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ORIGINAL PAPER

An Inter-disciplinary Approach to Evaluate Human Health Risks Due to Long-Term Exposure to Contaminated Groundwater Near a Chemical Complex

Marina M. S. Cabral Pinto[1] · Carlos M. Ordens[2,3] · M. Teresa Condesso de Melo[4] · Manuela Inácio[1] · Agostinho Almeida[5] · Edgar Pinto[5] · Eduardo A. Ferreira da Silva[1]

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Abstract

Potentially toxic elements (PTEs) are known to threat human health due to exposure to contaminated groundwater. Some of these PTEs can lead to long-term carcinogenic and non-carcinogenic health risks. The Estarreja Chemical Complex (ECC), NW Portugal, has had an intense industrial activity since the early 1950s, which lead to high levels of soil and groundwater contamination. Local populations traditionally rely on groundwater for human and agricultural uses. Although rehabilitation measures have been implemented for the last 20 years, groundwater contamination levels remain high for some PTEs, whose concentrations may be several orders of magnitude higher than human consumption. Two groundwater-sampling campaigns were conducted showing the temporal evolution of groundwater quality and allowing for the calculation of non-cancer and cancer risks due to exposure to PTEs by the ECC-surrounding population, considering groundwater ingestion and dermal contact as exposure pathways. Hair and urine PTE contents were collected during of the second sampling groundwater campaign and were used as biomonitoring to validate the exposure of local population to PTEs. The results show that As is the contaminant with highest non-cancer and cancer health risks for the exposed population, presenting high values particularly in Veiros, Beduído and Pardilhó localities. The most groundwater-contaminated areas coincided with the localities in which inhabitants exhibit higher hair and urinary PTE concentrations. Hair samples show high levels of As, Hg and Ni, while urine samples show high levels for Al, As, Cd, Hg, Pb, Ni and Zn are elevated in localities close to the ECC. Urine and hair proved to be suitable to evaluate short- and long-term exposure to PTEs, and are strongly correlated groundwater PTEs concentrations.

Keywords Groundwater contamination · Cancer risk · Non-cancer risk · Biomonitoring · Hair; urine · Arsenic

Introduction

Groundwater, which is an important source of drinking and irrigation water supply, is closely linked to the spread of chemical elements that have the potential to influence

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✉ Marina M. S. Cabral Pinto
mcp@uc.pt

[1] GeoBioTec, University of Aveiro, Campus de Santiago, 3810-193 Aveiro, Portugal

[2] University College London Australia, Adelaide, SA 5001, Australia

[3] Centre for Water in the Minerals Industry, Sustainable Minerals Institute, The University of Queensland, St Lucia, Brisbanef, QLD 4072, Australia

[4] CERIS, DECivil, Instituto Superior Técnico, Universidade de Lisboa, Lisbon, Portugal

[5] LAQV/REQUIMTE, Department of Chemical Sciences, Laboratory of Applied Chemistry, Faculty of Pharmacy, Porto University, 4050-313 Porto, Portugal

and impact human health. However, groundwater is still a neglected component of the hydrological cycle in what regards to water investigations and management (Re 2015). Moreover, groundwater has longer residence times than most of the other hydrological-cycle components and the impacts of aquifer degradation can remain unnoticed for decades, which can lead to an overlook of the long-term impacts of groundwater quality on human health. There are indeed many sources of potentially toxic elements (PTEs) to groundwater bodies, in turn threatening human health if this groundwater is ingested (e.g. through showering, cooking) or gets in contact with skin (e.g. through showering, irrigation or recreational activities) (Sun et al. 2010; Xie et al. 2011). Long-term shower exposure to PTE-contaminated water may pose a significant risk for the development of diseases, e.g. central nervous system neurotoxicity (Elsner and Spangler 2005). Dietary intake may be an important pathway of exposure to PTE (Ericson et al. 2008; Eggers et al. 2018), and groundwater PTE content has indirect implications on the dietary intake because PTE content of cultivated agricultural products may depends on the quality of the irrigation water (Inácio et al. 2014). Some of these PTEs can lead to long-term carcinogenic and non-carcinogenic health risks (Tartaglione et al. 2016; Yan et al. 2016; WHO 2017; Cabral Pinto et al. 2017a, b, 2018).

In many situations, single-discipline research approaches are not adequate to solve many of the current and pressing health issues that society faces (Hammond and Dubé 2012), and complex problems are not typically circumspect to disciplinary boundaries (Bellotti 2017). The effect of groundwater contamination on human health is arguably a critical and complex problem involving different disciplines such as geochemistry, hydrogeology and health sciences. Tackling such a complex problem requires an inter-disciplinary approach, which aims to integrate data and methods from different disciplines that can combine to solve a complex problem (Putzrath 2000; U.S. Environmental Protection Agency 2003; Komatina 2004; Callahan and Sexton 2007; Ryker and Small 2008). Groundwater chemical composition may cause metabolic changes, which may favour the occurrence of endemic diseases in humans. Consequently, the investigation of groundwater geochemistry is needed to understand the causes of such diseases (Panaullah et al. 2009; Yao et al. 2011).

Exposure to PTEs has been related to oncological disease and mortality (Hopenhayn-Rich et al. 1998; Villanueva et al. 2006; Karagas et al. 1998; Alavanja et al. 2004; Kavcar et al. 2009; Phan et al. 2010; Wongsasuluk et al. 2014; Rapant et al. 2017; Cabral Pinto and Ferreira da Silva 2019), breathing difficulties (Bouchard et al. 1992; Frampton 2001; Ize-Iyamu and Bernard 2007; Rahman et al. 2009; Golash and Gogate 2012; Schneider et al. 2013), cognitive problems among children (Needleman et al. 1990; Bouchard et al. 2011) and brain development damages (Liu et al. 2005). Early exposure to PTEs can interfere with developmental programming and induce subclinical alterations that may result in pathophysiology at a later life stage (Gorell et al. 1999; Centeno et al. 2002; Tchounwo et al. 2003; Zatta et al. 2003; Komatina 2004; Gupta et al. 2005; Charlet and Polya 2006; Dissanayake and Chandrajith 2009; Johnson and Atchison 2009; Exley 2012; Chin-Chan et al. 2015; Ahlskog 2016; Wu et al. 2016; Cabral Pinto et al. 2014, 2017a, 2018). Environmental and occupational exposure to Al, Cu, Fe, Hg, Mn, Pb and Zn appears to be a risk factor for Parkinson's and Alzheimer's diseases (Zatta et al. 2003; Elsner and Spangler 2005; Erikson et al. 2008; Schneider et al. 2006; Santamaria et al. 2007; Flynn and Susi 2009).

Biomonitoring is largely used to control the health risk of people exposed to contaminants (Alimonty and Mattei 2008). It evaluates the human exposure by comparison with appropriate reference values and goes by the knowledge of the relationship between environmental exposure and deriving degree of adverse health effects. Epidemiological studies often use hair, nails and urine as biological material of exposure because they are less invasive and the samples are easy to obtain in large populations. Although urine generally reflects recent exposures the chemicals (days/weeks), this is not straightforward for all elements. Metal biological half-life characterizes its elimination period from the body (Nriagu 2007). PTE of this study have the following half-lives: 10 to 12 years for Cd and Pb (inter-individual variability of about 30%); 9 months for Zn; 60 days for Hg, 30 days for Al, and 4 days for As and Ni (Ljunggren et al. 1991; Sällsten et al. 1994; Petersen et al. 2000). Hence, concentrations of different PTEs in urine may provide valuable information on exposure within different time spans, thus helping to better assess the health effects. Most PTEs are excreted via the kidney in the urine, and to a much lesser extent by the gastrointestinal tract (Dorne et al. 2011).

The use of hair for biomonitoring purposes offers the possibility to integrate a relatively long-term exposure in a single specimen analysis (WHO 2015). Studies on industrial workers and populations exposed to high levels of environmental contaminants have shown that there is a relationship between human hair contents of some metals and estimates of their exposure via ingestion, inhalation or dermal contact (Bencko 1995; Wright et al. 2006; Amaral et al. 2008; Eastman et al. 2013). Rodushkin and Axelsson (2000) suggested that human hair in trace elements analysis may provide suitable data that point towards diseases such as diabetes mellitus, coronary artery disease, and other cardiovascular diseases (Coelho et al. 2014) and many epidemiological studies use human hair (Rodushkin and Axelsson 2000, 2003; Brima et al. 2006; Gault et al. 2008; Ayodele and Bayero 2009; Sthiannopkao et al. 2010; Wu and Chen 2010; Coelho et al.

2012; Mohmand et al. 2015) as biological markers of long-exposure periods (Slotnick and Nriagu 2006).

The present study attempts to understand the relationships between environmental geochemistry and public health in the contaminated area surrounding the ECC, by analysing the evolution of groundwater quality data, calculating health risks and evaluating the metal body burden by determining hair and urine PTE content. The concentrations of PTE in the groundwater were used to evaluate the non-cancer and cancer risks for the residents that have lived long-term in the region of Estarreja. The methodology and guidelines used are those described by the USEPA (2011) for risk assessment of contaminated sites. This inter-disciplinary study was delineated with the main objectives of (i) evaluating groundwater quality in the ECC surroundings from 2006 to 2013; (ii) investigating the relationships between exposure to PTE groundwater contamination and inhabitants' cancer and non-cancer risks, including their temporal evolution; and, (iii) evaluating the effectiveness of PTE levels in hair and urine to detect relationships between environmental exposures and cancer and non-cancer risk in humans due to contaminated groundwater. To the best of our knowledge, this is the first time an inter-disciplinary approach is adopted aiming at integrating groundwater hydrochemistry and biomonitoring data to assess cancer and non-cancer risks in a contaminated aquifer. Pham et al. (2017) and Park et al. (2016) studied As concentration in urine as indication of exposure to groundwater contamination, although not in the context of cancer and non-cancer risks. Other studies correlate PTEs hair and/or urine concentration with health risks (including cancer), although not evaluating the environmental exposure to the contaminants (e.g. Kim et al. 2004; Iarmarcovai et al. 2005; McElroy et al. 2006).

Study Area

The study area is located in the surroundings of the ECC (Fig. 1a and b), which is a chemical–industrial complex located about 3 km to the north of the city of Estarreja. Surrounding populations historically rely on groundwater as a source of domestic water supply (preparing food, bathing and personal hygiene needs, washing clothes and dishes) and agricultural uses (despite the fact that the principal source of potable water supply in the region is currently surface water from the Vouga river). The ECC has been in operation since the 1930s, although its development was mainly triggered after the World War II, in the early 1950s. Nowadays the main companies within the ECC produce the following contaminants: polyvinyl chloride (CIRES); nitrobenzene, aniline, cyclohexylamine, cyclohexanol, sulphuric acid, nitric acid and sulphanilic acid (CUF), polymeric methylene diphenyl diisocyanate (DOW CHEM); pure and mixed

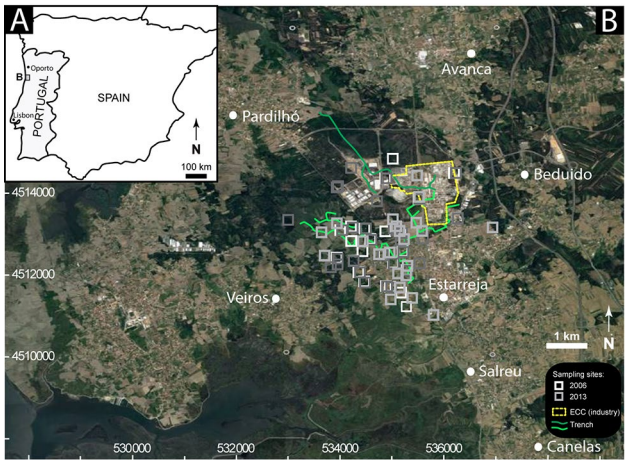

Fig. 1 Study area (*A*) including sampling locations (*B*)

gases for industrial and medical uses (Air Liquide); and, aluminium sulphates and polyaluminum chlorides in liquid form (AQP). The production of these chemicals within the ECC requires the use of a long list of potentially hazardous substances, which have left their environmental legacy in the surrounding environment. In the past, liquid effluents containing aniline, benzene compounds, NO_3, Cl, Al, As, Cd, Cr, Hg, Ni, Zn and Pb were discharged without any previous treatment into manmade permeable water channels, contaminating agricultural fields, surface water and groundwater (Inácio et al. 1998; Pereira et al. 1998; Castro et al. 1997; Leitão 1996; Borrego 1993; Barradas et al. 1992; Aristides Hall et al. 1987). Solid wastes comprised sludge containing pyrite, calcium hydroxide, Hg and As were deposited in permeable areas with no pre-treatment (Costa and Jesus-Rydin 2001). Despite the rehabilitation actions taken during the last 20 years, including the ERASE project (ERASE 2000), the footprint of the ECC industrial activity may still be identified in impacted air, soils, sediments, surface and groundwater quality around this Complex (Leitão 1996; Pereira et al. 2009; Van der Weijden and Pacheco 2006; Ordens 2007; Cachada et al. 2012; Inácio et al. 2014; Reis et al. 2015; Neves 2015; Patinha et al. 2015; Cabral Pinto et al. 2017a, b, 2018).

The Estarreja municipality has about 26,997 inhabitants (INE 2015) and is in the northern inland margin of the Aveiro lagoon (locally known as "Ria de Aveiro"), a shallow coastal lagoon of the western Portuguese coast and a protected ecosystem. The Aveiro Lagoon has unique environmental, cultural and socio-economic features facing increasing pressures and changes that put its ecological balance and heritage at risk (Lillebø et al. 2015). It is an area of large wetlands and lagoons with a low altitude and a flat topography. It has high environmental and economic importance, and intense touristic, agricultural, fishing and

industrial activities. It provides wintering areas for aquatic birds and has been classified as Special Protection Area under the Council Directive 2009/147/EC on the conservation of wild birds. Recently, Brower et al. (2018) have conducted a groundwater protection evaluation study in the Aveiro Lagoon area, which highlights the economic importance of the region's groundwater resources according to its quality.

Hydrogeological Characterization

The study area is part of the Aveiro Quaternary aquifer (AQA) (INAG 2011), and the shallow multilayer aquifer system has been described in detail by Ordens (2007) and Neves (2015). It is over 650 km^2 and is an integral part of the Lower Vouga sedimentary basin. The AQA consists of unconsolidated deposits of sand and gravel, with interlayered mud and fine silt lenses, deposited by fluvial and eolian processes. It is composed of two aquifer layers separated by a low permeability aquitard, which may locally confine or semi-confine the lower part of the aquifer system.

The AQA's natural baseline composition (Condesso de Melo and Marques da Silva 2008) is determined by the infiltration of rainwater of Atlantic origin, the reaction with aquifer matrix minerals and active redox processes. Human-related contamination (mainly nitrates, heavy metals and organic compounds) can be detected all over the extent of the shallow unconfined aquifer, where aerobic conditions prevail. The deeper semi-confined aquifer layer presents reducing conditions, which attenuate the high nitrate concentrations but can increase As, Fe and Mn concentrations. The study area is highly vulnerable to groundwater contamination due to the high permeability of the sediments, the reduced thickness of the unsaturated zone, the flat topography and high rates of groundwater recharge (> 300–400 mm/year). The groundwater flow is in general from east to west, crossing the ECC-related contamination sources before reaching the agricultural fields and streams/trenches to the west of the ECC (Fig. 1).

Methodologies

Groundwater Sampling

The two groundwater-sampling campaigns included in this study to characterize the temporal and spatial variability of the groundwater quality are part of large research projects aiming at characterizing the hydrogeochemistry of the study area, and consequently inferring aquifer contamination and attenuation processes in the surroundings of ECC. The campaigns were carried out in May 2006 and May 2013, and a total of 29 and 22 groundwater samples (Fig. 1b), respectively, were collected. The groundwater samples have been collected along the day at different times and the equipment does the automatic compensation for the different temperatures measured. The sampling procedure included measurements of physico-chemical field parameters (temperature, pH, electrical conductivity (EC), redox potential (Eh) and dissolved oxygen (DO) concentration) in a flow cell using HANNA instruments. Stabilization of physico-chemical parameters means that these parameters do not change over time. In practical terms, it means that all the water contained in the borehole has been flushed out, and water from the aquifer is flowing and the groundwater sample is representative of the aquifer formation. After the stabilization of the field parameters, a 100-mL volume water sample was titrated for on-field alkalinity analysis with a HACH alkalinity kit and two other water samples were collected and filtered through a 0.45 µm membrane for major, minor and trace elements by ICP-MS and ion chromatography at the Activation Laboratories (Ontario, Canada) which are ISO 17025 accredited and certified to ISO 9001: 2008. Analytical blanks and potential instrumental drifts were carefully monitored and instrument standardization and reproducibility were performed with certified standard reference materials from the National Institute of Standards and Technology (NIST 1643 and SLRS-5 for ICP). QA/QC results within an error of less than 2% indicated that the analytical instruments were operating within pre-defined specifications. The sampling and analyses methodologies were identical for both campaigns, and the same Laboratory was used.

The sampling design was based on a geophysical campaign conducted to map the spatial distribution of the groundwater contamination plume (Ordens et al. 2007). Local residents/farmers and ERASE administrators were engaged for a preliminary assessment of types and levels of contamination throughout the area, and for identifying sampling points. This engagement process was critical for local knowledge-gaining on the hydrogeology and contamination history, and securing access to sampling wells, which is a process strongly advocated under the concept of socio-hydrogeology (Re 2015; Re et al. 2017). The groundwater-sampling points included ERASE monitoring wells, irrigation wells and domestic-use wells.

Hair and Urine Sampling and Analysis

Human biomonitoring, defined as "the method for assessing human exposure to chemicals or their effects by measuring these chemicals, their metabolites or reaction products in human specimens", involves the measurement of biomarkers in different body fluids (e.g. blood, urine, breast milk) or tissues (e.g. hair, nails) (WHO 2015). The biomonitoring programme was conducted from January to September 2013 in 75 (hair) and in 103 (urine) permanent residents

(> 55 years old) living in or around the city of Estarreja. Participants were recruited to participate through Private Institutions of Social Solidarity. This included collecting samples in different localities of the Estarreja municipality: Avanca, Beduído, Canelas, Estarreja, Pardilhó, Veiros, and Salreu. The intention was to sample potentially exposed population groups with different degrees of vulnerability to contaminants. The participants were clearly informed about the aims of the study and those who have agreed to participate gave their written consent. Ethical approval for this study was obtained from the National Committee for Data Protection (No. 11726/2017).

Hair

Hair samples (ranging from 100 to 300 mg) were collected near the scalp, according to the international recommendations (Mayo Clinic Laboratories 2018). Only hair samples with their natural colour and from individuals residing permanently in the study area were considered for analysis. Following a procedure reported elsewhere (Bass et al. 2001), hair were duly washed to completely remove exogenous contamination without significantly altering endogenous trace elements content in the sample. After washing, samples were dried in a laboratory drying oven (Raypa, Barcelona, Spain) at 95 °C for 40 h (the time required to achieve a constant weight). Dried samples (~ 0.1 mg) were mineralized through a microwave-assisted acid digestion procedure with 1 ml of concentrated HNO_3 (> 65% m/m; TraceSELECT®, Honeywell, Fluka, Seelze, Germany) and 0.5 ml of H_2O_2 (≥ 30% v/v; TraceSELECT®, Fluka, Buchs, Switzerland) in a Milestone, mls 120 mega, Sorisole, Italy, high-performance microwave digestion unit equipped with an HPR 1000/10 rotor. The following microwave oven programme (W/min) was used: 250/1, 0/2, 250/5, 400/5 and 600/5. After cooling, sample solutions were made up to 8.5 mL with ultrapure water and stored in closed propylene tubes at 4 °C until analysis. Ultrapure water (at 25 °C the resistivity value is 18.2 MΩ cm) produced in aarium® pro (Sartorius, Gottingen, Germany) water purification system was used throughout the work. All the lab ware was duly decontaminated by 24 h immersion in a 10% HNO_3 bath and thoroughly rinsing with ultrapure water. A sample blank was prepared in each digestion run (10 samples). Average blank levels were subtracted from the samples values. For analytical quality control, the certified reference material (CRM) ERM-DB001 (Joint Research Centre, Institute for Reference Materials and Measurements (IRMM), Geel, Belgium)—human hair was used, acid digested using the same procedure.

Trace elements' concentrations were determined through Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) using a Thermo Fisher Scientific (Waltham, MA) iCAP™ Q instrument, equipped with standard components and accessories: a MicroMist™ nebulizer (Glass Expansion, Port Melbourne, Australia), a Peltier-cooled baffled cyclonic spray chamber, a standard quartz torch and a two-cone interface design (nickel sample and skimmer cones). High-purity argon (99.9997%; Gasin, Leça da Palmeira, Portugal) was used as the nebulizer and plasma gas. Before each analytical series, the ICP-MS instrument was tuned for maximum sensitivity and signal stability while keeping the formation of oxides and double-charged ions to a minimum. Commercially available multi-element standard solutions (*Plasma*CAL, SCP Science, Baie D'Urfé, Canada) were used to prepare calibration standards. Internal standard solution was prepared from Isostandards Material (Madrid, Spain).

The limits of detection were calculated as the concentration corresponding to three times the standard deviation of 10 replicate measurements of the blank solution (2% v/v HNO_3).

Urine

Urine samples were collected in polyethylene containers and stored at − 20 °C until analysis. All reagents used were of trace analysis grade or equivalent. All aqueous solutions were prepared using ultrapure water. Urine samples were defrosted 24 h before the analysis and 10-fold diluted with 1% v/v HNO_3 for elemental analysis of 7 PTEs (Al, As, Cd, Ni, Hg, Pb, and Zn) using a Thermo (Waltham, MA) X-series inductively coupled plasma-mass spectrometry (ICP-MS) instrument. Samples with concentrations above 200 µg L^{-1} were reanalysed after further 10x dilution. Samples with extremely high concentrations were also analysed by inductively coupled plasma-mass spectrometry-optical emission spectrometry (ICP-OES) using a Horiba JobinYvon Activa M instrument although the results were not significantly different. Freeze-dried human urine Seronorm™ Trace Elements were used in experimental studies on the validation of the analytical procedure used for PTE quantification in urine samples. This material was also analysed during each analytical run as a quality control (QC) sample. Results were well within the acceptable range for all metals. Urinary data are usually adjusted to a constant creatinine concentration to correct for factors unrelated to exposure, particularly the variable dilutions among spot samples (Barr et al. 2004). Hence, the results of urine samples (µg L^{-1}) were adjusted to creatinine (g L^{-1}) and reported as µg g^{-1}. The creatinine was analysed in AvLab commercial laboratory, in the city of Aveiro, Portugal and the analysis of metal(loid)s were performed in Central Laboratory of Analysis of University of Aveiro, Portugal.

Risk Assessment Model

The non-carcinogenic and carcinogenic risks for residents of the ECC surroundings were estimated according the United States Environmental Protection Agency methodology (USEPA 2001, 2011). The equations used to determine the exposure to toxic elements via ingestion and dermal contact are as follows:

$$\mathrm{CDI}_{\mathrm{oral}} = \frac{\mathrm{C} \times \mathrm{IR\_oral} \times \mathrm{EF} \times \mathrm{ED}}{\mathrm{BW} \times \mathrm{AT}}$$

$$\mathrm{CDI}_{\mathrm{dermal}} = \frac{\mathrm{C} \times \mathrm{EV\_shower} \times \mathrm{EF} \times \mathrm{ED} \times \mathrm{SA} \times \mathrm{AF} \times \mathrm{ABS} \times \mathrm{CF}}{\mathrm{BW} \times \mathrm{AT}},$$

where *CDI* denotes the chronic daily intake (mg.kg^{-1} day^{-1}); *C* denotes the concentration of chemical in groundwater (mg L^{-1}); *IR* denotes the ingestion rate of groundwater (L.day^{-1})—in the studied region, most households have public water supply by ADRA (2019), and the water quality is according to the Portuguese legislation (Portuguese Decree-Law 152/2017), as such groundwater is not usually used for drinking as the population is aware of potential risks due to contamination, but it is still used in many households for cooking, and for this reason, it was considered a lower daily ingestion rate of 0.15 L day^{-1}; EF: Exposure Frequency (250 days year^{-1}); *ED*: exposure duration, and it was assumed that a resident will spend half of his/her life exposed, so it was assumed 35 years; *BW*: body weight (70 kg); *AT*: averaging time (35 years × 250 days); *SA*: skin surface area available for contact (19652 cm^2); *EV*: the exposure time (0.2 h/day), *AF*: skin adherence factor (0.07 mg. cm^{-2}); *ABS*: dermal absorption factor (0.03 for As and 0.001 for other metals); *CF*; conversion factor (10^{-6} kg mg^{-1}).

The human health risk caused by exposure to PTEs is expressed as hazard quotient (HQ) = ADD/RfD. The ADD is the average daily dose to which a person is exposed. RfD is the reference dose which is the daily dosage that enables the exposed individual to sustain this level (USDE 2013). The HI is the chronic hazard index that is the sum of HQs for multiple exposure pathways. When HI values > 1, there is a chance that non-carcinogenic risk may occur; otherwise, HI < I the opposite applies. The carcinogenic risks were calculated for As exposure of ECC surrounding population, according to the Exposure Factors Handbook (USEPA 2011) and using the oral slope factor of 1.5. For carcinogens in drinking water, the USEPA considers risk levels of up to 10^{-6} to be protective limit of human health (USEPA 2010). The USEPA accepts cancer risk policies from states in the range of 10^{-6} to 10^{-4} (USEPA 1992). USEPA has not derived a reference dose for Al; therefore, the human health risk assessment was not performed for this metal.

Statistical Techniques

The Kruskal–Wallis test was used to compare the values of Al, As, Cd, Hg, Ni, Pb and Zn between the different sampling campaigns [2006, 2010 (Neves 2015) and 2013] in which measurements were made due to the large deviations to normality observed in the distribution of the measurements at each of the moments of analysis, as evidenced by the test of Shapiro–Wilk. Whenever statistically significant differences were found between the three moments, post hoc tests were applied to identify pairs that differed from each other. These comparisons were made using the Mann–Whitney test and subsequent application of the Bonferroni correction and are presented in the Supplementary file (Table S1).

The Kruskal–Wallis test was also used to compare the values of PTEs in hair and in urine between the residents of the different localities in which measurements were made due to the large deviations to normality observed in the distribution of the measurements at each of the moments of analysis, as evidenced by the test of Shapiro–Wilk. Whenever statistically significant differences were found between the seven localities, post hoc tests were applied to identify pairs that differed from each other. These comparisons were made using the Mann–Whitney test and subsequent application of the Bonferroni correction and are presented in the Supplementary file (Tables S2 and S3). The software used was SPSS, version 25.

Results and Discussion

Groundwater PTE Concentrations

Table 1 (i) summarizes groundwater quality results for the samples collected in 2006 and 2013, and for the samples collected by Neves (2015) in 2010; (ii) shows the AQA's natural baseline APA (2012); and, (iii) shows drinking water values form WHO guidelines (2011), USEPA (2009) and Portuguese legislation values (PV) (Portuguese Decree-Law 152/2017), which are only available for selected elements. WHO (2011) and EPA (2009) do not provide guideline values for Al and Zn. Nonetheless, the Portuguese legislation presents 200 µg L^{-1} for Al for reference.

PTE concentrations are well above the standards for human consumption provided by WHO (2011), USEPA (2009) and PV (2017), except for Pb (Table 1), for all sampling campaigns. These concentrations are well above natural background values for the aquifer (Table 1, NB), and have been shown to be associated with contaminant activities from ECC (Ordens 2007). Means and maximum values were often one–two orders of magnitude higher than the guidelines values, namely for Al, As, Cd, Hg and Zn. However, median values are significantly lower than mean levels,

Table 1 PTE concentrations (μg L^{-1}) from groundwater samples from ECC surroundings in 2006 and 2013

	Data from 2006 (n = 29)						Data from 2010 (n = 35) (see Neves 2015)						Data from 2013 (n = 19)						Guidelines			
	Mean	Median	Sd	Min	Max	% > WHO	Mean	Median	Sd	Min	Max	% > WHO	Mean	Median	Sd	Min	Max	% > WHO	NB (2011)	WHO (2011)	EPA (2009)	PV (2017)
Al	**3385**	**365**	7272	25	**34900**	48	**810**	**233**	1203	57	**4600**	66	**363**	41	1010	22	62*	26	NP	NP	NP	200
As	**759**	1.2	2244	0.0015	**9730**	35	**169**	1	481	0.15	**2550**	24	**479**	7.9	1450	0.1	35	37	1	10	10	10
Cd	**20.2**	0.4	90.6	0.02	**524**	21	2	0.3	3.7	0.01	**14.8**	15	0.5	0.3	0.5	0.03	21	0	0.5	3	5	5
Hg	**23.6**	0.1	125	0.1	**659**	4	**60**	0.9	79.9	0.1	**473**	3	1.2	0.05	5.1	0.005	4	0	0.2	6	2	1
Ni	**66.1**	13.7	114	0.4	**497**	31	**62.2**	8.9	137	0.8	**606**	18	3.9	2.7	4	0.4	31	0	4.9	70	NP	20
Pb	4.3	0.9	12	0.05	**59.9**	10	1.1	0.9	0.9	0.1	3.9	0	0.9	0.6	1	0.1	10	0	3	10	15	25
Zn	3176	360	8887	2	47100	52*	1099	145	2775	23	15100	36	266	106.4	324	10.1	1078	16*	86	NP	NP	NP

PTE concentrations (μg L^{-1}) from groundwater samples from ECC surroundings in 2010 collected by Neves (2015) are also presented for comparison. NB refers to AQA's natural baseline (INAG 2011). WHO, USEPA and PV refer to guideline values (μg L^{-1}) for drinking water from WHO (2011), EPA (2009) and Portuguese Legislation (Portuguese Decree 2017), respectively

Sd standard deviation, *Min* minimum, *Max* maximum, *DL* detection limit, *NP* not provided. % > WHO—percentage of values above WHO guidelines; * U.S. Environmental Protection Agency (USEPA). Risk Assessment Guidance for Superfund, Volume I: Human Health Evaluation Manual; EPA 540-1-89-002; U.S. Environmental Protection Agency: Washington, DC, USA, 1989. EPA (2009)http://esdat.net/Environmental%20Standards/US/Federal/US%20Federal%20MLCs.pdf * % > PV; **Proposed by WHO*** Portuguese Legislation (Portuguese Decree 1998)

The numbers that are marked in bold indicate that they are values higher than P95 presented by WHO guidelines

in most cases falling below human consumption standards. It is worth noting that the large difference between mean and median values found for some PTEs is due to a significant number of samples collected in low- or non-contaminated areas, which skews the median for lower values. According to Table 1, the percentage of samples above WHO (2011) guideline values is high: Al (48), As (35), Cd (21), Ni (31), Pb (10) and Zn (52) in 2006; Al (66), As (24), Cd (15), Ni (18) and Zn (36) in 2010; and, Al (26), As (37) and Zn (16) in 2013. Figure 2 shows the samples with PTE concentrations above WHO (2011) guideline values. All percentages are below 50%, with the exception of Zn and Al in 2006 and 2010, respectively. Highly variable contamination levels are due to complex hydrogeochemical processes occurring in the area, location/type of contaminant discharge to the environment, and the temporal evolution of contaminant activities (and attenuation processes).

Results show a decrease in contamination from 2006 to 2013, for some elements of up to one order of magnitude. This is particularly evident looking at the percentage of samples above WHO (2011) guideline values (Table 1), which, however, remain high for Al, As and Zn in 2013. Only the chemical elements Cd, Pb and Zn do not show significant differences (Kruskal–Wallis $p \geq 0.05$) between the sampling campaigns (supplementary Table S1); all the other studied PTEs show significant differences (Kruskal–Wallis $p < 0.05$) between campaigns, particularly between the first and the last one (Table S1). This seems to indicate that groundwater contamination in the study area is decreasing, which is most probably related to minimization measures that occurred in the mid-2000s (ERASE 2000). A seven-year interval gives an indication of the changing contamination conditions in the local aquifer. Further studies and new sampling campaigns in the area are urgently needed to assess whether the contamination levels are decreasing to more acceptable levels, and what are the current risks for humans and for the environment in the ECC surroundings. These studies will also assist in identifying possible PTE sources, transport processes controlling the contamination spatial–temporal evolution in the aquifer and fates of elements of concern, as all these factors impact human exposure risk. Nonetheless, this is important to assess contamination conditions that have a potential impact for human health.

Hair PTE Concentrations

The use of hair for biomonitoring purposes offers the possibility to integrate a relatively long-term exposure in a single specimen analysis, reflecting exposures occurring in the last months (WHO 2015). Hair PTE concentrations (μg g^{-1}) in Estarreja inhabitants according to their residence are shown in Table 2. Reference concentrations (median and minimum and maximum) available from the study of Rodushkin and

Fig. 2 Sample locations with PTE concentrations above WHO (2011) guideline values

Table 2 Hair PTE concentrations (μg g^{-1}) in Estarreja inhabitants according to their residence ($n = 75$)

Localities	Statistics	Al	As	Cd	Hg	Ni	Pb	Zn
Avanca ($n = 10$)	Median	5.0	0.04	0.01	0.77	0.10	0.40	165
	Range	0.5–14	0.03–0.13	0.001–0.11	0.69–0.90	0.03–1.0	0.04–2.0	131–**206**
Beduido ($n = 10$)	Median	2.93	0.1	0.002	**1.84**	0.09	0.23	180
	Range	1.1–12	0.05–**3.2**	0.0005–0.03	1.6–**2.5**	0.04–**8.7**	0.06–0.73	75–**301**
Canelas ($n = 10$)	Median	2.3	0.05	0.001	0.23	0.03	0.10	80
	Range	0.1–8.7	0.009–0.2	0.0001–0.002	0.002–0.7	0.004–0.1	0.004–0.5	4–**222**
Estarreja ($n = 15$)	Median	3.53	0.08	0.004	**1.57**	0.05	0.42	163
	Range	0.7–12	0.03–0.23	0.001–0.11	1.4–**3.7**	0.03–0.3	0.05–4.3	103–**282**
Pardilho ($n = 10$)	Median	3.3	0.06	0.004	**1.35**	0.04	0.27	143
	Range	1.1–22	0.04–**0.4**	0.001–0.008	1.3–**3.1**	0.03–0.1	0.1–3.7	63–**202**
Salreu ($n = 10$)	Median	2.6	0.06	0.002	1.2	0.063	0.23	173
	Range	0.9–4.1	0.045–0.1	0.001–0.003	0.9–**2.6**	0.06–0.08	0.11–0.42	151–**196**
Veiros ($n = 10$)	Median	4.48	0.08	0.003	**2.09**	0.09	0.36	153
	Range	0.8–24.0	0.03–**9.6**	0.001–0.03	1.9–**5.4**	0.02–0.2	0.08–2.4	52–**320**
Rodushkin and Axelsson (2000)	Median	6.4	0.0067	0.034	0.249	0.29	0.66	144
	Range	2.7–25.6	0.034–0.3	0.010–0.356	0.053–0.927	0.11–1.60	0.22–7.26	68–198

Reference concentrations (median and minimum and maximum) for non-exposed people shown in the table are available from the study of Rodushkin and Axelsson (2000)

Values in bold indicate those higher than the maximum value presented by non-exposed people

Axelsson (2000) for non-exposed people are also shown in Table 2. Figure 3 shows the ratio of PTE hair content in subjects to reference values, per locality and for median values.

In general, hair trace elements' median contents in this study with an environmentally exposed population fall within the range of values reported for non-exposed people,

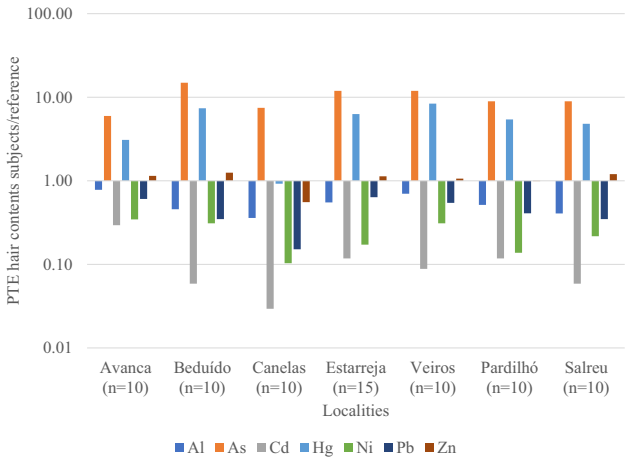

Fig. 3 Ratio of hair potentially toxic elements (PTE) concentrations of Estarreja inhabitants (according to their residence) and hair PTE reference concentrations (median) for non-exposed people from Rodushkin and Axelsson (2000)

except for Hg (Table 2). Pardilhó, Beduído and Veiros' inhabitants show higher levels of Hg in hair (3–6 times higher than that of non-exposed people) than inhabitants from Canelas and Salreu ($p < 0.05$, Table S2). These three localities are closer to ECC and more exposed to contaminated groundwater than Canelas and Salreu. Maximum values of As from inhabitants of Beduído and Veiros were above the maximum values found for non-exposed populations (Table 2). When observing median values, As hair contents are around 10 times higher than that for non-exposed people across the board (Fig. 3). Maximum Zn levels were also above the maximum contents found for non-exposed populations across the board (Table 2). The PTE body burden of the study group suggests a potential environmental exposure related to the ECC (Table 2 and Fig. 3).

Urine PTE Concentrations

Concentrations of different PTE in urine may provide valuable information on exposure within different time spans, thus helping to better assess potential health effects of contamination (Cabral Pinto et al. 2017a). Most PTE are excreted via the kidney in the urine, and to a much lesser extent by the gastrointestinal tract (Dorne et al. 2011). Summary statistics (median (50th percentile) and the 5th to 95th percentiles (P_5–P_{95}) values for PTE content in urine samples of residents in the different localities within Estarreja region are shown in Table 3. Table 3 also presents the same statistical values for healthy people available from a comprehensive study of Goullé et al. (2005). Wide ranges in urine element concentrations can be found in the literature (e.g. Goullé et al. 2005; Kazi et al. 2008; Kuiper et al. 2014), and as such, we found appropriate to compare the range and not only median values. Participants' PTE urinary levels largely exceed those reported in the literature for healthy people for all the studied elements, with Al, Cd and Zn being the elements that show urinary median levels out of P_5–P_{95} reference values from the study of Goullé et al. (2005). Remarkably, P95 PTE concentrations are around ten times higher than median concentrations, except for Al that is hundred times higher. This

Table 3 Urinary PTE concentrations (μg g^{-1}) in Estarreja region inhabitants ($n = 103$)

Localities	Percentiles	Al	As	Cd	Hg	Ni	Pb	Zn
Avanca ($n = 25$)	P50 (Median)	**18**	36	**9**	**3.9**	2.3	**7.8**	**534**
	P5–P95	9.1–**317**	5.0–157	0.4–**34**	0.3–**5.5**	1.2–**9.9**	0.4–**4.6**	279–**1092**
Beduído ($n = 17$)	P50 (Median)	**50**	114	**6.7**	**2.9**	**50**	**5.5**	**880**
	P5–P95	14.3–**34688**	5.9–**735**	0.6–**51**	0.7–**14**	2.6–**143**	1.9–**79**	183–**6171**
Canelas ($n = 12$)	P50 (Median)	**11**	4	**5**	0.8	1.1	1.5	**607**
	P5–P95	4.3–**48**	1.7–80	0.3–**9**	0.4–1.7	0.9–1.7	0.9–2.1	189–**964**
Estarreja ($n = 17$)	P50 (Median)	**27**	81	**1.9**	0.9	2.8	**2.5**	**591**
	P5–P95	5.8–**66**	13–**215**	0.5–**21**	0.2–2.4	1.0–**7.0**	0.7–15	208–**9206**
Pardilhó ($n = 15$)	P50 (Median)	**47**	67	**2.1**	**8.9**	2.5	1.9	**2124**
	P5–P95	4.6–**83996**	2.5–**305**	0.4–**18**	0.5–**5.4**	1.2–**6.6**	0.6–6.5	504–**7215**
Salreu ($n = 13$)	P50 (Median)	**18**	5.9	0.8	0.9	3.3	1.5	**593**
	P5–P95	3.2–**43**	1.4–48	0.4–**1**	0.6–1.0	0.9–**9.3**	0.5–3.3	218–**871**
Veiros ($n = 4$)	P50 (Median)	**17**	**294**	**2.5**	2	**4.2**	2.1	**739**
	P5–P95	7.6–**32296**	5.9–**369**	0.3–**66**	0.7–**2.3**	1.7–**4.9**	0.7–3.5	160–**1880**
Goullé et al. (2005)	P50 (Median)	2	19	0.2	0.6	1.8	0.6	195
	P5–P95	0.16–11.2	2.3–161	0.06–0.79	0.14–2.21	0.59–4.06	0.01–2.14	44–499

Reference concentrations (median and P_5–P_{95}) for healthy people shown in the table are available from Goullé et al. (2005)

Values marked in bold indicate those higher than P95 presented by healthy people

is an indication that there is a large range of PTE urinary concentrations in people exposed to contamination, and the sampling campaign covered exposed and non-exposed subjects (and locations). Interestingly, P5 values for the studied population are generally similar or slightly above those of healthy people from Goullé et al. (2005), while P95 are 2–53 times above for most elements and 3300 for Al, which is also an indication of the wide variety of PTE urinary concentrations in the sampled subjects.

Figure 4 shows the ratio of PTE urinary content in subjects to reference value per locality, using medians. When analysing PTE urinary concentrations per locality within the Estarreja region (Table 3 and Fig. 4), a large discrepancy can be observed, in which medians and P_5–P_{95} PTE urinary concentrations from the study subjects and the values of Goullé et al. (2005) for healthy people are shown. Beduído and Veiros inhabitants have very high urinary contents for all PTEs. This is not surprising, as reported before, they are the ones closer to ECC and more exposed to contaminated groundwater due to the groundwater flow direction (Ordens 2007). Pardilhó, Estarreja and Avanca subjects also show high levels of contamination. Canelas inhabitants show much lower levels of PTEs, particularly As and Hg ($p < 0.05$), in urine than other subjects for most of chemical elements, and are more similar to those reported by Goullé et al. (2005) for healthy people, which indicate that those inhabitants are exposed to much lower contamination levels. In fact, these localities are not directly affected by the contamination from ECC. The exceptions are Cd in Canelas, and Al in Salreu and Canelas inhabitants, suggesting that the PTEs' enrichment in the urine could not be only affected by groundwater, but could also result from other sources (e.g. air, soils, road dust and diet). Interestingly, these concentrations are very high across almost all localities. Canelas and Salreu inhabitants show As levels below reference values,

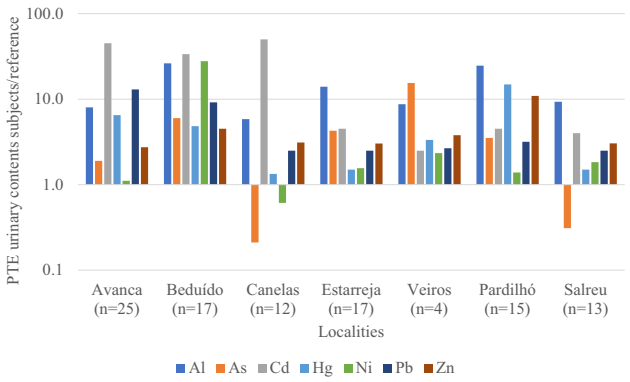

Fig. 4 Ratio of urinary potentially toxic elements (PTE) concentrations of Estarreja inhabitants (according to their residence) to urinary PTE reference concentrations (median) for healthy people from Goullét et al. (2005)

which is a PTE of major concern in the area and with special high concentrations in Beduído inhabitants.

Risk Assessment—Cancer and Non-cancer Risks

The results of the non-carcinogenic and carcinogenic health risks due to PTE exposure in groundwater collected in domestic-use wells in the Estarreja area are provided in Figs. 5 and 6.

Non-cancer Risk

Non-cancer risk is associated with long-term health problems (e.g. neurological or cardiovascular diseases). HI values are always lower than 1 for Ni and Pb, implying non-cancer low risk. Figure 5 shows the spatial and temporal evolutions of HI for Al, As, Cd and Hg. In 2006, these four PTEs are higher than 1 in some collected points, implying non-cancer high risk. In 2010 and 2013, Al and Cd concentrations do not imply risk. It can be noted that the non-cancer risk values for all PTEs decreased temporally and spatially, decreasing as the distance of the ECC increases. However, As and Hg maintained a high (> 1) risk in 2013. Therefore, the non-carcinogenic health risks via dermal and oral routes of groundwater from domestic-use wells were not within USEPA's acceptable risks.

Cancer Risk

Figure 6 shows the spatial and temporal evolutions of cancer risk for As. It can be noted that the cancer risk values decreased temporally and spatially, tending to decrease as the distance of the chemical complex increases. However, the risk associated with exposure to groundwater falls out of the threshold values above which environmental and regulatory agencies consider the risk unacceptable, in all sampling campaigns.

Integrative Discussion of PTE Content in Groundwater, Hair, Urine and Cancer and Non-cancer Risks

PTE contents in hair and urine show a clear enrichment in As, Hg and Zn, particularly in the localities where the groundwater quality was directly affected by the ECC (Tables 1, 2, and 3). Considering that As, Hg, and Zn contents in hair and urine have been suggested as being effective biomarkers of environmental exposure (e.g. Bencko 1995; Mortada et al. 2002; Morton et al. 2004; Amaral et al. 2008; Gault et al. 2008; Cabral Pinto et al. 2017a), these high PTE contents observed in Veiros, Beduído, Avanca, Estarreja and Pardilhó residents' hair indicate environmental exposure. Arsenic was the element showing

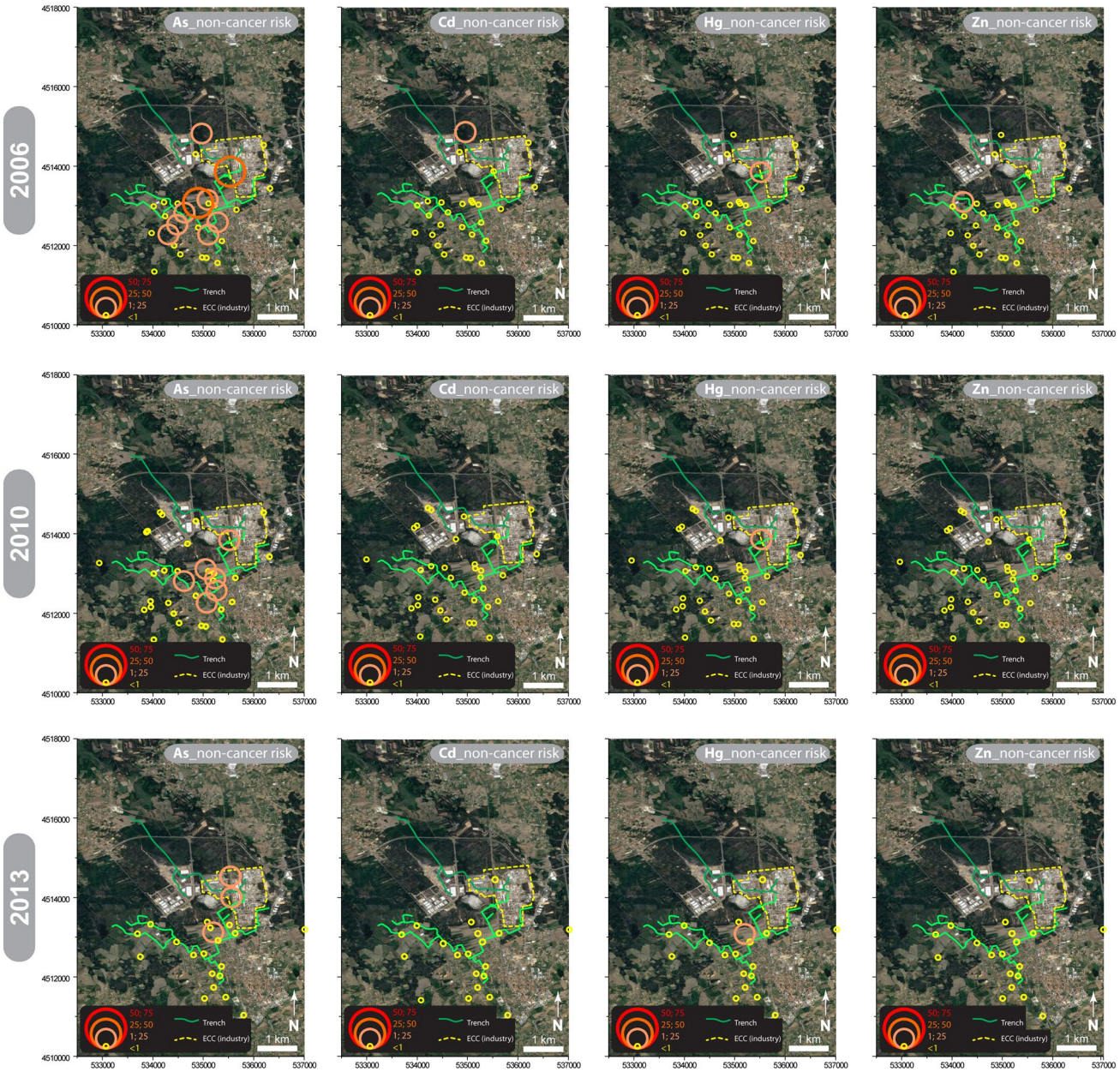

Fig. 5 Hazard index (HI) spatial and temporal evolutions for As, Cd, Hg and Zn

higher non-cancer risk and high cancer risk in the region in all sampling campaigns (Figs. 5 and 6), which is compatible with high groundwater contamination levels, and hair and urine concentrations (above non-exposed and healthy populations) (Tables 1, 2, and 3). Mercury also shows high non-cancer risk in all sampling campaigns, which is in agreement with high groundwater contamination levels, and hair and urine high contents (Tables 1, 2, and 3). WHO (2011) and EPA (2009) and PV (2017) do not provide Zn limits for drinking water and suggest that Zn has no negative health impact in humans. Zinc shows very high concentration in groundwater, particularly in the two first campaigns, and in hair and urine samples (Tables 1, 2 and 3), and results in non-cancer risk in a sample collected from a well in 2006 (Fig. 5).

In contrast to hair, urinary concentrations of Al and Ni, elements with short half-lives, were elevated relatively to typical ranges for healthy people (Goullé et al. 2005), and groundwater concentrations for these elements are above WHO (2011), EPA (2009) and Portuguese DV (2017) in all sampling campaigns (Tables 1, 2, and 3). However, the health risk assessment was not calculated for Al because USEPA has not derived a reference dose for this element. Nickel shows no non-cancer risk, and their concentrations

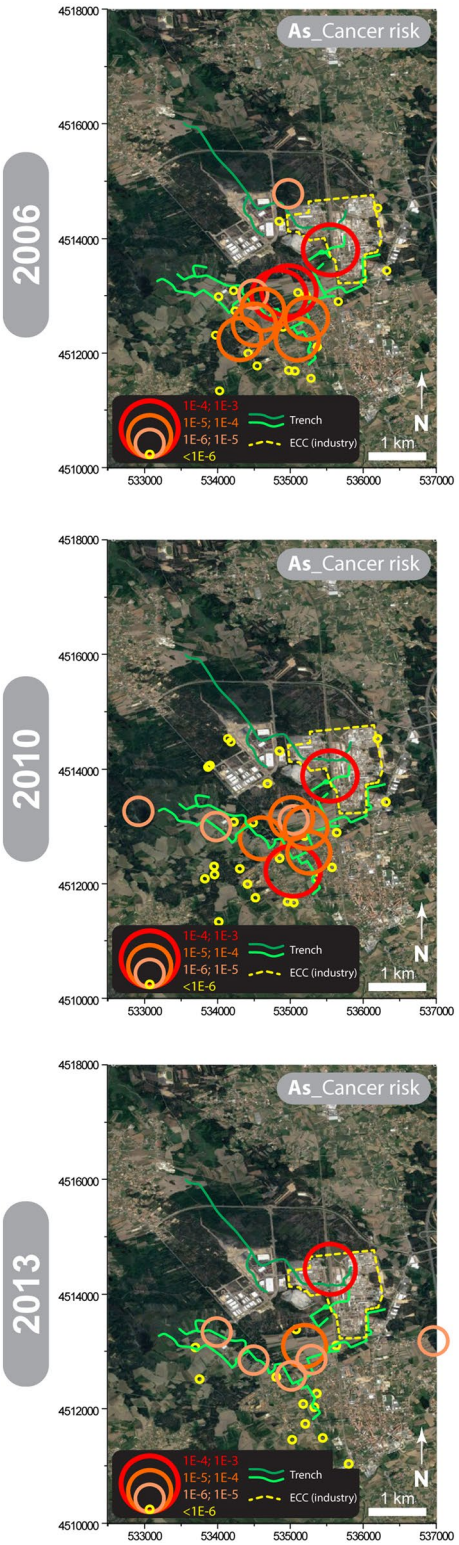

Fig. 6 Cancer Risk spatial and temporal evolutions for As

in groundwater and urine, although high, are not as elevated as other PTEs.

Urinary concentrations of Cd, and to a lesser extent Pb, were elevated relatively to typical ranges reported for healthy people by Goullé et al. (2005), even though recent groundwater concentrations were not above the guidelines for these elements. This could suggest that the enrichment of Cd and Pb in the urine could not be only influenced by groundwater, but could also result from other sources, such air, soils, cigarette fumes, exhaust from vehicles and diet. However, long-term exposure to contaminated groundwater could still be reflected in urine samples because Cd and Pb have long biological half-lives (Nriagu 2007; Dorne et al. 2011). Interestingly, of these elements, only Cd shows non-cancer risk in a sample from a well collected in 2006. For example, although Cd concentrations in groundwater samples were relatively low (below the permissible values), especially in the more recent sampling campaigns, a long-term exposure to Cd-containing water could still be reflected in urine samples because Cd has a long biological half-life and accumulates over time in the human body. Therefore, urine is likely to be a suitable specimen to evaluate short- and long-term PTE exposures, both for elements with low- and high-excretion rates.

Conclusions

The inter-disciplinary approach applied in this study comprising evaluation of groundwater contamination, calculation of cancer and non-cancer risks, and determination of contaminants concentration in inhabitants' hair and urine was successful in identifying trends and links between the different datasets, and consequently in investigating the potential effects of groundwater contamination on human health in ECC's surroundings. The local population strongly depends on agriculture and groundwater for their livelihood. The analysis of groundwater, hair and urinary PTE concentrations, and the calculation of cancer and non-cancer risks in the region of Estarreja show high health risks for the local population, mainly due to exposure to As. The most groundwater-contaminated areas generally coincided with the localities (Veiros, Beduido, and Pardilhó) in which inhabitants exhibit higher hair and urinary As, Hg and Zn contents, and localities not affected by ECC-related groundwater contamination are the ones with lower hair and urinary PTE concentrations (Canelas, Salreu). It is likely that PTE-elevated hair and urinary concentrations are related to the ingestion and dermal contact with contaminated groundwater, although this assumption requires further investigation, including that on other potential sources of contaminants for the local population, such as dietary intake of foodstuffs exposed to contaminated groundwater. This correlates well

with cancer and non-cancer risks for As in groundwater in ECC surroundings, showing that the health risk to the local population is high, particularly due to exposure to As.

Despite contamination remediation measures from the early 2000s, ECC surroundings remain a highly contaminated area, especially in As, and a serious concern for the environment and for human health. There is potential scope for further research in the study area in aspects that there were beyond the scope of this manuscript. This can include evaluation of the risks associated with dietary intake of products (e.g. vegetables) exposed to contaminated groundwater; evaluation of groundwater contamination and attenuation processes, including the current state of aquifer contamination; and the incidence of cancer and non-cancer diseases in the region (and how they may relate to groundwater contamination). The results of this study can be used by environmental and health authorities to better manage the complex situation created by groundwater contamination in Estarreja, which would require a joint effort and not isolated measures.

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