markivb@unican.es (B. Markiv).

https://doi.org/10.1016/j.envres.2023.115478
Received 25 August 2022; Received in revised form 9 January 2023; Accepted 9 February 2023
Available online 14 February 2023
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exposure to Mn can occur through various media and pathways, such as ingestion of food and/or water with a relatively high Mn content (Bouchard et al., 2011; Ntihabose et al., 2018), ambient air inhalation exposure is the most important route in the vicinity of industrial sources of airborne Mn (Fernández-Olmo et al., 2021; Markiv et al., 2022).

Although inhalation or oral Mn risk assessment often recognises the duality of Mn as an essential element at low doses and as a toxic metal at high doses, it was previously not possible to quantitatively describe Mn pharmacokinetics across dose levels and exposure pathways to account for mass balance, and to incorporate this information into a quantitative risk assessment (Boyes, 2010). In addition, the US EPA's own guidance identified a number of specific factors that contribute to the uncertainty in risk assessment, such as the speciation and oxidation state of Mn compounds, which may result in different toxicity (IRIS US EPA, 1998). This toxicity may be linked to soluble or bioaccessible species only, or to the total Mn content. This may explain the use of the bioaccessible concentration instead to the total concentration of pollutants in some health risk studies reported in recent literature (Huang et al., 2018; Ren et al., 2021). In addition, most of the Mn risk assessment studies are based on estimating exposure from different scenarios and stationary measurements data (Fadel et al., 2022; Hernández-Pellón et al., 2018). Furthermore, there is a limited number of datasets for environmental personal exposure monitoring (Fang et al., 2021; Li et al., 2022).

Therefore, direct estimates of environmental Mn exposure may lead to the calculation of a more accurate health risk assessment. The aim of this work was to estimate personal exposure to environmental Mn and to assess the individualised health risk from a cross-sectional study (n = 130) conducted near an industrial source of airborne Mn in the Santander Bay (northern Spain). A preliminary assessment of the contribution of the different media and pathways of Mn entry to the organism was also performed, which allowed us to identify the media and pathways that contribute the most to Mn exposure and associated risk.

2. Methodology

2.1. Sampling and analysis

The study was carried out in the Santander Bay, Cantabria (northern Spain), which is characterised by the presence of several metal emission sources, including a ferromanganese alloy manufacturing plant. This area has been previously described in the literature as being associated with high levels of Mn in ambient air (above the WHO guideline value of 150 ng/m^3) (Arruti et al., 2011; Hernández-Pellón and Fernández-Olmo, 2019a, 2019b; WHO, 2000).

For this reason, a cross-sectional study was conducted with PM personal samplers. Overall, 130 adult volunteers were recruited in this area; briefly, the sampling campaign started in November 2019 and ended in November 2020 being interrupted from March 2020 to June 2020 due to the COVID-19 pandemic lockdown. Each volunteer carried the personal sampler only once for 24 h, collecting individual $PM_{10\text{-}2.5}$ and $PM_{2.5}$ filters; further details of the sampling campaign and inclusion criteria are described in Markiv et al. (2022) and Ruiz-Azcona et al. (2022). The study population was dichotomised into highly (HE) and moderately exposed (ME) based on the distance of each residence from the main metal emission source: HE within 1.5 km from the source and ME at higher distances. This study was approved by the clinical research ethics committee of Cantabria (CEIC) and by the research ethics committee of the University of Cantabria (CEUC).

$PM_{2.5}$ and $PM_{10\text{-}2.5}$ daily samples were collected using a two-stage personal modular impactor (SKC PMI coarse) connected to a personal pump (SKC Aircheck XR5000) operating at a flow rate of 3 lpm. Polytetrafluoroethylene (PTFE) membrane filters of 25 (for $PM_{10\text{-}2.5}$) and 37 mm diameter (for $PM_{2.5}$), with PTFE mesh and a pore size of 1 μm (SKC, Pennsylvania, USA) were used.

Filters were analysed in a two-step procedure described by Expósito et al. (2021a). In summary, bioaccessible and total Mn concentrations were determined in $PM_{2.5}$ and $PM_{10\text{-}2.5}$ samples. For the in vitro bioaccessibility tests, gastric fluid was used for the $PM_{10\text{-}2.5}$ fraction and artificial lysosomal fluid (ALF) for the $PM_{2.5}$ fraction. The insoluble fraction was then digested according to the European Standard UNE EN 14902 (AENOR, 2006), which involves acid digestion (HNO_3/H_2O_2 with a 4/1 ratio, up to 220 °C) of the filter in a microwave system using closed PTFE vessels. Both fractions were analysed by ICP/MS (Agilent 7500ce, Agilent Technologies, California, USA), and bioaccessibility was determined by equation (1), where C_{bio} is the concentration of Mn in the leachate (mg/L), and C_{total} (mg/L) is the concentration of total Mn (bioaccessible + insoluble).

$$Bioaccessibility\ (\%) = \frac{C_{bio}}{C_{total}} * 100 \quad (1)$$

Further details on the Mn concentration measurement including quality assurance and quality control procedures can be found in Expósito et al. (2021b) and Markiv et al. (2022).

2.2. Health risk assessment

First, a preliminary assessment of the contribution of the different media (air, soil, food and water) and routes of Mn exposure to the health risk was performed, using an average scenario, i.e. considering the average concentration of Mn in $PM_{2.5}$, $PM_{10\text{-}2.5}$ and PM_{10}, the recommended daily intake of Mn from food, the intake of Mn-containing dietary supplements, and the consumption of tap water. Then, the individualised exposure estimates and health risk were calculated for all participants in the cross-sectional study.

Exposure to Mn present in ambient air was estimated using equations (2)–(4) (US EPA, 2009, 2004, 1989), taking into account the three possible routes of exposure: (i) direct inhalation of fine atmospheric particles ($PM_{2.5}$) through the mouth and nose; (ii) ingestion of coarse atmospheric particles ($PM_{10\text{-}2.5}$) that have been previously inhaled but are subsequently swallowed and end up in the gastrointestinal tract; and (iii) dermal absorption through particles adhering to exposed skin (PM_{10}).

$$C_{air-adj} = \frac{C_{air} * ET * EF * ED * CF}{AT} \quad (2)$$

$$ADD_{ing} = \frac{C_{medium} * InhR * EF * ED}{BW * AT} \quad (3)$$

$$ADD_{der} = \frac{C_T * AR * AF * SA * EF * ED}{BW * AT} \quad (4)$$

where $C_{air\text{-}adj}$ is the adjusted air Mn concentration or exposure concentration; ADD is the average daily dose of Mn (mg/kg/day); C_{air} is the total or bioaccessible Mn concentration in $PM_{2.5}$ (ng/m^3); C_{medium} is the total or bioaccessible Mn concentration in $PM_{10\text{-}2.5}$ (ng/m^3); C_T is the total or bioaccessible Mn content in PM_{10} (mg/kg); InhR is the inhalation rate (m^3/day); AR is the soil-skin adherence rate (mg/cm^2/day) according to the US EPA procedure (US EPA, 2011), but we assume that is equal to the PM_{10}-skin adherence rate; ET is the exposure time (hours/day); EF is the exposure frequency (days/year); ED is the exposure duration (years); BW is the body weight (kg); AT is the average time (days); CF is a conversion factor (1 day/24 h); SA is the skin surface available for contact (cm^2); and AF is the dermal absorption factor (dimensionless) (US EPA, 2011). For non-carcinogenic risk assessment, AT = ED*EF. It should be noted that Mn present in $PM_{10\text{-}2.5}$ that is inhaled but subsequently processed in the gastrointestinal tract was considered for the estimation of ADD_{ing}. When personal samplers are used, equation (2) can be simplified: $C_{air\text{-}adj} = C_{air}$.

The exposure estimates linked to Mn present in air may be calculated based on its total concentration, as used in the classical approach of exposure characterization, or based on its bioaccessible concentration,

as considered in alternative approaches to estimate such exposure. In the latter case, only the bioaccessible concentration is assumed to be associated with the toxicity and should therefore be used in health risk calculations.

Secondly, regarding the exposure to Mn present in soil/dust, the ingestion of Mn by hand-mouth contact of soil was assumed to be negligible, since the present study has been conducted in adults, and this route is more feasible in children (US EPA, 2011). On the other hand, there is a specific procedure to characterise the exposure associated with ingestion of resuspended soil/dust that is previously inhaled, using the Mn content in dust and local soil; however, it was assumed that this exposure was already estimated according to equation (3), since PM collected by personal samplers is assumed to include resuspended soil and/or dust particles. Another possible risk linked to soil/dust is dermal contact, although this has not been included in the procedure, because it is a more frequent route for children (in contact with dust on the floor of the dwelling, or on the floor of a garden or playground). It may also be relevant for certain occupations and activities, such as gardening, but given the nature of this cross-sectional study and the characteristics of participants, it was considered reasonable not to include this exposure estimate in the calculations.

Finally, ingestion exposure occurring via consumption of drinking water and food was also estimated. For food, Trumbo et al. (2001) recommended an intake dose of Mn for adults of 2.3 mg/day for males and 1.8 mg/day for females. An average daily dose of 2.05 mg/day was used in equation (5):

$$ADD_{ing,f} = \frac{C_{daily\ recommended}}{BW} \quad (5)$$

In addition to the usual dietary intake, the ingestion of some dietary supplements containing Mn may also contribute to the ingestion route (equation (6)). For the calculation of the contribution of dietary supplements to the overall exposure to Mn, the intake of a generic supplement containing 0.5 mg Mn per capsule was used, considering an intake of 2 pills per day as recommended in the leaflet.

$$ADD_{ing,suppl} = \frac{C_{daily,suppl}}{BW} \quad (6)$$

For drinking water, equation (7) was used, using a water intake rate (IngR) for population over 21 years of 16 mL/kg/day and the Mn concentration measured in local tap water (0.38 μg/L):

$$ADD_{ing,w} = \frac{C_{medium} * IngR * EF * ED}{AT} \quad (7)$$

Once the exposure was characterised, the estimation of the non-carcinogenic health risk from exposure to Mn was determined by its hazard quotient (HQ) according to equations (8)–(10).

$$\text{Inhalation} \quad HQ_{inh} = \frac{C_{air-adj}}{RfC} \quad (8)$$

$$\text{Ingestion} \quad HQ_{ing} = \frac{ADD_{ing,PM}}{RfD_{nd}} + \frac{ADD_{ing,f}}{RfD_{d}} + \frac{ADD_{ing,suppl}}{RfD_{d}} + \frac{ADD_{ing,w}}{RfD_{nd}} \quad (9)$$

$$\text{Dermal contact} \quad HQ_{der} = \frac{ADD_{der}}{RfD_{nd} * GIABS} \quad (10)$$

where RfC/RfD is the reference concentration/dose for chronic exposure to Mn by inhalation/ingestion (ng/m^3 or mg/kg/day). The US EPA defines the dermal reference dose as the oral RfD multiplied by the GIABS factor (fraction absorbed from the gastrointestinal tract), being 4% in the specific case of Mn (US EPA, 2004). An HQ > 1 is considered an indicator of adverse health effects in the exposed population. It should be noted that, although personal samples correspond to a short period of time (acute exposure), it is assumed that the subjects are chronically exposed to similar levels of airborne Mn, so RfC and RfD for chronic exposure are used. Thus, a RfC value of 50 ng/m^3 was used (IRIS US EPA, 1998); regarding the RfD value for Mn, the US EPA distinguishes between the diet-linked value (RfD_d), 0.14 mg/kg/day and the non-diet value (RfD_{nd}) of 0.024 mg/kg/day (IRIS US EPA, 1998).

Lastly, the hazard index (HI) associated with Mn exposure is calculated as the sum of the HQ_i for all exposure pathways and media, as shown in equation (11).

$$HI_i = \sum_1^i HQ_i \quad (11)$$

2.3. Statistical analysis

Data analysis was performed using R (version 4.0.5) and Microsoft Excel 365 (version 2204). All quantitative variables in the study were tested for normality using the Kolmogorov-Smirnov test with Lilliefors correction, and since the distributions were non-normal, the non-parametric Mann-Whitney *U* test was used.

3. Results and discussion

The study population is described in Markiv et al. (2022). Participants' age ranged from 20 to 71 years, with a mean of 41.75 ± SD = 13.97 years. The highly exposed population resided within 0.8 km (0.25–1.5 km) of the ferromanganese alloy factory, while the moderately exposed population resided within an average radius of 7.3 km (2–34 km).

As explained in Methodology, the assessment of which means and routes contribute to a higher health risk from Mn exposure was first carried out. Supplementary Table 1 describes the information used to calculate the contribution of the studied media and routes to the total risk (HI) from Mn exposure, as well as the ADD/$C_{air-adj}$ and the HQs for each of the exposure media and routes considered. The HQ values were calculated using both the classical approach, which considers the total concentration of the pollutant in PM_x, and the most innovative approach, which advocates the use of the bioaccessible concentration. According to the recent literature, bioaccessibility-based assessment more accurately reflects the health risk via inhalation exposure compared to that based on the total contents of metal(loid)s in PM, since the bioaccessible species are more likely to be capable of inducing toxicity (Huang et al., 2018; Ren et al., 2021).

Regarding exposure to airborne Mn, the HQ values obtained for the inhalation route (1.27 and 1.58 considering bioaccessible and total Mn in $PM_{2.5}$, respectively) agree well with the results of Hernández-Pellón et al. (2018), finding HQ values higher than 1 for scenarios that considered different timeframes over which exposure occurred, when the non-carcinogenic risk associated with the inhalation of Mn bound to PM_{10} collected in the vicinity of the mentioned Mn source was assessed, using data from PM stationary samplers. In the present study, this approach is improved by using personal samplers and separating the different PM fractions according to their fate in the body, obtaining that the greatest health risk is associated with the entry of Mn via inhalation, through the finest particles.

Regarding the ingestion route of Mn associated with the $PM_{10\text{-}2.5}$ fraction previously inhaled, it is observed that although the concentrations of Mn are similar to those found in $PM_{2.5}$, the derived risk is much lower (HQ in the range of 10^{-4}).

Finally, for dermal contact exposure to PM_{10}, a non-negligible contribution is observed (0.24 and 0.29 for Mn bound to bioaccessible and total PM_{10} respectively). However, for the calculation of the risk associated with this pathway, the values used in the US EPA procedure (AR = 0.07 mg/cm^2/day and SA = 5700 cm^2) may overestimate this exposure, since this AR value was derived after considering direct contact of skin with soil, as occurs in gardening activities (US EPA, 2011, 2004) and the skin surface area in contact with PM during most of the year is less than 5700 cm^2. However, no alternative AR values have been found in the literature for PM adhered to skin; furthermore, the same methodology and AR values have been used to assess dermal risk linked

to PM-bound pollutants in some studies (Aguilera et al., 2022; Al-Harbi et al., 2021; Fadel et al., 2022; Roy et al., 2022).

In addition to exposure to airborne Mn, individuals are also exposed to Mn through the diet (present in tea, legumes, nuts, etc.). Moreover, some dietary supplements may contain Mn, so the intake of a Mn-containing generic supplement was used also to calculate the contribution of this route to the overall risk, as explained in Methodology.

Since the diet was not exhaustively studied in our work, a constant Mn intake equivalent to the average recommended daily allowance for men and women was considered, deriving an HQ of 0.18, one-fifth of the threshold value that is considered safe for health. Furthermore, the contribution of ingested water was quantified based on US EPA (2011) guidelines, considering the measured concentration of Mn in the local tap water analysed in this study. Supplementary Table 1 shows that health risk associated with water ingestion is very low and of the same order of magnitude as ingestion of previously inhaled $PM_{10\text{-}2.5}$.

Fig. 1 shows the percentage contribution of each medium and route to the total HI, considering both the classical methodology ($[Mn]_{total}$) and the alternative methodology ($[Mn]_{bioaccessible}$). Using the classical methodology, air contributed to 88% of the total HI (74% via the inhalation route and 14% via dermal absorption), with diet accounting for the remaining 12% (8% in the form of recommended daily intake and 4% in the form of supplements). These percentages are slightly modified when considering the alternative approach, where the contribution of air becomes 85% (71% via the inhalation route and 14% via dermal absorption), with the dietary contribution increasing (10% in the form of food intake and 5% in the form of supplements).

After observing a higher contribution of air to the HI, each of the routes was studied in detail, observing that in the two approaches the contribution was the same: 84% through inhalation of $PM_{2.5}$ and 16% through dermal absorption, with the contribution of Mn ingestion present in $PM_{10\text{-}2.5}$ being practically negligible.

After analysing the contribution of the different media and routes of Mn exposure for this case study, the individualised health risk was determined for all participants in the cross-sectional study. For these calculations, the Mn concentration to which each participant has been exposed was used to estimate the health risk from the "air" media, considering both the classical method based on total Mn concentration and the alternative method based on bioaccessible concentration. Regarding the dietary contribution, a correct estimation of individualised exposure requires information on the concentration of Mn in each food ingested by each participant, as well as the ingestion rate (US EPA, 2021). However, since this route was not the focus of this study, the recommended daily dose was used, distinguishing only between the dose of men and women. On the other hand, since only two individuals reported the consumption of dietary supplements containing Mn, it has not been included in the individualised health risk. Finally, Mn present in tap water was not considered in the calculation of the individualised risk, since the water intake of each participant was not registered and the contribution to the total risk was found to be negligible in the previous section.

Once the HI due to Mn exposure for the 130 participants of the cross-sectional study had been calculated, the statistics summarising the main results of the study clustered according to exposure (moderate/highly exposed) were calculated, considering both the classical and the alternative approaches (Table 1).

Following the classical method, significant differences in the health risk caused by Mn exposure are observed between the high and moderately exposed groups. Firstly, for the moderately exposed group almost all the health risk derives from the inhalation of Mn in air (HQ_{inh} = 0.26) and from the background provided by the average daily food intake. However, in the highly exposed population, the inhalation route and the dermal contact are the two most relevant Mn exposure pathways (HQ_{inh} = 0.89, HQ_{der} = 0.11). In Supplementary Fig. 1, the difference between the two exposure groups can be clearly seen, with the median of the most exposed group being practically at the threshold value (HI_{air} = 0.95), exceeding this value when dietary intake is considered (HI_{total} = 1.14), which may have consequences for the health of these individuals.

This trend is maintained when the health risk is calculated considering the bioaccessible concentrations of the different Mn fractions. Thus, the risk from air inhalation induces a HQ_{inh} = 0.16 for the least exposed, rising significantly to 0.68 for the most exposed population. Again, the dermal contribution is more pronounced in the most exposed group (HQ_{der} = 0.088). In contrast to the classical approach, when considering only bioaccessible concentrations, the median of HI_{total} remains below the threshold value proposed by the US EPA (Supplementary Fig. 2).

There is some discussion in the literature about the use of the total or

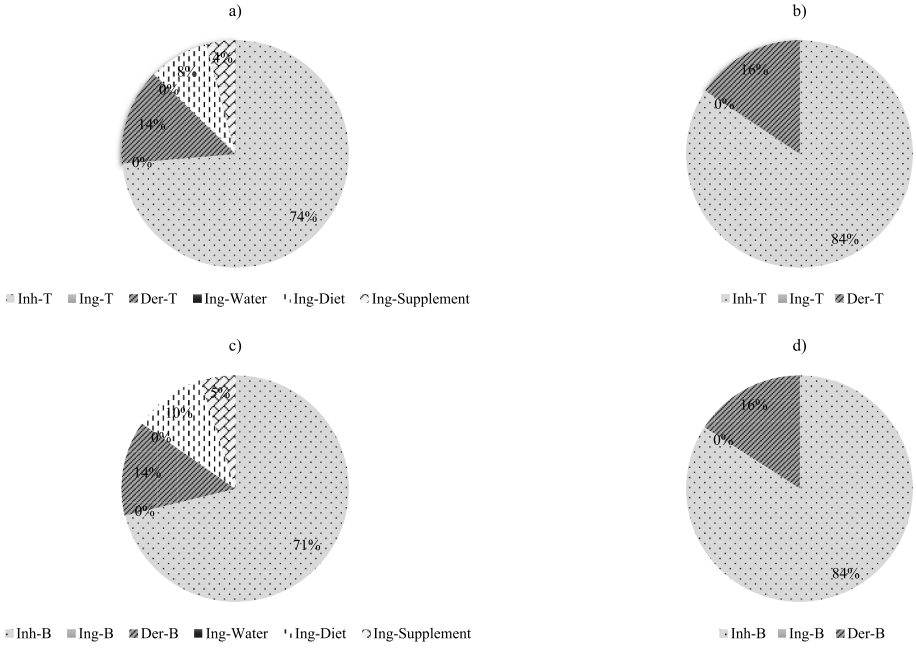

Fig. 1. Contribution (%) of each medium and route of exposure to HI_{total}: a) based on total Mn concentration and including all media; b) based on total Mn concentration and for air exposure; c) based on bioaccessible Mn concentration and including all media; d) based on bioaccessible Mn concentration and for air exposure.

Table 1
Descriptive statistics of HQ and total HI as a function of exposure (HE (highly exposed); ME (moderately exposed)).

Classical approach

	ME				HE					Total			
	N	AM (SD)	Median	P_{95}	N	AM (SD)	Median	P_{95}	p-value*	N	AM (SD)	Median	P_{95}
HQ_{inh}	65	0.64 (0.97)	0.26	3.14	65	2.52 (3.80)	0.89	10.07	<0.001	130	1.58 (2.92)	0.50	7.01
HQ_{ing}	65	2.010^{-4} ($3.3*10^{-4}$)	$1.0*10^{-4}$	$6.0*10^{-4}$	65	$1.1*10^{-3}$ ($2.5*10^{-3}$)	$4.0*10^{-4}$	$2.9*10^{-3}$	<0.001	130	$6.0*10^{-4}$ ($1.8*10^{-3}$)	$1.0*10^{-4}$	$2.5*10^{-3}$
HQ_{der}	65	$4.5*10^{-2}$ ($6.6*10^{-2}$)	$2.0*10^{-2}$	0.19	65	0.27 (0.64)	0.11	1.01	<0.001	130	0.16 (0.47)	$4.1*10^{-2}$	0.84
HI_{air}	65	0.68 (1.03)	0.27	3.49	65	2.80 (4.31)	0.95	10.94	<0.001	130	1.74 (3.29)	0.54	7.80
HI_{total}	65	0.86 (1.03)	0.45	3.67	65	2.98 (4.31)	1.14	11.12	<0.001	130	1.92 (3.29)	0.72	7.98

Alternative approach

	ME				HE					Total			
	N	AM (SD)	Median	P_{95}	N	AM (SD)	Median	P_{95}	p-value*	N	AM (SD)	**Median**	**P_{95}**
HQ_{inh}	65	0.47 (0.81)	0.16	1.72	65	2.20 (3.57)	0.68	9.44	<0.001	130	1.33 (2.72)	0.34	6.31
HQ_{ing}	65	$1.0*10^{-4}$ ($2.9*10^{-4}$)	$<1.0*10^{-4}$	$4.0*10^{-4}$	65	$9.0*10^{-4}$ ($2.1*10^{-3}$)	3.0*10-4	$2.3*10^{-3}$	<0.001	130	$5.0*10^{-4}$ ($1.5*10^{-3}$)	$1.0*10^{-4}$	$2.2*10^{-3}$
HQ_{der}	65	$3.4*10^{-2}$ (5.9*10-2)	1.3*10-2	0.17	65	0.23 (0.55)	$8.8*10^{-2}$	0.92	<0.001	130	0.13 (0.40)	0.03	0.75
HI_{air}	65	0.50 (0.86)	0.18	1.93	65	2.42 (4.02)	0.78	10.25	<0.001	130	1.46 (3.05)	0.37	7.07
HI_{total}	65	0.69 (0.86)	0.36	2.11	65	2.60 (4.02)	0.96	10.44	<0.001	130	1.64 (3.05)	0.55	7.25

N = Total number of samples.
AM (SD) = Arithmetic Mean (Standard Deviation).
P_{95} = 95th percentile.
*Mann Whitney *U* test.

bioaccessible concentration of pollutants for the calculation of inhalation risk. Thus, some studies reported the use of the bioaccessible concentration and the same RfC value, as it may better reflect the risk of exposure to such pollutants (Hernández-Pellón et al., 2018; Mbengue et al., 2015; Nie et al., 2018; Ren et al., 2021; Weggeberg et al., 2019). Since the RfC values are usually derived from studies where the total not the bioaccessible concentration is determined, it can be questioned if new RfC values based on the bioaccessible concentration of pollutants need to be derived or if the current RfC values have to be used. It should be considered that the procedure by which the RfC of the different pollutants is derived includes different uncertainties associated with the final value of the RfC that take into account among others the toxicity of the species of the pollutant being assessed, and this toxicity may be linked to the pollutant bioaccessibility. In particular, for the case of the Mn RfC, the original study from which this value was derived is an occupational exposure study carried out in a MnO_2 battery plant, sampling the respirable fraction of particles, and analysing the total Mn content in this fraction (Roels et al., 1992). Subsequently, several uncertainty factors are considered, including a factor of 10 for database limitations reflecting both less chronic exposure periods and lack of developmental data, as well as potential but unquantified differences in the toxicity of different forms of Mn (IRIS US EPA, 1998), not specifying exactly whether speciation, solubility, bioaccessibility, etc. are taken into account in the toxicity of different forms of Mn. According to this, both approaches can be applied for the health risk assessment. Thus, the approach based on total concentration would lead a higher HI than that based on the bioaccessible concentration.

The importance of the inhalation route respect to the total health risk for Mn is also found in the literature (Fadel et al., 2022; Nie et al., 2018), with ingestion being practically negligible. However, these studies do not consider the ingestion of $PM_{10-2.5}$ previously inhaled, but rather PM deposited on food, water or different surfaces that are then ingested (Dahmardeh Behrooz et al., 2021). On the other hand, the health risk from exposure to PM-bound Mn by dermal contact is relatively low in the literature. For example, Fadel et al. (2022) reported a HQ_{der} of 0.0002 versus HQ_{inh} of 0.0812–0.1080 in Beirut (Lebanon); Nie et al. (2018) obtained a HQ_{der} of 0.0001 versus HQ_{inh} of 0.558 in Yangzhou (China).

Hernández-Pellón et al. (2018) carried out a stationary sampling at two sites in Santander Bay: in the vicinity of the Maliaño ferroalloy factory, and in Santander, 7 km from this industry, reporting a Mn concentration in PM_{10} of 901.1 ng/m^3 in Maliaño, which decreases significantly in the Santander area (74.6 ng/m^3). For the health risk calculation, they considered the average bioaccessible concentration (both in ALF and Gamble's solutions), obtaining that the non-carcinogenic risk in the vicinity of the ferroalloy plant was significantly higher than the threshold value defined by the US EPA for all the scenarios considered. Even in the less exposed area (Santander), HQ_{inh} values above the threshold were found for some specific exposure scenarios (mainly for residents who spent all their time in the study area), which highlights the need for a more exhaustive study of the risk associated with Mn exposure in the Santander Bay. Therefore, the results obtained in this paper represent a considerable improvement on previous literature as they are based on the individualised risk of the different participants.

Finally, an individualised risk map of all participants of the cross-sectional study has been elaborated following the classical approach, i.e. based on the total Mn concentration (Fig. 2). A colour legend ranging from green to red shows the variability of individualised health risk, from $HI_{total} < 1$ for safe health values (green) to $HI_{total} > 1$ that may lead to adverse health effects (yellow to red). A health risk map using the alternative approach, i.e. based on the bioaccessible Mn concentration was also shown in Supplementary Fig. 3.

Wind roses in previous studies carried out in this area indicated that the predominant wind direction is SW (Fernández-Olmo et al., 2016; Ruiz et al., 2014), mainly in the winter period, leading to higher PM-bound Mn concentrations for receptors located N/NE of the ferroalloy plant, resulting in a higher risk associated with Mn exposure, as shown in Fig. 2. These results agree with the study by Otero-Pregigueiro et al. (2018), where maximum modelled PM_{10}-bound Mn concentration levels were obtained in the vicinity of the ferromanganese alloys plant, with daily average concentration levels of up to 5000 ng/m^3 in Maliaño (under moderate intensity SW wind conditions). Furthermore, the model indicates that under a SW wind scenario the Mn plume can reach the city

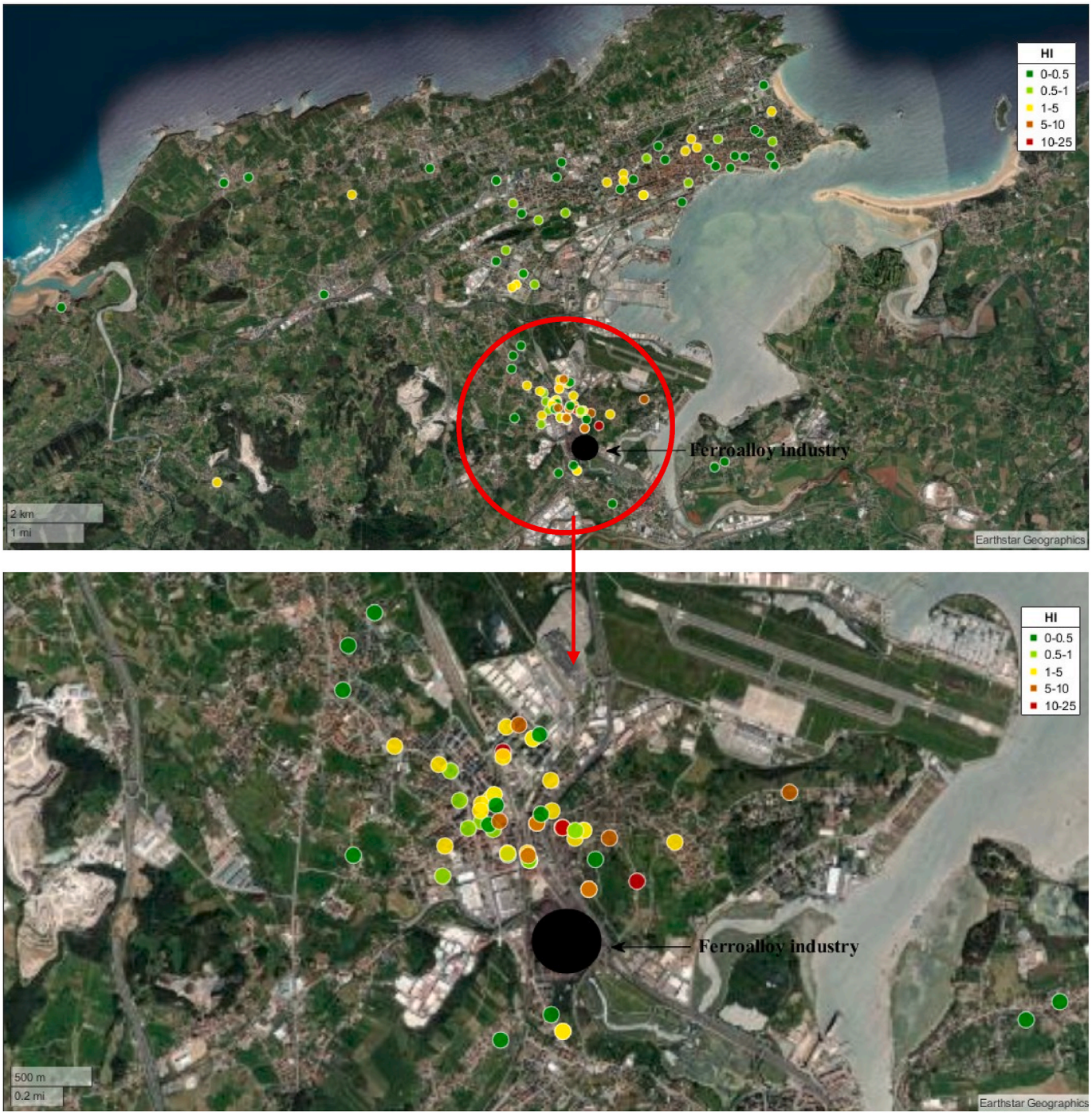

Fig. 2. Health risk map for Mn exposure according to participants' residence. HI based on total Mn concentration.

of Santander and can lead to concentration levels around 200 ng/m^3 (Otero-Pregigueiro et al., 2018). In this sense, HI values higher than 1 (particularly, in the range between 1 and 5) can be found for some participants living in Santander city (see Fig. 2).

4. Conclusions

The individualised health risk of Mn exposure through different media (air, diet, soil) and pathways (inhalation, ingestion and dermal absorption) was assessed near an industrial source of airborne Mn according to the procedure defined by the US EPA. Preliminary results on media and routes of entry into the body confirmed that inhalation of $PM_{2.5}$-bound Mn was the most important route contributing to the overall non-carcinogenic health risk related to environmental Mn.

Personal PM sampling allowed a more accurate Mn exposure estimation and thus the calculation of a more precise non-carcinogenic health risk associated with environmental Mn exposure. Thus, the determination of the hazard index (HI) for Mn following the methodology proposed by the US EPA showed that the population living in the vicinity of this industrial source of airborne Mn is more susceptible to adverse health effects. In addition, people living in Santander, the capital of the region, located 7–10 km from the Mn source, may be at some risk (HI $>$ 1) under specific wind conditions (SW).

This type of investigations, such as health risk assessment studies based on personal sampling of key air pollutants, can help policy makers to better understand the health risks that may occur in different areas

affected by the emission of such pollutants.

Author contribution

B. Markiv: Investigation, Writing – original draft preparation, Formal analysis; A. Expósito: Investigation (samples analysis); L. Ruiz-Azcona: Investigation (samples collection); M. Santibáñez: Supervision, Funding acquisition, Formal analysis; I. Fernández-Olmo: Conceptualization, Methodology, Reviewing and Editing, Supervision, Funding acquisition.

Funding sources

This work was supported by the Spanish Ministry of Science and Innovation (Project CTM2017-82636-R, funded by MCIN/AEI/10.13039/501100011033 and "ERDF A way of making Europe"). Bohdana Markiv also thanks the MICIU for her predoctoral contract (PRE2018-085152, financed together by MCIN/AEI/10.13039/501100011033 and "ESF Investing in your future").

Ethics approval

The study was approved by the ethical committee of clinical research in Cantabria (CEIC) and by the ethical committee of research of the University of Cantabria (CEUC).

The authors state that the participants in the human research gave their informed consent for the publication of the results obtained in this cross-sectional study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.115478.

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