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Influence of environmental and dietary exposures on metals accumulation among the residents of a major industrial harbour (Fos-sur-Mer, France)

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ABSTRACT

Objectives: We sought to determine whether the residents living closer to the core industrial zone (Fos-sur-Mer) had higher trace metals blood and urinary levels than residents who lived further away (Saint-Martin-de-Crau).
Materials and Methods: As part of The INDEX study, we measured the following trace metals into blood and urine samples of 138 participants (80 in the core industrial zone and 58 in the reference area): Antimony, Arsenic, Cadmium, Chromium, Cobalt, Mercury, Nickel, Lead and Vanadium. Participants were recruited using a stratified random sampling method and had to meet the following inclusion criteria: 30–65 years old, living in the area since at least 3 years, not working in the industrial sector, non-smoker. We used single-pollutant multivariate linear regression models, using substitution when censored data were under 15 % and Tobit models alternatively, adjusting for personal physiological, social, dietary, housing characteristics and leisure activities. We also measured these trace metals in samples of lichens (*Xanthoria parietina*) and atmospheric particles ($PM_{2.5}$).
Results: We showed higher lichen and air levels of several metals (Cd, Cr, Co, Ni and Pb) in the exposed area. Living close to the core industrial zone was significantly associated with an increase in blood levels of lead (adjusted geometric mean = 17.2 [15.8–18.7] vs 15.1 [13.7–16.7] $\mu g.L^{-1}$, $p < 0.05$). We report significant increase of some metals urinary levels among residents of the industrial port zone, as the result of the use of the environment, itself contaminated by industrial activities: dietary history of self-consumption of vegetables (Cadmium), eggs and poultries (Vanadium). However, Vanadium levels were greater among self-consumers of poultry in the reference area and gardeners had circulatory levels of Lead greater than non-gardeners only in the reference area. Consumption of non-local sea-products increased the level of Cadmium.
Conclusions: These results brought interesting clues, in complement to national programs, regarding the exposure to trace metals of residents living in a major industrial harbor.

1. Introduction

The city of Fos-sur-Mer (France) is located in the direct vicinity of one of the largest port zones in Europe, characterized by an intense industrial activity (e.g. petrochemical, steel industry, organic chemistry or solid waste incinerator) [1]. Environmental monitoring studies and measurements of the industrial exhaust in the region have confirmed the presence of diverse contaminants (trace metals, organochlorine pollutants, PAHs and benzene) in all environmental compartments (soils, vegetables, sea and atmosphere) [1–5]. In the industrial area of Fos-sur-Mer and Lavera (industrial core 8 km away), 1 500 tons of PM_{10} were emitted in 2016 by industry (excluding diffuse and unreported emissions) [6].

The cross-sectional INDEX study was conducted in response to the health concerns expressed by the local community [7] and the results from subsequent health studies conducted in the region [8–10]. Residents worried about their body burden in several anthropic industrial contaminants (metals, PAH, dioxins/furans and PCBs) characterized by long lifetime and potentially severe toxicity via inhalation and/or local food consumption. In particular, some specific metal contaminants (As,

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Cd, Cr, Ni) are recognized as carcinogenic (group I) to humans [11,12] or associated to other adverse effects such as neurotoxicity (Pb and Hg), kidney toxicity (Cd) or various other threats to health (Mn, Pb) [13–15].

The objective of this article was to report the results of the metal exposure assessment in the mainstream populations living in Fos-sur-Mer affected by the nearby industrial zone, and Saint-Martin-de-Crau located 25 km away, considered here as the reference area. The results of impregnation levels in blood and urine, adjusted on numerous individual factors, were also triangulated with the results of atmospheric particulate matter analysis and lichen biomonitoring, conducted throughout the human sampling campaign.

2. Materials and methods

2.1. Study areas and enrollment of the participants

The study methodology was fully described elsewhere [16,17]. Briefly, we investigated two distinct areas (Fig. 1): the city of Fos-sur-Mer (~15,800 inhabitants) as the exposed area, and the city of Saint-Martin-de-Crau and nearby village of Mouriès (~13,400 and ~3450 inhabitants, respectively), as the reference area. The community of Saint-Martin-de-Crau is located 15 km apart from any facilities, registered in the IREP (French National Registry of Pollutant Emissions) that declared metals canalized emissions (As, Cd, Co, Cr, Ni, Pb, Sb, V and Hg). Both towns are subjected to comparable road transport emissions (i.e. a nearby highway and a logistic area leading to high contributions of heavy-duty truck traffic). All residents were included by phone using a stratified random sampling method by site, age and gender (Sept-Nov. 2016) from the local census supplied by the town councils. Participants were selected with strict criteria (30–65 years old, living in the area since 3 years at least, not working in the industrial sector, being non-smoker). The specific exclusion criteria were: being employed in the past ten year in industrial installations that declared metals canalized emissions within the IREP registry, being employed in another city than the one of residence, being pregnant or breastfeeding in the past year, being smoker or former smoker < 1 year. Finally, 138 participants were sampled for blood and urine after a face-to-face questionnaire collecting individual characteristics about physiology, residential environment, dietary history, socioeconomics, work and free time activities.

2.2. Biological samples and chemical analyses

Sampling - For lead sampling, volumes of 5 mL of blood were collected (fasting state). For the other metals, first urine samples in the morning were collected. Dedicated blood tubes (BD® trace-metal free tubes) and urine flasks (polypropylene flasks previously tested to ensure the absence of metal contamination) were used. The whole set of samples was then stored (between −18 °C and −20 °C for urine, between +2 °C and +8 °C for blood) and sent to the partner laboratories.

Analyses - Lead was determined in blood (LOQ: 0,5 $\mu g.L^{-1}$) whereas other metals were determined in the urine of the subjects. Inorganic Arsenic (AsI) and its methylated metabolites (MMA: Monomethylarsonic Acid and DMA: Dimethylarsinic Acid) that mainly represent not dietary sources of As were determined in Toxicolabo (Nantes, France) by hydride generation atomic absorption spectrometry (HG-AAS), with an analytical limit of quantification (LOQ) of 5 $\mu g.L^{-1}$ for the sum of the three species. This method can distinguish between AsI and methylated derivatives, but only the sum of Asi+MMA+DMA is further presented in this article as both sanitary and biological reference values are determined in this way. Besides, total As (AsT) including both Asi+MMA+DMA as well as organic species of As (Arsenobetaine AsB, and

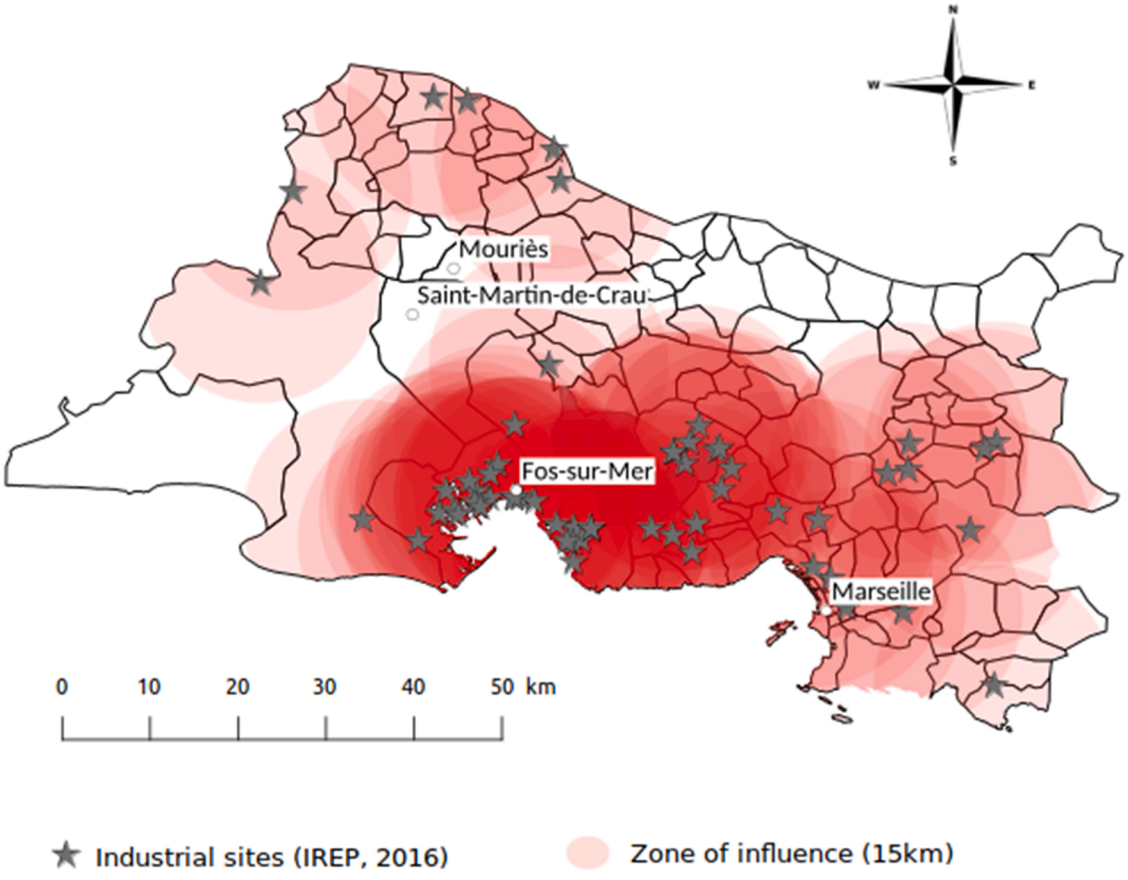

Fig. 1. Map of the region.

Arsenocholine AsC) resulting from dietary sources (fish, crustacean, shellfish) was determined separately. In the rest of this manuscript, Asi+MMA+DMA+AsB+AsC will thus be referred to as AsT whereas Asi+MMA+DMA as ASI. Urinary metals (AsT, Al, Cd, Co, Cr, Ni, Pb, Sb, V, Hg) and blood lead were determined by inductively coupled plasma mass spectrometry (ICP-MS Thermo Scientific X Series 2). Rhodium was used as internal standard to correct for any matrix effects. Samples were measured in triplicate and the mean value was used for the results provided that the Relative Standard Deviation (RSD) was lower than 10 %. The LOQ are listed hereafter: Total Arsenic (AsT) = 3.02 $\mu g.L^{-1}$; Cadmium (Cd) = 0.10 $\mu g.L^{-1}$; Cobalt (Co) = 0.19 $\mu g.L^{-1}$; Chromium (Cr) = 0.39 $\mu g.L^{-1}$; Nickel (Ni) = 1.16 $\mu g.L^{-1}$; Lead (Pb) = 0.6 $\mu g.L^{-1}$; Antimony (Sb) = 0.06 $\mu g/L^{-1}$; Vanadium (V) = 0.19 $\mu g.L^{-1}$. Limits of Quantification were calculated as 10 times the signal resulting from the injection of blank matrix (Nitric Acid HNO_3 1 %). Inorganic Mercury was determined by cold vapor atomic absorption spectroscopy (CV-AAS) with a LOQ of 0.5 $\mu g.L^{-1}$. Blank samples (empty blood tubes and empty urine flasks filled with HNO3 1 %) were regularly included in the analytical batches (every 20 samples) to check the absence of contamination. Procedures were integrated in a certified quality assurance system and most of the analytical methods were accredited (ISO-15189). The accuracy of the analytical methods used was ensured by successful participations to External Quality Assessment Schemes (EQAS) for trace elements (monthly to European Occupational and Environmental Laboratory Medicine "OELM", and yearly to German "G-EQUAS" scheme). Two levels of Quality Controls (Clinchek Recipe Controls) were injected every ten samples in order to check the stability of the analytical equipment. The results (except from blood lead) were normalized to the urinary creatinine, the latter being determined by the enzymatic method.

Finally, all the participants and their attending physicians received the results of blood and urine analyses from the Grenoble University Hospital, which containing reference values when applicable.

2.3. Research ethics

The protocol was approved by a steering committee, by the French National Agency for Medicines and Health Products Safety (ANSM) (N°2013-A01727–38, 2014/04/28), the French Advisory Committee on Information Processing in Material Research in the Field of Health (CCTIRS) (N°13.727bis, 2014/04/16), the Protection to Persons Committee (CPP Sud Mediterranée II) (N°214 R07 MS2, 2016/01/08) and the French Authority for Data Confidentiality (CNIL) (N°914464, 2016/07/13). Participants signed an informed consent form, which was approved by the above-mentioned instances. Data were collected anonymously.

2.4. Environmental monitoring

Metals were determined in both lichens and $PM_{2.5}$ particles by the Drôme departmental laboratory (https://www.ladromelaboratoire.fr/). The methodologies were fully described elsewhere for lichen [4] and $PM_{2.5}$ [1].

We sampled lichens (*Xanthoria parietina*) on October, 24–26th, at the end of the 2-month atmospheric particles sampling period in both exposed (N_{sites} = 5) and unexposed areas (N_{sites} = 4) and in other reference locations (N_{sites} = 6) used in our previous works to provide comparison points [2,4]. This lag matched with the 2-month equilibrium time evaluated for the bioaccumulation of metals in *X.parietina* [18]. Lichens (10–20 g) were sampled on trees at least 1-meter high in order to limit the influence of soil, using a ceramic knife and protection gloves. Prior rinse off with ultra-pure water was realized in order to limit substantial deposit and facilitate the detachment from the bark, and the sampled lichens were immediately stored in HDPE tubes at 4 °C. Further cleaning of the lichen samples was operated within 24 h to remove dust, bark, or unwanted species. They were then freeze-dried and reduced to a thin powder by means of a ball mill equipped with zirconium oxide beads and bowls, and finally sent to the laboratory with certified materials.

Atmospheric particles were sampled on quartz fiber filters on a 24 h-basis in both communities during the study period by two units, equipped with a $PM_{2.5}$ high volume sampler (DA-80 DIGITEL, 30 $m^3.h^{-1}$). Samples were then pooled into week of sampling (N = 7 filters for each sample) to optimize the detection of the analytes, assuming that a 1-week rate was representative enough towards bioimpregnation results.

2.5. Statistical analysis

2.5.1. Blood and urine samples

The characteristics of the population were presented as mean ± standard deviation (sd) for quantitative variables and counts and proportions (%) for categorical variables. We provided geometric means, as the concentrations were skewed. Concentrations were log-transformed to meet the normal assumption. Variations of dilution/concentration of urine can occur and vary between individuals. These variations can influence the biomarkers concentrations. In the literature, the normalization of biomarkers by the creatinine is commonly used to tackle this parameter [19]. However, a possible residual intra- and inter-individual variability of creatinine can still be observed, independently of the urine concentration. The latter cause problems of interpretation, that could be linked to Body Mass Index (BMI), age and gender, for instance [19]. In order to take into account this effect and be in accordance with the literature, we adjusted our models with creatinine.

We used statistical t-tests to compare of concentrations between communities when conditions of homoscedasticity were observed after log-transformation, and a Wilcoxon test in other cases. Final concentrations were estimated using different models adjusted for personal physiological, social, dietary, housing characteristics and free-time activities, depending on the percentage of left-censored data (values below the LOQ). Models were performed on metals when this percentage was under 40 % (e.g. Pb, V, Cd, Ni, Sb, Co, AsT), excluding Hg (56 %), AsI (62 %) and Cr (68 %) from the analysis. We used single-pollutant linear models using substitution (LOQ/2) when censored data were under 15 % and tobit models [20] alternatively.

Models were fitted as follows: 1) confusion factors unrelated to exposure area were selected; 2) potential confusion factors were selected using a bidirectional stepwise procedure based on Akaike Criterion (AIC); 3) zone-specific confusion factors and interactions with variables of the previously selected model were introduced.

The adjusted geometric mean is then defined through Population Marginal Means [21], which consists in adjusted means to correct for unbalanced characteristics [22], using a standard population for both area (exposed and reference). Standard must be understood in the sense of a population with average values for quantitative variables and with an equirepartition in the different modalities of qualitative variables. As we performed multiple tests on environmental practices, we controlled for the False-Discory-Rate (FDR), tolerating 5 % of false positives. We computed FDRs from p-values using the Benjamini-Hochberg procedure [23]. Collinearity was assessed using the Variance Inflation Factor (VIF). We performed all statistical analyses using the R software (v. 3.2.3 or higher) [24]. Geometric means were calculated using the "*DescTools*" [25] and "*emmeans*" [26] packages, VIFs with the "*CAR*" package [27], and the correlation matrix (Pearson correlation coefficient) with "corrplot" package [28].

2.6. Atmospheric samples

Bioaccumulation concentrations in lichens were presented by quartile. The differences of levels in lichens collected in the industrial core zone (N = 5) and the reference area (N = 4) were tested using a non-

parametric Wilcoxon test. Moreover, we used weekly pooled filters (same time periods) in both areas (N = 12 in each area) for $PM_{2.5}$ samples data. Non-parametric Wilcoxon tests were performed on matched data. Differences between the three-month averages across both areas were also tested.

3. Results

3.1. Spatial and temporal variability of atmospheric concentrations

Fig. 2a, b and c map the distribution of the metals in lichens samples across the region. Apart from Hg, all metals were detected in lichens samples. Concentrations in lichens were significantly higher in the

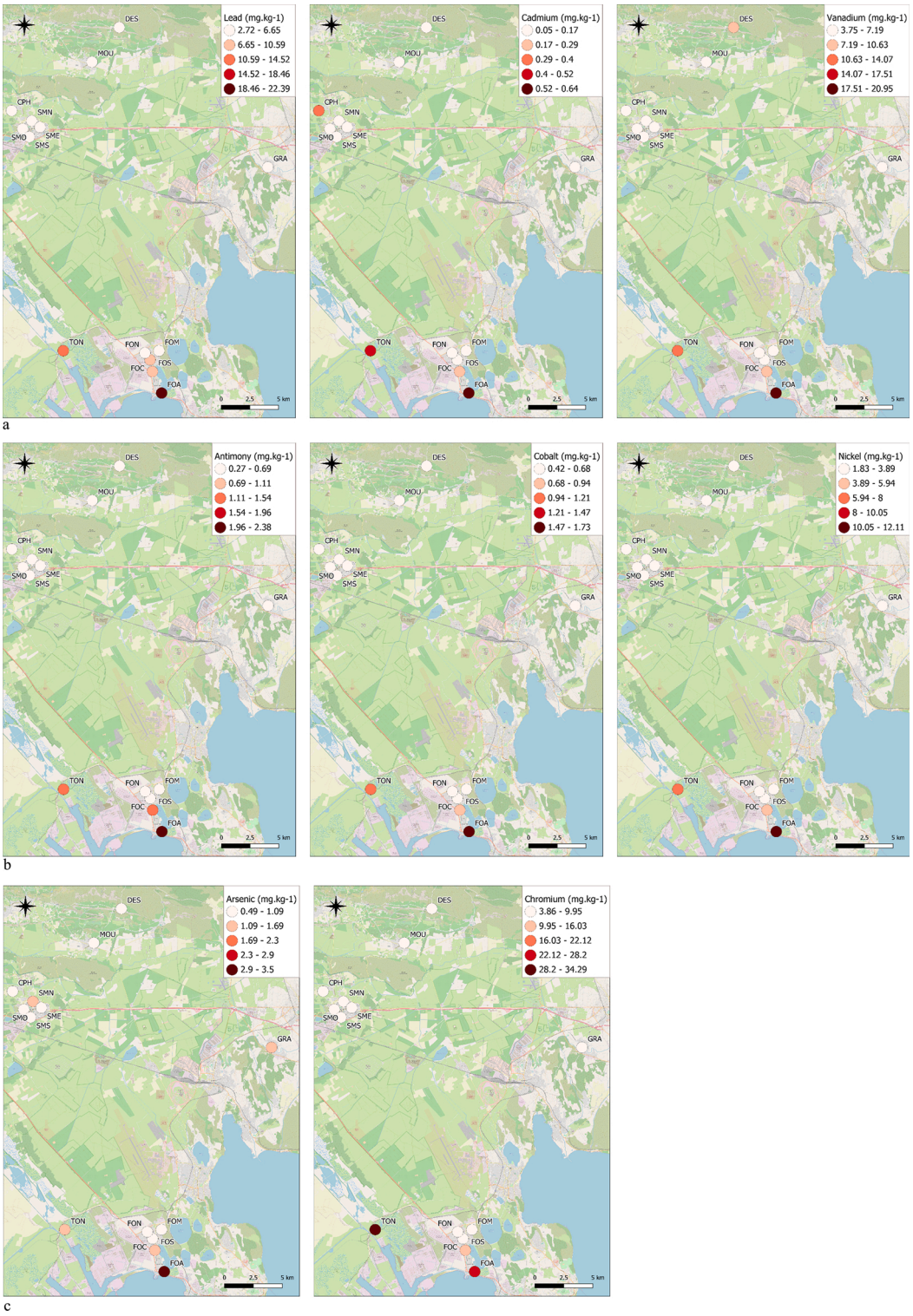

Fig. 2. a. Concentrations of trace metals in lichens across the region during the INDEX sampling campaign (mg.kg^{-1} dry weight). 2b. Concentrations of Metals in lichens across the region during the INDEX sampling campaign (mg.kg^{-1} dry weight). 2c. Concentrations of Metals in lichens across the region during the INDEX sampling campaign (mg.kg^{-1} dry weight).

exposed area compared to the reference one (Table 1) for Cd (0.23 ± 0.23 mg.kg^{-1} vs 0.06 ± 0.01 mg.kg^{-1}, respectively, p-value < 0.01), Cr (10.72 ± 7.51 mg/kg^{-1} vs 5.18 ± 1.06 mg.kg^{-1}, respectively, p-value < 0.05), Ni (5.10 ± 3.96 mg.kg^{-1} vs 2.15 ± 0.29 mg.kg^{-1}, respectively, p-value < 0.01), Co (0.84 ± 0.51 mg.kg^{-1} vs 0.5 ± 0.07 mg.kg^{-1}, respectively, p-value < 0.05) and Pb (10.39 ± 6.93 mg.kg^{-1} vs 3.82 ± 1.22 mg.kg^{-1}, respectively, p-value < 0.01) (further details on data in Tables S3 & S4). These results were statistically corroborated by airborne $PM_{2.5}$ measurements averaged over the whole period, for Cr (0.55 ± 0.27 ng.m^{-3} vs 0.11 ± 0.12 ng.m^{-3}, p-value < 0.05), Co (0.04 ± 0.03 ng.m^{-3} vs 0.03 ± 0.01 ng.m^{-3}, p-value < 0.01)and Ni (de 0.86 ± 0.70 ng.m^{-3} vs 0.47 ± 0.33 ng.m^{-3}, p-value < 0.01), exclusively. Other metals such as As (0.46 ± 0.19 ng.m^{-3} vs 0.36 ± 0.10 ng.m^{-3}, p-value ≤ 0.05) and V (2.10 ± 1.64 ng.m^{-3} vs 1.16 ± 0.85 ng.m^{-3}, p-value < 0.001) were significantly higher in $PM_{2.5}$ samples (but not in lichens) in the exposed area. Although no statistical differences were observed between both areas for Sb in lichens and $PM_{2.5}$, a spatial heterogeneity was observed in lichens from the exposed area.

3.2. Study population

The demographic characteristics of the studied populations were presented elsewhere [16]. Briefly stated, the stratified random sampling method by age, gender and area permitted to obtain a homogeneous population details across both areas. We observed no significant difference between both areas concerning gender, age, occupational categories, smoking situation and BMI. The average age of the population was 47.6 (± 9.5) years and female were a bit overrepresented (Female/Male = 1.26). In both areas, men were underrepresented in the youngest age category (30–39 yrs) because more smoked and/or had occupational exposures through professional activities in the industrial sector (two of our exclusion criteria). Finally, we did not observe significant differences regarding the frequency of vegetable and meat consumption across both areas. However, the food origin was different. Indeed, volunteers living in the exposed area consumed fewer home grown products than in the reference area, but more local fish.

Table 1
Environmental concentrations (Lichens and $PM_{2.5}$).

	Mean concentrations in lichens (mg.kg^{-1})[a]			Mean concentrations in $PM_{2.5}$ (ng.m^{-3})[b]		
	Fos	**Smc**	**p-value***	**Fos**	**Smc**	**p-value***
Trace Metals						
Pb	**10.39 ± 6.93**	**3.82 ± 1.22**	**< 0.01**	3.41 ± 1.47	3.35 ± 1.24	–
V	8.87 ± 7.07	4.56 ± 0.78	–	2.1 ± 1.64	1.16 ± 0.85	–
Cr	**10.72 ± 7.51**	**5.18 ± 1.06**	**< 0.05**	**0.55 ± 0.27**	**0.11 ± 0.12**	**< 0.05**
Co	**0.84 ± 0.51**	**0.5 ± 0.07**	**< 0.05**	**0.04 ± 0.03**	**0.03 ± 0.01**	**< 0.01**
Ni	**5.10 ± 3.96**	**2.15 ± 0.29**	**< 0.01**	**0.86 ± 0.7**	**0.47 ± 0.33**	**< 0.01**
As	1.5 ± 1.19	0.84 ± 0.38	–	0.47 ± 0.19	0.36 ± 0.1	–
Cd	**0.23 ± 0.23**	**0.06 ± 0.01**	**< 0.01**	0.1 ± 0.04	0.08 ± 0.03	–
Sb	1 ± 0.86	0.47 ± 0.18	–	0.53 ± 0.26	0.49 ± 0.2	–

*Wilcoxon test:
aFos: Fos-sur-mer (exposed area) - mean of the 5 stations (FOM, FOC, FOA, FON, FOS)
aSmc: Saint-Martin-de-Crau (reference area) - mean of the 4 stations (SMS, SME, SMO, SMN)
bFos: Fos-sur-mer (exposed area) - mean of the 12 sampling periods for the single PM station in Fos-sur-mer.
bSmc: Saint-Martin-de-Crau (reference area) - mean of the 12 sampling periods for the single PM station in Saint-Martin-de-Crau.

3.3. Blood and urine levels of metals

Table 2 shows the geometric means of metal levels in urine (in µg.g^{-1} creatinine) and blood (in µg.L^{-1}), with confidence intervals. The percentages of samples under the LOQ ranged from 2.2 % to 68.1 %. A majority of metals had a percentage of censored-data under 35 % (Pb < V < Cd < AsT < Ni < Sb < Co) and some others above 50 % (Hg < AsI < Cr). After performing an univariate analysis, none of the metals concentrations were significantly different between exposed and reference populations.

The correlations among the concentrations of the different metals are shown in Fig. S1. Weak but significant positive correlations were observed between Ni and Co (r = 0.58), Cd (r = 0.50) and AsT (r = 0.49), all other were below r = 0.45 in absolute values.

3.4. Predictors of exposures

3.4.1. Main non-zone-specific predictors

Tables S1 and S2 show the results of non-zone-specific predictors from the multivariate analyses for Pb, V, Cd, AsT, Ni, Sb and Co. The most explicative common predictors selected in the models were physiological, such as: creatinine (11–48 % of the variability), age (1–30 %), gender (2–13 %), BMI and weight variation (2–5 %), ferritin (3–13 %) and vitamin D (2–3 %) (see Table S1). The others, explaining up to 5 % of the variabilitywere found to be related to the occupation (occupational status, working place in the industrial zone), domestic exposure (wood heating, barbecue use, pesticide use, use of repellent, hunting, handiwork, age of housing), food consumption (meat, seafood, offal, eggs, vegetables, wine and mushrooms), and area of residence (proximity to road traffic, consumption of local food or home-grown vegetables) (see Tables S2).

Table 2
Blood or urine concentrations of metals by zones.

Metals				GMean[a] [range] [IC95 %]		p-value
	Matrix	N[b]	<LOQ (%)[c]	Exposed	Reference	
Lead (Pb)	Blood	129	2.2 %	16.4 [14.3–18.8]	16.0 [13.7–18.6]	0.80
Vanadium (V)	Urine	135	3.7 %	0.42 [0.36–0.48]	0.49 [0.42–0.58]	0.13
Cadmium (Cd)	Urine	135	5.9 %	0.23 [0.21–0.26]	0.23 [0.20–0.27]	0.94
Nickel (Ni)	Urine	135	17.8 %	1.50 [1.33–1.68]	1.59 [1.37–1.85]	0.52
Antimony (Sb)	Urine	135	22.2 %	0.07 [0.06–0.08]	0.07 [0.06–0.08]	0.75
Cobalt (Co)	Urine	135	32.6 %	0.21 [0.17–0.25]	0.25 [0.20–0.31]	0.21
Mercury (Hg)	Urine	126	52.9 %	0.42 [0.35–0.51]	0.39 [0.32–0.49]	0.63
Total Arsenic (AsT)	Urine	135	13.3 %	10.2 [7.96–13.1]	8.33 [6.24–11.1]	0.94
Inorganic Arsenic (AsI)	Urine	135	62.2 %	3.56 [3.03–4.20]	3.60 [2.96–4.37]	0.29
Chromium (Cr)	Urine	135	68.1 %	0.21 [0.19–0.25]	0.26 [0.21–0.32]	0.14

[a] GMean: Geometric mean, expressed in µg.L^{-1} (blood level of Pb) and in µg.g^{-1} creatinine (urinary levels of V, Cd, Ni, Sb, Co; Hg, As and Cr)
[b] N: Number of samples conformed among 138 participants
[c] <LOQ (%): percentage of samples under the Limit Of Quantification

3.5. Zone-specific predictors

Living in the exposed area was significantly associated with an increase in Pb blood levels (adjusted geometric mean, GM_a = 17.2 [15.8–18.7] vs 15.1 [13.7–16.7] $\mu g.L^{-1}$, $p < 0.05$) but not other metals (Cd, V, AsT, Sb, Ni and Co) (Table 3). In the reference area, gardening was significantly associated with an increase of blood lead level (+ 34 %, $p < 0.05$) and a decrease in Sb urinary level (−22 %, $p < 0.05$). Self-consumption of vegetables (i.e. growing and eating) was associated with higher Cd levels in the exposed area compared to the reference area (0.29 [0.25–0.34] against 0.23 [0.20–0.27] $\mu g.g^{-1}$ creatinine, $p < 0.05$).

We also observed opposite interactions between the self-consumption of poultry or eggs and the study area ($p < 0.01$) (Table 3). The self-consumers of poultry living in the reference area had significantly higher V concentration levels than self-consumers of the exposed area (GM_a = 0.48 [0.34–0.70] against 0.17 [0.10–0.31] $\mu g.g^{-1}$ creatinine). Conversely, self-consumers of eggs had higher V urinary concentrations in the exposed area (0.96 [0.60–1.53], compared to the reference area (0.54 [0.41–0.70] $\mu g.g^{-1}$ creatinine).

An interaction between the frequency of seashell consumption and the provenance, local (Gulf of Fos - Berre Lagoon) or not, was observed for Cd ($p < 0.05$) (Table 4). While no difference was observed among casual (never-monthly) consumers given the seashell origin, concentrations were significantly higher among frequent consumers (weekly-daily) of non-local seashells (0.35 [0.27–0.44] against 0.14 [0.08–0.25] $\mu g.g^{-1}$ creatinine, $p < 0.01$) compared to local seashells. Moreover, among the consumers of local seashells, the frequent consumers had significantly lower concentrations than the casual ones (0.26 [0.21–0.31] against 0.14 [0.08–0.25] $\mu g.g^{-1}$ creatinine, $p < 0.05$). Inversely, among the consumers of non-local seashells, the frequent consumers had significantly higher Cd concentrations than the casual ones (0.35 [0.27–0.44] against 0.26 [0.24–0.28], $p < 0.05$).

4. Discussion

This is the first time that these metals were measured in human samples (urine or blood) in the region. Living close to the core industrial zone was significantly associated with an increase in blood levels of lead only. We noticed a discrepancy between results from atmospheric samples / lichen samples and biological levels. These differences may have several explanations. First, internal doses of metals reflect much more than inhalation exposure to industrial pollutants. Indeed, exposure can result from many other sources, such as passive smoking, diet, occupational sources or medical devices (dental prosthesis, metallic prosthesis). It is thus more challenging to assess exposure differences based on biological samples rather than on air samples. Moreover, kinetics can strongly influence the amount of metals absorbed or eliminated, through various processes such as digestive metal transporters, accumulation (lead in bones, cadmium in kidneys) or homeostatic regulations based on metallothioneins. Secondly, current exposures to metals in general population are very low, generally between 0 and 1 $\mu g.L^{-1}$, making it tricky to identify strong determinants of exposure. Even large environmental studies including more than two thousand subjects and various variables, such as the French ENNS or Esteban studies, failed to identify the main determinants of exposure. For instance, in ENNS study, the percentage of urinary levels variability explained by the studied variables was only 2.6 % for Ni, 3 % for Cr, 4.4 % for Sb, 5.6 % for Co, 11 % for V, 12 % for inorganic As and 18 % for V [29]. Only hair Hg and blood Pb variabilities were better explained by the studied determinants, respectively 37 % and 52 %. It is thus not surprising that we were not able to identify all the determinants of exposure on a smaller sample set, neither to identify statistical differences between the two groups for some metals.

Thirdly, it is likely that sampling issues (sampling moment) and analytical issues (sensitivity of analytical methods, uncertainty) may have influenced the accuracy of biological results in the context on an

Table 3
Consumption of food, gardening and zones, adjusted geometric means for blood lead and urinary metals (cadmium, vanadium and antimony).

	Blood Lead ($\mu g.L^{-1}$)			Cadmium ($\mu g.g^{-1}$ creatinine)			Vanadium ($\mu g.g^{-1}$ creatinine)			Antimony ($\mu g.g^{-1}$ creatinine)		
	GM adjust [95 %CI]			GM adjust [95 %CI]			GM adjust [95 %CI]			GM adjust [95 %CI]		
	Exposed	**Reference**	**p**	**Exposed**	**Reference**	**p**	**Exposed**	**Reference**	**p**	**Exposed**	**Reference**	**p**
Zone	17.2 [15.8;18.7]	15.1 [13.7–16.7]	*	0.27 [0.25;0.30]	0.25 [0.23;0.28]		0.48 [0.44;0.53]	0.55 [0.50;0.62]		0.08 [0.07;0.09]	0.07 [0.07;0.08]	
Self-consumption of poultry												
No							0.52 [0.47;0.57]	0.56 [0.50;0.63]				
Yes							0.17 [0.10;0.31]	0.48 [0.34;0.70]	* *			
Self-consumption of eggs												
No							0.44 [0.40;0.49]	0.56 [0.49;0.63]				
Yes							0.96 [0.60;1.53]	0.54 [0.41;0.70]	* *			
Self-consumption of vegetables												
No				0.26 [0.23;0.29]	0.26 [0.23;0.31]							
Yes				0.29 [0.25;0.34]	0.23 [0.20;0.27]	*						
Gardening												
No	16.6 [14.4;19.1]	12.4 [10.2;15.1]								0.07 [0.06;0.08]	0.09 [0.08;0.11]	
Yes	17.5 [15.7;19.5]	16.6 [14.8;18.6]	*							0.08 [0.07;0.09]	0.07 [0.06;0.07]	*

Table 4
Consumption of seafood and origin. adjusted geometric means for urinary Cadmium.

	Urinary Cadmium (μg.g^{-1} creatinine)		
	GMadjust [95 %CI]		
Origin	**Local**	**Non local**	
Consumption of seashells			
Never-monthly	0.26 [0.21–0.31]	0.26 [0.24–0.28]	
Weekly-daily	0.14 [0.08–0.25]	0.35 [0.27–0.44]	* *

environmental study. Despite many precautions during sampling (trace-element free tubes), storage (frozen) and analysis (QC, regular blank analysis, successful participation to EQAS), reaching sufficient sensitivity and accuracy in environmental studies remains challenging.

To date, relatively few biomonitoring studies have investigated exposure to trace metals in populations residing near or in industrial zones. Mostly from Italy, the studies assessed the trace metals exposure of children/adolescent [30,31] and adults [32–39] in multiple biological matrices (blood, urine, hair and nails). Two studies compared an exposed area (to industries) with a control area. In 2007, a cross-sectional study from Belgium assessed the impact of iron and steel industry and waste incinerators on adults exposure to organochlorine and trace metals (Cd, Hg and Pb) pollutants [38] and reported no differences between the exposed and reference area. A more recent study from Korea assessed the exposure to trace metals among residents in an industrial complex as part of the national cohort study [35] in men of the exposed group (living < 5 km from the complex), compared to the reference one. The latter and the urinary levels of Cd were also more elevated among women of the exposed area. We also observed higher circulatory levels of Pb among the exposed population in the current study.

Finally, one French study assessed, in 2008–2010, the blood and urinary levels of 14 metals (including Sb, AsT, Cd, Co, Cr, Hg, Ni, Pb and V) in a large general adult population (2 000 pers, 20–59 years-old) living in a Northern metallurgical region (The IMEPOGE study) [40]. Urinary or blood concentrations were greater than our findings for AsT, Cd, Co and Ni, in the same order of magnitude for Sb, and less elevated for Pb, V and Hg.

4.1. Atmospheric exposure

We showed that several metals (Ni, Cr, Cd and Pb) were significantly more concentrated in lichens in Fos-sur-Mer, located right by a major industrial port zone, compared to Saint-Martin-de-Crau, located 25 km away. These results were corroborated in $PM_{2.5}$ measurements for Cr and Ni. Interestingly, after a strict selection of subjects and controlling for a great variety of common known physiological, dietary and habits factors, we observed that living in Fos-sur-Mer was significantly associated to greater blood levels of Pb, when compared to Saint-Martin-de-Crau.

4.2. Blood and urinary levels of metals

Broadly, we reached satisfying percentages of sample above the LOQ (e.g. Pb, V, Cd, Ni, Sb, Co, AsT), except for certain metals that we excluded from the multivariate analysis (Cr, Hg and AsI) (Table 2). Crude impregnation levels of metals (geometric means) were in the same order of magnitude compared to those reported the last decade by the national health agency Santé Publique France in their general population studies ENNS in 2011 [29] and Esteban in 2021 [41,42]. Comparison between studies has to be done cautiously taking into account various parameters (study period, sampling, analytical and data processing methods). In the first study [29], the samples had been collected between 6 and 11 years before those here and the regulations became more stringent since then, reducing the atmospheric emissions of several activities and pollutants. The recent Esteban study [41] was realized on a very comparable period (2014–2016). However, populations' age structures (18–75 against 30–65 years old) were different and we excluded smokers at the first selection step, which is a strong predictor of exposure for several metals (Pb, Cd). Moreover, methodologies differed in other different key aspects (sample design, weighting of data, treatment of missing values and censored data). Thus, further analysis would be necessary to increase comparability between our study and this national programme. The international literature documenting metals levels in human blood is also important in Europe [29,40,42,43] and worldwide [15,44]. The comparisons are even more uncertain than with national studies and is, in fact, not the purpose of the study.

Our results are nevertheless comparable with recent findings of the Esteban study [42], that reported a significant influence of seafood consumption on metal biological concentrations. Indeed, the consumption of seashells, crustacean or mollusks was associated in the study with an increase of some metals concentrations, respectively + 9 % for Hg, + 2.5 % for Cd, + 19 % for AsT, + 9.3 % for AsI, + 3.3 % for Pb. The consumption of fish was also associated with an increase of 11 % for urinary Hg and 4 % for urinary Cr. The consumption of poultry / meat / eggs was associated with a 12 % increase of Pb blood levels. However, it is worth noting that none of these studies assessed the influence of industrial emissions on internal doses of metals in general population.

4.3. Exposure area-related factors

We adjusted our models on well-known non-zone-specific factors (Tables S1 and S2), such as physiological (age, gender, BMI and weight variation, creatinine, ferritin and vitamin D), mostly related to the food consumption (seafood, meat, offal, eggs, vegetables, wine and mushrooms), and to a lesser extent to the occupation (occupational status, working place in the industrial zone), domestic exposure (wood heating, barbecue use, pesticide uses, former smokers, use of repellent, hunting, handiwork, age of housing). In the present paper, the emphasis is on the zone-related factors in order to describe and discuss the specific exposure of the inhabitants of the region.

Self-consumption of poultry and eggs - we observed that V levels were significantly higher among self-consumers of eggs in the exposed area whereas the V levels were greater among self-consumers of poultry in the reference area. The transfer of V from the poultry to the eggs had been characterized by the indirect supply of V in the alimentation of reared poultry through the supplementation with natural phosphates naturally rich in V [45]. A study showed that V was weakly transferred towards eggs compared to other trace elements [46]. A difference of speciation of V between the both zones could explain our surprising results. Indeed, the V emitted by diesel vehicles (about 80 % of the French fleet) is largely in the form of V^{IV} [47]. To our knowledge, there is no data about speciation of atmospheric V from industrial activity. But one study conducted on soils from an industrial region reported that the soils were characterized by an important contamination by the form of V^{V} [48]. The speciation of V has not been investigated regarding poultry-eggs transfer but, forms V^{IV} and V^{V} are not metabolized in the same way in blood and tissue [49], possibly leading in difference of accumulation in both eggs and poultry. The hypothesis could explain our observations but a real speciation study in the environmental matrices of the region would be more robust. Self-consumption of eggs and poultry results should be taken carefully regarding limited effective.

Gardening and self-consumption of vegetables - we found that Cd levels were significantly higher among self-consumer of vegetables in the exposed area. Cadmium is a metal that is bio accessible in soils [50] and vegetables [51]. We showed elsewhere [52] that Cd was widely available in soils and with a high bioaccumulation in lettuces in the study area. Interestingly, the concentrations in these matrices were significantly more elevated in the exposed area. Finally, the works of Austruy et al., 2021 highlighted the predominance of the foliar pathway

in bioaccumulation of many metals (including Cd) in the exposed area, testifying of atmospheric uptake. A recent local study showed a significant link between diabetics patients (over 65 years-old) and Cd atmospheric exposure, using a spatial Bayesian approach on a large number of variables within a fine territorial scale [53]. Especially given the fact that diabetes is elevated in the region, and that the local actors alerted on this topic [54].

Gardeners had circulatory levels of Pb significantly greater than non-gardener only in the reference area. Contaminations are possible through soil dust flight, tillage and by the presence of an ammunition construction and storage site that could have led to historical pollution and soil dust dispersion. The interaction between the exposed area and gardening was moderate ($p = 0.10$). Interestingly, we showed elsewhere a bioaccumulation of Pb and Cd in leafy vegetables in Fos-sur-Mer with concentrations in consumed parts more than twice as high than in other places in the North of the territory comparable to the reference area (Fig. 1) [52]. As with Cd, this work showed that the foliar pathway was predominant in the uptake of Pb by plants on the exposure area. However, bioaccessibility of Pb in the vegetables was quite weak (<40 %) whereas Cd was inversely very high (100 %) in the soils and salads and was significantly higher in the exposed area. It might be the reason why the self-consumers of vegetable had greater levels of Cd only, while gardening overexposed residents to Pb through dust ingestion. Gardening has also a protective effect on Sb accumulation in the reference area, while this activity tends to increase Sb levels (although non significantly) in the exposed area. It is possible that this protective effect is the results from difference of lifestyle of gardeners. Indeed, some exposure routes of Sb have not been studied, such as the contamination by food-grade plastics [55]. The protective effect would not be observed due to simultaneous ingestion of soils during gardening. In fact, a precedent study [52] showed that Sb levels were much higher in the exposed area compared to other places in the region. Our reference area was not investigated but there was no source of Sb around. Finally, there were few transfer in the vegetables cultivated, which may explain why the self-consumption of vegetables in the exposed area was not associated to accumulation of Sb.

Consumption of contaminated seafood of local origin - We observed both that Cd urinary levels were significantly higher among consumers of non-local seashells (i.e. out of the Gulf of Fos - Berre Lagoon) and that the frequent consumption of seashells from non-local origin increased the urinary level of Cd, compared to casual consumption. This might be due to the weak contamination of local waters by Cd [56] compared to other region of France. Indeed, the estuary of Gironde, that hosts an important part of the French seashell production is subject to historical contamination [57,58] Moreover, the national monitoring network of the chemical contamination of the littoral (ROCCH: Réseau d'Observation de la Contamination CHimique du littoral) reported that the median concentration of Cd in the mussels from de Gulf of Fos was under the national median for the 2003–2007 period [59].

4.4. Reference area

Saint-Martin-de-Crau is located North-West off the exposed area, approximately 25 km ok the industrial core zone. The city is still, although to a lesser extent, exposed to the industrial atmospheric pollutants through southeast sea breeze events [18]. However, Saint-Martin-de-Crau was selected to be at more than 15 km away from any facilities declaring in 2016 metals canalized emissions within the French National Registry of Pollutant Emissions (IREP) (Fig. 1). Moreover, the town is located, as Fos-sur-Mer, near a major road and logistic platform with an intense similar road traffic. Finally, Fos-sur-Mer is only one of the tens cities surrounding the Berre lagoon where more than 240, 000 inhabitants are living.

5. Conclusions

Our findings showed higher lichen and air levels of several metals (Cd, Cr, Co, Ni and Pb) in the exposed area. Results were more constrated regarding internal levels. Body level variations were shown due to the residency in the industrial fenceline (Pb) and via the resident practice of this particular environment itself, via local and self-produced food consumption and gardening (Cd and V). The findings were in line with previous studies conducted in the area, regarding the contamination of soils and plants, as well as atmospheric and marine environments.

CRediT authorship contribution statement

Maxime Jeanjean: Data curation, Formal analysis, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Sylvaine Goix:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – review & editing. **Julien Dron:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. **Marine Periot:** Formal analysis, Investigation, Software, Visualization. **Annabelle Austruy:** Investigation, Methodology, Resources, Writing – review & editing. **Khaled Douib:** Data curation, Resources, Software, Visualization. **Renaud Persoons:** Formal analysis, Investigation, Resources, Writing – review & editing. **Marie-Pierre Etienne:** Formal analysis, Methodology, Resources, Writing – review & editing. **Gautier Revenko:** Formal analysis, Investigation, Resources, Software. **Philippe Chamaret:** Conceptualization, Funding acquisition, Project administration, Supervision, Validation, Writing – review & editing.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jtemb.2022.127021.

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