Human biomonitoring as a tool for exposure assessment in industrially contaminated sites (ICSs) - lessons learned within the ICS and Health European Network

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ABSTRACT

BACKGROUND: The use of human biomonitoring (HBM) for impact assessment is increasing in Europe. A European initiative, HBM4EU, aims at developing a harmonised approach to organise HBM in Europe in order to support and feed European policy making, based on data of the general European population. However, the mixed nature of industrially contaminated sites (ICSs) leads to heterogeneity in exposure and health risk of residents living nearby, which is different from that of the general European population. Health, environment, and social aspects are strongly interconnected in ICSs, and local communities are often concerned about potential health impact and needs for remediation. Therefore, the COST Action IS1408 on Industrially Contaminated Sites and Health Network (ICSHNet) decided to reflect on the potential and limitations of HBM to assess exposure and early health effects associated with living near ICSs.

OBJECTIVES: This paper intends to discuss challenges and lessons learned for addressing environmental health impact near ICSs with HBM in order to identify needs and priorities for HBM guidelines in European ICSs.

METHODS: Based on the experience of the ICSHNet research team, six case studies from different European regions that applied HBM at ICSs were selected. The case studies were systematically compared distinguishing four phases: the preparatory phase; study design including sampling schemes; selection of the target population and biomarkers; study outcome and how results were communicated and finally the impact of the results at scientific, societal and political levels.

RESULTS: All six case studies identified opportunities and challenges for applying HBM in ICS studies. In all six case studies HBM was primarily used to assess internal human exposure to environmental pollution associated with the ICSs, triggered by local public concern or by elevated levels of contaminants measured in environmental samples. The selection of the study population was based on distance to the industrial site or based on environmental modelling to delineate areas of high exposure. The contaminant specific results of the study population were compared with those of a control group or with national reference values. The HBM data often revealed other questions about health relevance, exposure routes or vulnerable sub-populations, which could be partially answered depending on the study design and the exploitation of questionnaire data that provided additional information on personal characteristics, life style and health status. Combining biomarkers of exposure with biomarkers of (early) biological effects, data from questionnaires or other environmental data enabled fine-tuning of the results and allowed for more targeted remediating actions aimed to reduce exposure. A smart choice of (a combination of) sample matrices for biomarker analysis produced information about relevant time-windows of exposure, that matched with the activities of the ICSs. Open and transparent communication of study results with contextual information, and involvement of local stakeholders throughout the study helped to build confidence in the study results, gained support for remediating actions and facilitated sharing of responsibilities. Using HBM in these ICS studies helped in setting priorities in exposure and health effects of concern, in policy actions and in further research. Limitations were the size of the study population, difficulties in recruiting vulnerable target populations, availability of validated biomarkers and coping with exposure to mixtures of chemicals.

CONCLUSIONS: Based on the identified positive experiences and challenges the paper concludes with formulating recommendations for a European protocol and guidance document for HBM in ICS. This could advance the use of HBM in local environmental health policy development and evaluation of exposure levels and promote coordination and collaboration between researchers and risk managers.

Key words: industrially contaminated sites, human biomonitoring, biomarkers, study design, human exposure

KEYPOINTS

What is already known?

- Residents near industrially contaminated sites (ICSs) may be exposed a range of different contaminants.
- Human biomonitoring is often initiated to address public concern on health risks related to residence in ICSs.

- Human biomonitoring (HBM) aggregates uptake from all exposure routes and allows to measure (early) biological effects.

What this paper adds?

- Based on a geographically balanced selection of six European case studies challenges and lessons learned on using HBM in ICSs are discussed.
- Our analysis resulted in specifying advantages and challenges of HBM in ICSs.
- The paper concludes with formulating recommendations for preparing HBM guidelines in European ICSs.

1. INTRODUCTION

Industrially contaminated sites (ICSs) include a wide diversity of settings (1) and are diverse with respect to the origin of contamination, the nature of the contaminants, duration of exposure, the exposure pathways, the number of residents in these areas, and the socio demographic characteristics of the residents (2). In recent years, ICSs represent a major public health concern in most European countries (1, 3-5) and contaminated sites and waste have been included in 2017 for the first time as one priority area in the final Declaration of the 6th Ministerial Conference on Environment and Health signed by the 53 Member States of the WHO European Region (6).

Many studies near ICSs are indicating an increased incidence and prevalence of a broad range of several chronic health conditions over last decades, including cancers, respiratory diseases, diabetes, obesity and adverse reproductive health outcomes (7, 8). One potential cause of this wide variety of health effects is complex exposure both in terms of pollutants (e.g. heavy metals and metalloids, polycyclic aromatic hydrocarbons, pesticides, dioxins) and affected environmental media (soil, air, water, biota, food-chain, etc.).

Health, environment, and social aspects are strongly interconnected in ICSs, and local communities are often concerned about potential health impact and needs for remediation. This public concern is however mostly addressed by studying single aspects, such as collection of emission data and chemical analysis of environmental samples and locally grown food, which can be used for exposure modelling. Environmental data are usually fragmented, often taken on ad hoc basis and as such not representative for the daily exposure situation (9). Moreover, this assessment procedure may not be able to address the real health impact experienced by populations living in a contaminated area.

Human biomonitoring (HBM) measures concentrations of environmental contaminants, their metabolites, or markers of (early) biological changes, in easily accessible body fluids (e.g. blood, urine or saliva) or body tissues (such as hair, nails) on an individual level. HBM data reflect the total body burden or biological effect resulting from all routes of exposure and take into account inter-individual variability in exposure levels, metabolism and excretion rates. Hence, HBM allows direct and more precise assessment of the distribution of exposure in the population incorporating individual variability in exposure (10, 11). In addition, personal information of health and life style may be collected.

The use of HBM as a tool for environmental policy and research in general is developing quickly in Europe, with national or regional programmes (12, 13) in e.g. France, Germany, Sweden, the Czech Republic, Slovenia, and the Flanders region of Belgium. In 2017, the European Joint Programme HBM4EU was launched, to support national and European policy making based on evidence on actual exposure of the general population (14). It represents a joint effort of 28 countries and the European Commission and is co-funded by Horizon 2020. However, there is not yet a focus on residents near ICSs.

In a recently published special issue on the environmental health challenges arising from industrial contamination (5), different contributions address the issue of HBM in ICSs. These papers showed HBM is used in ICSs in surveillance studies (15), exposure assessment for epidemiological studies (16), mechanistic process studies (17) and health risk assessment (18), although the use of HBM in ICS studies is still limited to a small fraction of the available published studies (8). These studies are often characterised by a fragmentation of objectives, methods and approaches (environmental monitoring, ecological or human biomonitoring, health risk and impact assessment, epidemiological surveillance) but are rarely designed with an integrative multidisciplinary approach. It is therefore urgent to promote coordination and collaboration between researchers and risk managers to identify common strategies at European level to deal with the impact of ICSs more systematically.

In response to challenges related to ICSs, the COST Action IS1408 on Industrially Contaminated Sites and Health Network (ICSHNet) was launched in 2015 (supported by the European Cooperation in Science and Technology (COST)). The ICSHNet Action aims at consolidating an European Network of experts and relevant institutions, and developing a common framework for research and response with the production of information for decision makers who have to deal with ICS issues (5). As part of the action, the potential and limitations of human biomonitoring to assess exposure and early health effects associated with living near ICSs was considered as another research strategy.

The purpose of this paper is to describe experiences on exposure assessment and detection of early biological effects related to ICS with HBM, based on a selection of HBM case studies conducted in different countries in Europe. This analysis intends to identify challenges and lessons learned for addressing environmental health impact and for promoting public health interventions in ICS based on HBM results. We conclude with formulating recommendations for a European protocol and guidance document for HBM in ICS.

2. MATERIALS AND METHODS

Based on the goals of ICSHNet COST Action (https://www.icshnet.eu/) and on discussions during the Third Plenary Conference of this Action, held on the Aristotle University of Thessaloniki (Greece), 6-10 February 2017, one of the targets of the ŏExposure assessmentô working group (WG2) was, to reflect on the use of HBM to assess exposure and early health effects related to ICSs and formulate advice and lessons learned from the HBM-experts of WG2. With the ambition to present a balanced distribution from different European geographical areas, covering also some cultural and socio- economic diversity of Europe, a selection of case studies distributed across different European countries was conducted and discussed during the Fourth Plenary Conference of this Action, held on WHO European Centre for Environment and Health (ECEH), UN Campus, Bonn, Germany, 21-22 February 2018. This strategy resulted in six case studies: (1) ICS Genk-Zuid in Belgium, (2) the community of Mammari in Cyprus, (3) the red mud disaster in Hungary, (4) Modena in Italy, (5) the Piekary ś lŃskie area in Poland and (6) the Panasqueira mine area in Portugal. All case studies concerned the residential exposure of people living within the vicinity of one or more ICSs.

We requested information from the centres that conducted the studies and asked for both published and unpublished information. The following information was obtained, if available: location of the study site, main expected contaminants at the study site, size and age of the study population, inclusion criteria, biomarkers of exposure and effects analysed by HBM, additional personal information on health, diet, life style and socio-economic status.

The analysis was conducted to identify differences in the process pursued in each case study to set up and run an HBM study using a four-stages HBM framework from our own experiences (Table 1): (i) the pre-phase, (ii) the study design and fieldwork, (iii) the results and interpretation and (iv) the impact of the study.

The so-called prephase is conducted prior to the start of the HBM study. Following five key elements were checked: (a) availability of data on environmental pollution and health conditions of the residents, (b) public concern and awareness, (c) involvement of stakeholders and other actors in early stages of the process, (d) key decisions that facilitated the instigation the HBM study and (e) how the study was funded.

In the second stage (study design and fieldwork), the information was checked that related to (a) type of study and the research question, (b) selection of biomarkers of exposure and (c) selection of health outcomes, (d) determinants of exposure studied, (e) selection of the study population and (f) definition of the study area.

The third stage is on study results and included information on, (a) participation rates, (b) exposure levels, (c) health assessment, (d) identified determinants of exposure or effects and (e) indications for vulnerable sub-populations. Each case study was evaluated also on (f) the way these results were communicated and which audiences were reached.

The fourth stage (impact) of evaluation concerned the available information on the (a) short-term impact and (b) long-term impact of the study results, (c) on the level of these impacts (scientific, societal and policy-making levels) and (d) whether stakeholders were involved in this process.

Table 1: Four stages of a HBM-study and key-criteria

(i)	**Pre-phase**
a)	Data available on environmental pollution and residents' health conditions
b)	Public concern
c)	Involvement of stakeholders and local actors
d)	Key decision to set-up HBM
e)	Funding
(ii)	**Study design and fieldwork**
a)	Type of study
b)	Biomarkers of exposure and selection criteria
c)	Biomarkers of effect and selection criteria
d)	Information on determinants of exposure
e)	Selection of the study population
f)	Selection of the study area
(iii)	**Results**
a)	Participation rate
b)	Exposure assessment
c)	Health assessment
d)	Identified determinants of exposure or health effects
e)	Identified vulnerable populations
f)	Communication of the results: which audiences targeted
(iv)	**Impact of the study**
a)	Short-term impact
b)	Long-term impact
c)	Levels: scientific, societal, policy making
d)	Involvement of stakeholders and local actors

The main characteristics of the six case studies are summarised in tables 2 and 3. A short description of each of the case studies is also given below.

Table 2: summary of the characteristics of the selected case studies

	Country	Information for site	Main contaminants	Number of participants in the study	Inclusion Criteria
1.	Belgium	The eastern part of Flanders,Genk-Zuid industrial area	Heavy metals, dioxins, PCBs and PAHs	200 adolescents of Genk-Zuid and 200 adolescents Flemish reference group	Age:14-15 yrs. old Social inequalities The vicinity of the site
2.	Cyprus	Mammari (a village located in the Nicosia District of Cyprus north of Kokkinotrimithia)	Arsenic	Fifty-six (56) nail specimens from Mammari non-smokers and forty-eight (48) matched controls	The vicinity of the site
3.	Hungary	Kolontár, Devecser, and Somlóvásárhely, an area of about 1,000 hectares	Heavy metals	351 children (176 from the affected area and 175 from the control area)	Age: 6- 14 years (most girls) The vicinity of the site
4.	Italy	The industrial/rural area of Modena, a medium sized town located in the middle of the Emilia-Romagna region, in the Po Valley (a circular area with radius of 4 km)	Ten metabolized polycyclic aromatic hydrocarbons (PAHs) Heavy metals PM10	488 participants	Age: 18-69 yrs. old, living within 4 km from the incinerator, randomly selected from the population register
5.	Poland	Silesian voivodeship, located in the southern part of Poland (smelter heap, gasoline station, car workshop, industrial plants, busy roads)	Heavy metals such as lead and cadmium	678 pre-school children:341 girls and 337 boys	Age: 3-6 years,
6.	Portugal	The Panasqueira mine is located in Castelo Branco district, Central Portugal	Ag, As, Bi, Cu, Cd, Sb, Sn, W, and Zn	122 subjects: 41 living in villages located in the vicinity of the mine (16 males and 25 females), 41 male workers from the mine (occupationally exposed), 40 additional subjects	The vicinity of the mine

Table 3: summary of biomarkers of the selected case studies

	Case study	Biomarkers of exposure	Biomarkers of effect	Influencing factors
1.	Belgium	Heavy metals (Cd, Pb, Ni, Cr, Mn, Tl, Sb, As, Hg) POPs (PCBs, HCB, DDE,	Oxidative stress, DNA-damage, asthma, allergy, hormone levels, puberty,	Sex, age, BMI, Diet, smoking, socio-economic status, locally produced

		dioxins, PBDEs) PAH-marker, benzene marker	neurological tests	food, pesticide use, stoves and wood/waste burning, distance to industrial site, concentrations in ambient air
2.	Cyprus	Arsenic	Increased incidence of cancer	Exposure to higher concentrations of arsenic in drinking water
3.	Hungary	Toxic metals (As,Cd, Co,Cr, Ni, Pb, Sr, Mn, V), particulate matter (PM_{10})	Respiratory diseases	Sex, age, air, drinking water
4.	Italy	Particulate matter PM, PAHs, from naphthalene to chrysene, 1-hydroxypyrene and twelve metals (Cd, Cr, Cu, Hg, Ni, Pb, Ni, Zn, V, Tl, As, Sn)		Sex, age, diet, smoking, traffic, occupation and personal characteristics, the proximity of SWI
5.	Poland	Lead, cadmium		The vicinity of the sites (smelter heap, gasoline station, car workshop, industrial plants, busy roads), time spent outdoor parental level of education, smoking at home, age and sex of children
6.	Portugal	As, Cr, Mg, Mn, Mo, Ni, Pb, S, Se, Si and Zn	Immunotoxicity biomarkers (lymphocytes), DNA-damage, genotoxicity biomarkers	Sex, age, smoking habits, lifestyle factors, health conditions, medical history, medication, diagnostic tests, water and fish consumption, agriculture practice

2.1. Case study for Belgium

Genk-Zuid is an industrial area of approximately 16 km^2, located in the eastern part of Flanders, (Belgium) with a diversity of industrial activities (more than 200 companies), such as a stainless steel plant, a car assembly plant (closed in 2014) and its suppliers, a glue production plant, a chipboard plant, and a coal- and biomass-powered electricity facility, combined with heavy traffic. Some residential areas are located at a short distance (100 meters) from the border of the industrial area. The residential areas are densely populated (approximately 2,000 inhabitants per km^2) and some of them concentrate a high proportion of ethnic minorities, a high degree of poverty, high unemployment rates, and social housing (19). Since 1980, Genk was identified as a region with elevated levels of heavy metals (nickel (Ni), chromium (Cr), molybdenum (Mo) and vanadium (V)) in ambient air. From 1990s, contamination of groundwater with BTEX (benzene, toluene, ethylene and xylene) and heavy metals was detected at the industrial site. In 2004, an increase in concentrations of Ni and Cr in ambient air was documented, with concentrations of Ni (86 ng/m^3) exceeding the annual mean threshold value of 20 ng/m^3.

2.2. Case study for Cyprus

In July 2009, in the community of Mammari (Cyprus), measured concentrations of arsenic in the groundwater with potable use exceeded the legal limit by almost 2 times (18-19 µg As/L compared with 10 µg As/L) (20). The water supply was discontinued and clean drinking water was distributed to the area's residents. This historical pollution was spread over an area of 25 km^2, inhabiting approximately 3,000 people.

2.3. Case study for Hungary

On October 4^{th}, 2010, the dam of a red mud reservoir ruptured causing a large ecological disaster. The red mud contained a residue from aluminum production (a sodium hydroxide solution known as lye) and the processed mud was stored in open reservoirs using wet disposal techniques. The dam, constructed from soot and sludge, was not designed for wet disposal and collapsed under the pressure. About 1.5 million m^3 of strongly alkaline red sludge flooded the areas of Kolontárand Devecser (2 and 5 km downstream of the dam) and reached five other villages, as well as the Torna and Marcal rivers. A total area of about 1,000 hectares was flooded. Quick actions were taken in the affected area to neutralize the high pH of the red sludge to curtail the corrosive effects in order to protect human health and to prevent contamination of the River Danube (21).

2.4. Case study for Italy

The ICS is located in Modena, Italy, a medium-sized town (180,000 residents) located in the middle of Emilia-Romagna region, in the Po Valley. The site is characterized by a flat topography and meteorological conditions that favour accumulation of atmospheric pollutants and their associated deposition. In the Emilia-Romagna region eight municipal solid waste incinerators (MSWIs) are operative. The MSWI in Modena has been operating since 1980. MSWIs can be significant sources of environmental pollution, potentially exposing nearby populations to hazardous chemicals at toxic levels. Approximately 38% of the whole municipal population lives within the exposure area, defined as a circular area with radius of 4 km, centred on the incinerator (22, 23).

2.5. Case study for Poland

The Silesian voivodeship (South Poland) was a heavily industrialised region, characterised by elevated environmental concentrations of heavy metals. About a quarter of the Piekary ś lŃskie area consists of a large landfill containing lead, cadmium and zinc, making this one of the most polluted cities of this region (24). The city covers 40 km^2, with a population density of 1,472 people/km^2. In Piekary ś lŃskie 8,141 children are registered, with 2,196 children in pre-school age. Most of the children attend kindergartens (1,752; 79.7%), including 3-year-olds - 332 (54.1% of the population), 4 years - 442 (79%), 5 years - 509 (96.9%) 6 years old - 467 (93.8%) (data of the education department in the city, 20.02.2012).

2.6. Case for Portugal

The Panasqueira mine is an active mine located in Central Portugal, Castelo Branco district. The activity of the mine started in the last decade of the 19^{th} century and covers an area of 2,000 ha (25). During this time, concentrated ore residues were deposited in the Rio and Barroca Grande tailings and mud dams. The total volume of the concentrated ore residues which contains metals is over 9,200,000 m^3 and growing. If due to slippage zones, the Rio tailings collapses, mining waste will be deposited in the Zêzere river, the main water supply of Lisbon. Since the 1990s the mining activities are carried out in Baroca-Grande, and the rejected materials are deposited in Baroca-Grande tailing and mud dam, which are exposed to weather events and longer-term climatic conditions.

In the surroundings of the mining area there are villages of which the inhabitants are strongly dependent on the mine (mostly men), private agriculture (mostly women) and groundwater, both for irrigation and drinking. The impacted study area (not including considered background areas) covers about 32 km^2 and includes S. Francisco de Assis, Barroca Grande, Dornelas do Zêzere, Barroca and S. Martinho villages. In 2011, the total residents in these villages was estimated to be 2,268. The site is characterized by deep valleys and hills.

3. RESULTS

Although a human biomonitoring study consists of several stages, the information published in peer-review papers is mostly restricted to a description of the study design, fieldwork and the results of the HBM-study. In the case studies analysed, information on the prephase (e.g. public concern, decision point to use HBM), selection criteria for biomarkers, stakeholder involvement, communication of the results or on the impact of the study on societal and policy level are often scarcely available from the study description, or are only available through other sources, such as reports in the local language or personal communication. The first three stages are present in each of the case studies discussed. The fourth stage (impact) is sometimes missing or less well documented compared to the other stages.

3.1. Stage 1: Pre-phase

For all six case studies, **environmental exposure data** were available before the commencement of HBM activities (Table 4). The data mostly consisted of measurements of contaminants in environmental media (soil, ambient air, water and sediments). In the Belgian and Hungarian case studies, toxicity profiles of particulate matter (PM) were also available (26), while in the Italian case study modelled PM-concentrations due to the plant activities were used to inform the HBM-study design (22, 23). At the start of the HBM studies, health data from the ICSs were only available in the Belgian and Hungarian case studies (Table 4).

Public concern was noticed in the case studies of Belgium, Cyprus, Hungary and Poland. The extent of the catastrophe, the number of casualties and the partial evacuation caused major concern in the Hungarian case study. Despite available information on contaminant levels in soil, ambient air, house dust and vegetables, there was growing concern among citizens in the Belgian case study about to what extent pollution was entering the human body and how this might affect health. High concern of the citizens in Cyprus when the pollution incidence was discovered back in 2008 was showcased, with the Ministry of Health establishing an interdisciplinary team composed of governmental departments from different Ministries and academics from universities. In the Polish case study parents were concerned about their childrenὂs health and quality of life.

In these four case studies **stakeholders and/or local actors** were involved from the start of the HBM study. In the Belgian case study, a community-based participatory approach was used. At the start of the study a Community Advisory Board was established, consisting of societal gatekeepers as well as representatives of the local government and industry. When the HBM study was about to start, changing economic conditions lead to reduced activities of one of the largest companies at the industrial site. The relevance of organizing an HBM study given the changing exposure situation was discussed with the Community Advisory Board. In the Hungarian case study, during the incident, the Crisis Centre of the Office of the Chief Medical Officer was in regular contact with health service providers, local organizations of the National Public Health and Medical Officer Service, experts of the background scientific institutions, emergency response authorities, the armed services. The World Health Organisation (WHO) was also kept informed. The Chief Medical Officer established an assessment committee consisting of experts of different fields. The Committee performed hazard and risk analyses and ordered an environmental health surveillance as well as HBM. A collaboration between scientists, the community and local government was also established in the case studies of Cyprus and Poland. In the case study of Cyprus this collaboration was used to identify possible sources of exposure and to evaluate health effects. In the Polish case study, the collaboration also involved key representatives of the target population. No information on public concern or stakeholder involvement was available for the case studies of Portugal and Italy.

The **decision point to organise an HBM study** was comparable in all six case studies: to what extent can the environmental pollution that is associated with the ICS enter the human body.

Gouvernamental **funding** for the HBM studies was received in the case studies of Belgium, Cyprus, Hungary, Italy and Poland. In Portugal the study received funding from scientific grants. In the Belgian case study a follow-up study using HBM was organised which was co-funded by industrial partners, the local gouvernment and the Flemish gouvernment.

Table 4: Summary of the available pre-phase information for each of the six case studies.

Data available on environmental pollution and health conditions residents					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
			Published		
Toxicity profile of particulate matter: increased mutagenic and estrogenic activity, a higher inflammatory potential and a higher oxidative capacity (26) Ambient air concentrations of heavy metals (27)	In drinking water a concentration level of arsenic which exceeded the legal limit by almost 2 times (18-19 μgAs/L compared with 10 μgAs/L) (20)	Concentrations of toxic pollutants in soil (e.g. arsenic, cadmium, cobalt, lead, titanium, strontium, etc.). Concentrations of PM10, PM2,5 and heavy metals in ambient air. Toxicity profiles of PM. Ten people died in the catastrophe. Most of the injured suffered chemical burns from the lye, post-traumatic stress, sleeping problems and respiratory diseases. (21)	At address level, calculated PM_{10} concentrations were available using fallout maps of PM_{10} emitted by the plant. The presence of other environmental exposure sources at the residence was assessed with respect to to: zone classification, traffic and residential heating (22, 23).	In the gardens of Piekary ślŃskie soil levels for lead and cadmium reached mean values of 569.7 (201–2159) mg/kg for lead and 16.9 (5.52–58.6) mg/kg for cadmium, raising health concerns. Blood tests for children conducted between 1991 and 2009 showed decreasing, but still high levels of heavy metals (24).	Presence of potentially toxic elements (silver (Ag), As, bismuth (Bi), copper (Cu), Cd, antimony (Sb), tin (Sn), tungsten (W), and Zn) in soils, road dust, plants for human consumption, groundwater, stream waters and sediments, on the surroundings of the mine (28-30).
			Other		
Ambient air concentrations of dioxins, polychlorinated biphenyls (PCBs) and polycyclic aromatic hydrocarbons (PAHs). heavy metals in soil, vegetables of local gardens and indoor dust higher cancer risk for both Ni and Cr exposure, lower scores for perceived health status and a higher indication of respiratory symptoms					
Public concern					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
			Published		

Other					
Growing concern among the citizens, who were anxious about how much pollution was entering the human body and what effect this might have on their health.	High concern of the citizens when the pollution incidence was discovered back in 2008, but interest is still strong even in 2019 as the residents want to be informed if they are still exposed to Arsenic.	The extent of the catastrophe, the number of injured people and casualties and the partial evacuation caused major concern. The dust from the dried red sludge caused significant respiratory symptoms that further increased the concern of the population		Persistent concern of parents about the health of their children and their future quality of life.	
Involvement of stakeholders and local actors					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
Published					
	A mixed community-local government collaboration was established to identify the causes of environmental pollution and also to evaluate possible health effects associated with these exposures. (20)				
Other					

When the HBM study was about to start, changing economic conditions lead to reduced activities in one of the largest companies at the industrial site. The relevance of organizing a HBM study under these conditions was discussed with the Community Advisory Board.		The Crisis Center of the Office of the Chief Medical Officer was in continuous contact with the health service providers, the local organizations of the National Public Health and Medical Officer Service, the experts of the background scientific institutions, the emergency response authorities, and the armed services and also informed the WHO. The Chief Medical Officer established an assessment committee consisting of experts of different fields. The Committee performed hazard and risk analyses and ordered an environmental health surveillance as well as human biomonitoring.			
Decision point to start HBM					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
Published					
	Various exposure sources for arsenic (20)	To strengthen the exposure estimates, based on model analysis (21)	As part of the authorization process for the solid waste incinerator in Modena, Italy, the degree to which people living and working in the proximity of the plant were exposed to SWI emissions was studied using HBM (23).	Because of the still high lead and cadmium blood levels in children and taking into account the stability of lead and cadmium in soil and insufficient remediating actions, it was decided in 2013 to perform a study on correlations between the level of heavy metals in blood and determinants of exposure (24)	To evaluate whether environmental and occupational contamination related to the Panasqueira mine activities is associated with the internal dose of several pollutants (As, Cd, Cr, Hg, Mn, Nobellium (No), Ni, Pb and Selenium (Se)) measured in blood, urine, hair and nails (25).
Other					

Despite the closing of one of the factories, the elevated environmental measurements caused growing concern of citizens about the body burden and health risks due to this chemical exposure.	To prevent adverse health effects, the authorities started a medical investigation immediately to establish the degree of exposure of the residents to arsenic and the potential health effects.				
Funding					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
Published					
The HBM study was funded by the Environment Department, the Health Department and the Department of Scientific Innovation of the Flemish government (31)	The HBM study was funded by the Ministry of Health (32)			Project was co-financed by the National Fund for Environmental Protection and Water Management, City Hall of Piekary ś lŃskie and Institute for Ecology of Industrial Areas (24)	The study was funded by the Foundation for Science and Technology (FCT Portugal) with research grants SFRH/BD/63349/2009, SFRH/BD/47781/2008 and SFRH/BPD/26689/2006, and project PTDC/SAU-ESA/102367/2008. (33)
Other					
		The costs of the laboratory tests were financed from government sources, from the fund created specifically for the expenses in relation to this event.	The study was funded by the Province of Modena in the frame of the authorization for an upgrade of the local SWI.		

3.2. Stage 2: study design and fieldwork

In all six case studies a cross-sectional study design was used. The case studies of Belgium (19, 31), Italy (23) and Poland (24) compared results from people living in the study area with available national reference values or with guidance values. In the case studies of Cyprus (20), Hungary (34) and Portugal (25) results from residents living in the target area and hence potentially high exposed, were compared with those of people living outside the area of interest. The aim was to detect differences in biomarker levels between both groups (Table 5).

Delineation of the study area was mostly based on the proximity of the ICS (Table 5), in the Belgian and Italian (22) case studies this process was supported with calculations from air quality dispersion models.

In all six case studies, the selection of biomarkers of exposure was based on available pollutant levels measured in e.g. industrial emissions, soil, water, sediments or locally grown food (Table 5). The available environmental data were used to identify pollutants of concern, which were subsequently included in the HBM study design if adequate/viable biomarkers to be analysed in human samples were available. The preferred sampling matrix for collection depends of the chemical properties of the substance and the biomarker characteristics (stability, half live of elimination in the matrix, etc.). For a number of pollutants, parent compounds and/or metabolites can be measured in several different human matrices, often giving information about a different exposure time-window. In the case study of Portugal (25), the relative importance of different time windows of exposure was one of the research questions and therefore blood and urine samples, as well as nails and hair samples were collected to measure biomarkers of exposure. In the Belgian case study (19, 27), blood and morning urine samples were taken, enabling measurements of some substances (e.g. cadmium) in both matrices, providing information on short-term as well as longer-term exposure to these compounds. In the Italian (23) and in the Hungarian case studies (34) spot urine samples were collected to measure biomarkers of exposure. Concentrations of biomarkers measured in urine samples need to be corrected for dilution and creatinine was used within these case studies. Blood was used as a human matrix in the Polish case study (24) and toenails in the Cypriot case study (20).

Biomarkers of effects (Table 5) were included in the case studies of Belgium (31), Cyprus (32), Hungary (21) and Portugal (35). Selection of these biomarkers of effect was driven by the available evidence of health effects associated with the studied biomarkers of exposure based on internationally published scientific information.

Selection of the study population depended on whether the research question required information on the potentially most exposed population, the most vulnerable population or a representative sample of the study population. In Belgium (19), Hungary (34) and Poland (24) biomarkers were measured in children, because of their known vulnerability to environmental exposure, as well as the potential to estimate the contribution of environmental exposures as opposed to other routes of exposure due to the lack of occupational exposure and a negligible impact of active smoking in this sub-population. The research questions were focused on the impact of living near the ICSs on citizensô health. In Italy (23), Cyprus (20) and Portugal (25) (healthy) adults were recruited and also occupationally exposed people were included to address living as well as working in the ICS.

One of the advantages but also challenges of HBM is that it reflects aggregated exposure, mostly originating from multiple sources and entering the body through several routes. This makes it difficult to attribute the observed biomarkers of exposure to a specific source, such as an ICS. Therefore, additional information is often needed. In all case studies, except the one from Hungary, participants completed (sometimes extensive) questionnaires to provide information on possible routes of exposure, their contact with possible other sources of the contaminants under study and their personal characteristics, including their health status (Table 5). Multiple regression models were used to account for these modifying factors and/or identify determinants of exposure.

Table 5: Summary of the study design and fieldwork of the six case studies.

Study design					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
Published					
Results from adolescents with residence in the study area were compared with the results of a Flemish reference group of the same age (31) Community-based participatory approach: At the start of the study a Community Advisory Board was established, consisting of societal gatekeepers as well as representatives of local government and industry (36).	Investigate a group from the Mammari population (exposed population) and an unexposed population from the rest of Cyprus. (20)	Biomarker levels in children from the exposed settlements were compared with those of a control group To observe changes in concentrations over time To compare the measured concentrations to the values published in the international literature. (34)	Biomarker levels in residents of the exposed area were compared with those of a control group (22) Cross-sectional study of residents near the ICS (23)	Cross-sectional study (24) During the project implementation scientifists were closely cooperated with the self-government authorities of the Piekary ś lŃskie Municipal Council, the kindergarten managements, the Silesian Children's Association "Bratek" and the Medical Center EKO-PROF-MED in Miasteczko ś lŃskie and also with the Children's Foundation "Miasteczko ś lŃskie" (37).	Biomarker levels of residents near the mine area were compared with levels of subjects living in a control area (25)
Other					
The Community Advisory Committee discussed and co-constructed the study design, the recruitment strategy, definition of the study area and selection of the biomarker. Community members also actively engaged in study promotion and door-to-door visits to help recruit participants.					
Biomarkers of exposure and selection criteria					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**

Published					
Markers for heavy metals, POPs, PAH, benzene (19) selected based on available emission data from the industrial plants and the environmental measurements (27)	Arsenic in nails, based on elevated levels in drinking water (20).	Metals (such as Cadmium, Nickel, Vanadium, Chromium, Cobalt and Arsenic) in the urine samples. Selection of the metals studied was based on the metal concentrations observed in the particulate matter and on their risk to human health (34).	Ten metabolized polycyclic aromatic hydrocarbons (PAHs), from naphthalene to chrysene, 1-hydroxypyrene and twelve metals (Cd, Cr, Cu, mercury (Hg),Ni, Pb, Zn, V, thallium (Tl), As, Sn) were measured in spot urine, selected based on literature data, monitoring data of the emissions of the incinerator and results of the pilot study (23)	Based on soil measurements and previous measurements in blood of children, lead and cadmium blood levels were measured (24).	Metal(loids) (As, Cr, Cu, Hg, Mg, Mn, Mo, Ni, Pb, S, Se, Si and Zn) in blood, first morning urine, hair and nails (toe finger) samples. selection was based on results from previous studies on samples of soil, road dust, plants for human consumption, superficial and groundwater and stream sediments (25).
Other					

Biomarkers of effect and selection criteria					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
Published					
For health effects related to these exposure biomarkers in literature, appropriate biomarkers of effect were selected, such as markers for DNA damage, renal function, inflammation, endocrine system, cardiovascular disorders, neurotoxicity, allergy and asthma (31).	Possible dermatitis and dermal lesions in exposed population (32)	Respiratory diseases, asthma, post-traumatic stress, sleeping problems (21)			Biomarkers for immunotoxic and genotoxic effects, based on the health effects associated with the metals reported in literature (35, 38).
Other					

Information on determinants of exposure					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
Published					

All participants signed an informed consent and completed an extensive questionnaire to provide information about socioeconomic factors, home environment, habits, diet and life style factors. Multiple regression models were used to study the effect of residence in the ICS on biomarker levels, after correcting for other modifying factors (19, 27, 39).	Questionnaire regarding socioeconomic, demographic factors and smoking habits (Pavlou et al., 2012)		Influencing factors, such as diet, smoking, traffic, occupation and personal characteristics were assessed by questionnaires and objective measurements, and included into multivariate linear regression models (Gatti et al., 2017)	Questionnaire about determinants of exposure, such as sources of pollution with heavy metals in the home environment and socioeconomic factors. Statistical analysis consisted of ANOVA Kruskall-Wallis or Mann Whitney U test and Stepwise regression models (Kowalska et al., 2018).	Questionnaires provided information about the individual health conditions, medical history, medication, diagnostic tests (X-rays, etc.) and lifestyle factors. Multiple regression models to estimate the effect of the exposure, adjusted for influencing factors (25)
Other					

Selection of the study population					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
Published					
200 adolescents (14-15 years old), The number of participants needed was assessed by statistical power calculations. Adolescents were selected as study population since they are not subjected to occupational exposure and their physical and mental development makes them a susceptible population (19, 27, 31, 39).	Exposed group (n=56) and control group (n=48). The selection of the two groups was made taking into account the results of a questionnaire regarding socioeconomic, demographic factors and smoking habits to maximize the representability and comparability (20).	Children: because their exposure to environmental compounds is higher compared to the adult population, their developing bodies makes them more vulnerable to health effects and exposure through active smoking could be eliminated. The study group was composed of 351 children, aged 6-14 years, 50% from the flooded area, 50% from the control area (34).	65 subjects living and working within 4 km of the incinerator and 103 subjects living and working outside this area (22) 500 people, aged 18-69 years, living within 4 km from the incinerator (23)	Preschool children (n=678) were selected as study group since they spend a lot of time playing outdoor and they are not occupationally exposed (24).	122 subjects (41 environmentally exposed, 41 occupationally exposed (miners) and 40 in the control group) (25)
Other					

Selection of the study area					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**

Published					
Based on location of industrial activities, environmental data, health survey data, population density (27)(Vrijens et al., 2014)	Based on the coverage of the population exposed to the contaminated drinking water source (Makris et al., 2012)	Two flooded areas, Kolontár and Devecser, and a control area close to the dam but not flooded, Ajka (34).	4 km from the incinerator. The study area was defined by exposure to particulate matter (PM) emitted from the SWI estimated using fall-out maps from a quasi-Gaussian dispersion model, also taking into account the results of the pilot study (23)	Based on location of industrial sources of hazard, environmental data and number of preschool children.In the vicinity of the non-ferrous metal smelters concentration of lead and cadmium in soil exceed the limit values for residential buildings and areas of cultivated soil (24, 40).	Villages near the Panasqueira mine and a control area (25)
Other					
Air quality dispersion models were used to define the possible contaminated area and the study area.					

3.3. Stage 3: study outcome

In all case studies, with the exception of the Hungarian case study (34), significantly elevated levels of several biomarkers of exposure were observed in the ICS study population compared to the control population or national reference values (Table 6). In the case studies of Belgium (27), Italy (23) and Portugal (25), where an extensive set of biomarkers of exposure was measured, the studies allowed identification of a selection of substances of concern for internal exposure. In the Portuguese case study it was also possible to identify separate exposure profiles for the environmentally and the occupationally exposed group. Moreover, the study provided information about the duration of different exposures: the environmentally exposed group showed pronounced and continuous (past (nails) and recent (urine)) exposure to As, moderate and continuous exposure to Mg (blood), Mn (urine, nails and hair) and Zn (blood and hair), recent exposure to Mo (blood) and past exposure Cr (nails), Ni (nails) and S (hair and nails), while the occupationally exposed group showed continuous exposure to Zn (blood and hair), recent exposure to Se (blood) and long-term exposure to As (nails), Mn (hair) and Pb (hair). In the Cyprus (20) and Italy (23) case studies the elevated exposure levels were not considered to be of concern because they were in line with previous studies or with levels reported in literature.

In the six case studies, these descriptive data helped to answer initial questions about for which environmental pollutants and to which extent local residents experienced elevated body burdens of contaminants. However, these descriptive results about internal exposure in residents near ICS evoked, usually other questions:

- Q1: Are these exposure levels associated with health effects?
- Q2: What sources contribute to this exposure?
- Q3: How can this exposure be reduced?

To answer these questions, additional information on the health relevance of the observed exposures and on the local situation is needed.

Q1: Are these exposure levels associated with health effects?
Observing elevated levels of exposure in populations residing near ICSs compared to control groups or reference populations does not *de facto* mean these exposures will pose a health risk. One way to assess health risks of observed exposure levels is to compare them with available (health-based) guidance values in human matrices, such as HBM-I and -II values derived by the German HBM-commission (41) or published Biomonitoring Equivalents (BE-values) (42) derived by other groups. In the case studies of Belgium (27) and Poland (24) HBM guidance values were available for some of the measured biomarkers of exposure. Comparing the observed levels in the ICS study populations with these guidance values, showed some health risks of concern in the Belgian case study (20% of the participants exceeded the HBM-I-value for urinary cadmium (0.5 µg/L) and 64% exceeded the BE-value (6.4 µg/L) for urinary toxic relevant arsenic levels) and in the case study of Poland (32% of the children exceed the health-based guidance value for lead in blood (2 µg/dl)).

Health risks can also be further assessed by association of biomarkers of exposure with biomarkers of effect or with health outcomes in the same individuals. In cross-sectional studies biomarkers of exposure and of effect should be carefully chosen, when testing for associations between both. For example, if short-term biomarkers of exposure are associated with early biological effects (such as DNA damage), it only shows that current exposures have a measurable effect on DNA damage which is often repairable. Interpretation in terms of increased cancer risk is unreliable. If the association is tested between biomarkers of exposure and health outcomes such as asthma or cancer it is assumed that current exposure represents long lasting exposure over a long time window as these health outcomes usually arise after a latency period and may be due to prior exposures or early events in vulnerable time windows of exposure. In the case studies of Belgium (Table 6) and Portugal (38) DNA-damage and/or genotoxicity markers (mostly short-term effect markers) were interpreted as predictors of elevated health risks compared to the control groups, as well as immunology biomarkers in the Portuguese case study (35). Having data on exposure levels and health effects of the same subjects allows studying associations between exposure and health outcomes. In the case studies of Belgium (43) and Portugal (38) (35) these data allowed to observe statistically significant associations between the elevated exposures and the elevated biomarkers of effect.

What sources contribute to internal exposure (Q2)? How can internal exposure be reduced (Q3)?

Both questions are related to each other. Identification of factors that contribute to levels of biomarker of internal exposure provides options for remediating actions to reduce exposure. Given that biomarkers of exposure provide an aggregate indicator of all sources of exposure, additional information is needed to estimate the fraction of exposure attributable to ICS sources. Typically, information from either other databases and measurements (emissions, soil, ambient air, water, etc.) or from questionnaire data are used.

In the Italian case study (23), the study area was subdivided into spatially defined areas corresponding to different levels of modelled air concentrations of particulate matter attributed to the ICS activity. Thus, geographic location of receptors was used as a proxy for the contribution to biomarker levels attributable to the activities of the ICS. The internal contaminant levels of residents living in each of the three areas was compared in relation to the modelled air pollution levels. In the Belgian case study distance of the residence to the ICS and to the ambient air measurement station located near the ICS were used as proxy variables, showing associations with some of the biomarkers of exposure (27). An association was also reported between chromium concentrations in ambient air within the ICS area three days prior to the urine sampling and urinary chromium levels in residents. In the Belgian case study, the contribution of the ICS to measured biomarkers of internal exposure was also assessed by adding the parameter ӕresidence in ICSô last to the multiple stepwise regression models, after correction for other determinants related to personal habits, life style or diet of the participants. A similar method was used in the case study of Poland (24). When using indicators of exposure such as geographical location of residence or distance to the ICS, attention should be paid to possible misclassification of exposure, which is more likely to occur for industrial sites with high stacks ((16). Complementing these indicators with environmental data can increase their quality.

Data from questionnaires to identify determinants of internal exposure levels were used in five of the six case studies (Table 6). Determinants such as smoking, diet and traffic showed significant associations with biomarkers of exposure (23-25, 27). These determinants represented possible routes of exposure (e.g. locally produced food in the diet), additional sources other than the local industry (e.g. heavy traffic because of the activities in the ICS), as well as other non-ICS related sources (e.g. smoking).

Identifying vulnerable sub-populations or higher exposed groups

Questionnaire data helped to identify sub-populations within the residents near the ICSs that are likely to experience relatively greater exposure or to identify sub-populations that are more vulnerable to this exposure. In the case studies of Belgium (19), Italy (23) and Poland (24) social inequalities in the exposure metrics employed were observed. For some markers of exposure, a lower attained education level was associated with higher exposure; but for other markers of exposure higher levels were associated with a higher attained level of education. In the Italian case study foreign citizenship was associated with higher levels of some of the biomarkers of exposure. Other identified groups with elevated biomarkers of exposure are often related to age and sex of the participants (Table 6). Differences in assimilating properties of the pollutants or differences in metabolism can be part of the reason for these observations.

Communication of study results

Personal results were provided to the participants in the Belgian and the Italian case studies (Table 6). In the Polish case study parents of children with elevated levels were informed to consult a medical doctor. Also, in the Belgian case study participants with levels exceeding human biomonitoring health-based guidance values were contacted and all participant were offered the opportunity to have a consult with the study medical doctors to discuss their personal results. In the Belgian case study, a stepwise communication strategy was developed in which study participants received the study results before local stakeholders, press and the general public. Study results were available in public reports in the Belgian, the Cypriot, the Italian, the Polish and Hungarian case studies.

Table 6: Summary of the available information on study results and communication strategy of the six case studies.

Participation rate					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
Published					
Other					
Exposure assessment					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
Published					
Substances of concern identified: compared to the Flemish reference group ICS-study participants had higher blood levels of Cr (+32%), Cu (+5%) and Tl (+11%), higher urine levels of Cd (+18%), Cu (+11%), toxic arsenic components (+32%) (27).	arsenic concentration of about 2.84 times higher for Mammari's population as compared to the control population (20).	No statistically significant difference in the urinary levels of any metals between the exposes area and the control area. Measured concentrations in the range of the published data measured in other countries. No increasing tendency in the urinary level of the measured components during the 7 months of the study, except for chromium during the non-heating period in both areas (34).	Compared to Italian reference limits, urinary metal concentrations in the study area were comparable or higher. Identified substances of concern: Cr, V, naphthalene and phenanthrene. Metal levels showed no clear association with calculated PM exposure categories of the solid waste incinerator (SWI). For some PAHs (naphthalene, fluorene, fluoranthene and pyrene) positive associations with SWI exposure were observed. In particular fluorene levels were significantly higher in samples from participants with residence in exposure zone 3 and 4 (23).	preschool children living in Piekary ś lŃskie are exposed to lead and cadmium (24)	Substances of concern identified: both exposed groups higher values for As, Cr, Mg, Mn, Mo, Ni, Pb, S, Se and Zn, occupationally exposed group higher levels of Cu, Mn and Pb in hair and Se in blood. Environmentally exposed group: pronounced past and recent exposure to As, moderate exposure to Mg, Mn and Zn, recent exposure to Mo and past exposure Cr, Ni and S. Occupational exposed group: continuous exposure to Zn, recent exposure to Se and long term exposure to As, Mn and Pb (25).
Other					

Substances of concern identified: compared to the Flemish reference group ICS-study participants had higher urinary levels of a polycyclic aromatic hydrocarbons (PAHs) marker (+33%).					
Health assessment					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
Published					

HBM guidance values for internal exposure exceeded in: 19.6% of the participants for urinary Cd, in 64.5% of the participants for toxic relevant arsenic, in 0.5% of the participant for blood Cd (27). higher levels of biomarkers reflecting DNA-damage associated with higher urinary levels of the PAH marker and the benzene marker, higher urinary concentrations of cadmium, chromium and nickel, higher blood levels of arsenic, DDT and HCB and higher levels of methylmercury in hair (43).	the study did not show a health risk for the population, based on the assessment of dermatitis or skin lesions (20).	Increase in respiratory diseases, post-traumatic stress and sleep problems. Increase in PM10 levels associated with increase in respiratory diseases. (21, 34)		When compared to HBM guidance values for lead in blood 32% (n=218) of the children exceeded the value of 2 µg/dl, 8.5% (n=58) exceeded the value of 5 µg/dl and 0.9% (n=6) exceeded the value of 10 µg/dl. The reference value for cadmium of 5 µg/dl was exceeded in 0.8% of the children (24).	Environmentally exposed group: lower levels of T cytotoxic lymphocytes(CD8+) and higher CD4+/CD8+ ratios. Occupational exposed group: decrease in T lymphocytes (CD3+) and T helper lymphocytes (CD4+) and increase in natural killer cells(CD16+56+) (Coelho et al., 2014b). All measured biomarkers of genotoxicity increased in the exposed groups generally higher levels in the environmentally exposed compared to the occupational exposed participants(Coelho et al., 2013). Higher blood levels of Mn associated with decrease of T cytotoxic lymphocytes (CD8+) and B lymphocytes (CD19+) and increase in the CD4+/CD8+ ratio (Coelho et al., 2014b). Higher Mn and As levels in toenails associated with increased genotoxicity markers (38). Higher concentrations of lead in toenails associated with increasing levels of immunotoxicity biomarkers (35), as well as with higher genotoxicity markers (38).
Other					

DNA damage was the main health effect of concern. Higher levels of biomarkers reflecting DNA-damage (+26% and +69%) the adolescents residing the ICS compared to the Flemish reference group, after correction for confounders and covariates.					
Identified determinants of exposure or health effects					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
Published					
Age, gender, smoking habits, season, fish consumption, urine density, proximity to ICS, immission data (27)	This high level of the concentration was probably linked to the consumption arsenic contaminated drinking water for an unknown period of time (20).		Tobacco smoking was associated with higher levels of almost all PAHs, as well as Cd and Pb. Traffic exposure was associated with higher urinary levels of Acy, Phe and Ant. Females had higher levels of Cu, Pb, Cd, Ni and As. Increasing age was associated with higher urinary levels of Pb, Cd, As and V (23).	Higher blood levels of lead in younger children and associated with a higher attained level of education of the father, exposure to cigarettes smoke at home and living in the vicinity of any environmental hazard. Higher cadmium levels in blood associated with an older age and not living near environmental hazard (24).	Females higher levels of As, Cr, Mg, Mn and Se in urine, fingernails and toenails, and Hg in hair, males higher levels of Fe, Hg, Mg, Pb, S and Zn in blood and hair samples. Older age associated with higher levels in blood and urine of As, Cu, Mg and Zn, younger age associated with higher concentrations of As, Cr, Fe, Mg, Mn and Se in nails and hair. Almost all biomarkers were significantly higher in smokers compared to non-smokers, with exception for Hg in hair which was higher in non-smokers (25).
Other					

Identified vulnerable populations					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
Published					
Identified socio-economic groups as vulnerable subpopulations for exposure to environmental compounds. adolescents with low socio-economic status (SES) had higher internal exposure of Cd, Cu, lead and PAHs compared to adolescents with higher SES (19).			Social inequalities in exposure were reported: higher internal doses of Cu, Pb and V were associated with lower education levels, while higher urinary Hg levels were associated with higher education levels. Foreign citizenship was associated with higher urinary levels of Sn, Tl and all PAHs, except acenaphthene and anthracene (23).	The highest risk was documented in children living in the vicinity of metallurgical slag heaps located in Brzeziny district, this region also had the highest concentration of both pollutants in the soil (24).	Populations living nearby and working in the mine are exposed to several metal(loid)s originated by mining activities, particularly to As (25).
Other					

Communication of the results, audiences					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
Published					
Other					

Flemish and local authorities implemented a communication strategy to inform citizens about the study results. All participants first received the collective results of the study as well as their personal results, if requested, followed by informing the local authorities about the collective results, and finally, the press and the general public. All participants were given the opportunity to consult a physician, to discuss their personal results.		The study results were included in reports on the health consequences of the red sludge catastrophe, which are available to the general public. The results were also mentioned in policy briefs. No press communication was organized.	Personal results were reported back to participants who indicated to be willing to receive their results.	The research was accompanied by informational and educational activities addressed to parents, carers, educators of kindergartens and other members of the Piekary ś lŃskie community. Printed educational materials were prepared, as well as an electronic information and educational package "How to protect children against lead and cadmium?" posted on the websites of each kindergarten. Information meetings were organized with the municipality's self-government and the kindergartens' directorates as well as two educational and information campaigns during local public events. Information on the implementation of the project was included in local and regional media.	The study results were not communicated to the participants or to the general public.

3.4. Stage 4: impact of the study

HBM-results in ICS studies can have impacts on scientific, societal and political levels.

The **scientific level** impacts usually consisted of increased scientific knowledge on the human exposure to environmental contaminants and associated health concerns, valorised in scientific publications or PhD thesis. Sometimes these HBM studies initiated additional research such as long-term follow up studies in the areas of concern (e.g. Belgian and Cypriot case studies).

Concerning impacts at **societal level**, returning accurate information about health impact of exposure from in ICS activities to residents is mentioned in the case studies of Belgium, Cyprus and Poland (Table 7). The results can contribute to awareness raising about the impact of certain factors on levels of exposure to environmental pollutants. The accompanying information that is provided on exposure sources and routes can also empower people to reduce exposure by making changes in personal choices. However, the subject can be very complex and difficult for a lay audience to understand. In the Belgian case study, more than 100 individuals asked for a personal consultation with the study physician, because they needed more information about the significance and implications of their results. Also, scientists and policy makers received a lot of questions during the public communication events. In Poland the case study also resulted in educational material and activities, available to parents, kindergartens and other community members.

At the **political level**, these case studies aimed to draw political attention to certain areas or to initiate remediating actions and create leverage for political decisions. The case study of Poland identified several participants in need of medical follow-up and assessment of potential sources of exposure. In that case study, as well as the case study in Portugal, results emphasised that actions in specific areas are needed to improve quality of life. The Belgian case study, using an analytic-deliberative process from the beginning and throughout the study, involving experts, local and national policy makers and local stakeholders, resulted in an improved communication between all actors and in an understanding of shared responsibilities (36). The policy uptake of the HBM-results, using the same analytic-deliberative approach, resulted in complementary action plans by the Flemish and local authorities. Short-term actions often consist of more detailed and focused environmental monitoring, while longer-term follow-up studies were organised for the case studies of Belgium and Cyprus. In the Belgian case study, a second HBM study was organised to further monitor exposure of the residents near the ICS and to evaluate the effectiveness of remediating actions. This second HBM study was more focused on the identified biomarkers of concern, based on results of the first study. In the case studies of Poland and Portugal policy advice based on the HBM-results was formulated by researchers, but no information was available about policy uptake. In the case study of Hungary, the results were mentioned in policy briefs and due to the acute nature of the risk, remediation was already initiated prior to the end of the HBM-study.

Table 7: Summary of the available information on impact of the six case studies.

Short term impact					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
Published					
Improved communication between authorities, industry and citizens and in shared responsibilities, elaboration and adjustment of the environmental monitoring (36)	Contaminated water source (groundwater) was not used and residents connected to source of water free from arsenic (measured data)			Improved communication between authorities and citizens (parents and preschool teachers), and in shared responsibilities about health status of children	
Other					
Awareness raising about the health impact of environmental pollution. More than 100 individuals asked for a personal consult with the study physician, because they needed more information.	To give residents more accurate information about the magnitude of risk to which they had been exposed	Remediation (cleanup of the red mud) was completed before the end of biomonitoring of metals in urine of school children.		The study identified 160 participants for which potential sources in their environment should be assessed an 6 participants for which medical care should be implemented. There is no information on the implementation of these recommendations.	
Long term impact					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
Published					
Additional research projects concerning locally grown food, sources of environmental pollution and exposure routes, a follow-up program on public health in the ICS region, additional research on local sources of PAHs and facilitating communication between local					

stakeholders (36)					
Other					
Building trust in the study results and in the local and Flemish authorities Actions reducing emissions (such as an inventory of emission sources, creating green buffer zones, optimizing spatial planning and traffic circulation) and measures stimulating a healthy life-style (such as informative sessions, awareness rising, brochures, website and health monitoring).	Two years after the discontinuation of exposure a follow-up study was initiated including nail arsenic measurements.			The study emphases that improvements of environment quality in Piekary ś lŃskie are necessary to assure expected quality of health in children and local efforts achieve the desired goals are to be continued. To continue informing parents and nurseries about environmental hazards of heavy metals and how behavior and life style can interact with exposure is important.	
Levels: scientific, societal, policy making					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
Published					

Policy uptake: use of an analytic-deliberative and iterative process, involving experts, policy makers and stakeholders (36). This resulted in an improved communication between authorities, industry and citizens and in shared responsibilities. Actions on elaboration and adjustment of the environmental monitoring, additional research projects concerning locally grown food, sources of environmental pollution and exposure routes, a follow-up program on public health in the ICS region, additional research on local sources of PAHs and facilitating communication between local stakeholders.					
Other					

Societal level: Contribution to awareness raising about the health impact of environmental pollution. Information on determinants of exposure can offer solutions for reducing exposure to environmental chemicals. Using an open and transparent communication strategy throughout the study helped building trust in the study results and in the local and Flemish authorities. However, the subject is very complex and often difficult to understand for a lay audience. More than 100 individuals asked for a personal consult with the study physician, because they needed more information. Also scientists and policy makers received a lot of questions during the communication events.	**Societal level:** Helped to give residents more accurate information about the magnitude of risk to which they had been exposed	The results were mentioned in policy briefs.		Obtained results helped community to understand how important is environmental hazard and individual prophylaxis to health status of preschool children. The research was accompanied by informational and educational activities addressed to parents, carers, educators of kindergartens and other members of the Piekary ślŃskie community. Printed educational materials were prepared, as well as an electronic information and educational package "How to protect children against lead and cadmium?" posted on the websites of each kindergarten. Information meetings were organized with the municipality's self-government and the kindergartens' directorates as well as two educational and information campaigns during local public events. Information on the implementation of the project was included in local and regional media.

Policy: Well-informed and socially robust policy actions of the Flemish government were complemented with a seperate policy plan initiated by the local authorities of the ICS. Actions on reducing emissions (such as an inventory of emission sources, creating green buffer zones, optimizing spatial planning and traffic circulation) and measures stimulating a healthy life-style (such as informative sessions, awareness rising, brochures, website and health monitoring).	**Policy:** Specific recommendations on further monitoring and remediating actions				
Involvement of stakeholders and local actors					
Belgium	**Cyprus**	**Hungary**	**Italy**	**Poland**	**Portugal**
Published					
		The established Committee ensured that technical guidelines, general information materials on the potential health risks and their prevention, and answers for frequently asked questions were readily available (34).		All interested were informed about the final results: - city authorities and kindergartens received a full report - parents received educational materials - parents of children with elevated heavy metal concentrations have been informed on necessity of contact with medical doctor (24)	
Other					

The human biomonitoring study used a community-based participatory approach: community members, practitioners, researchers and local authorities were involved in all aspects of the research process.					

4. DISCUSSION: LEARNING FROM EXPERIENCES

HBM studies are used to assess human exposure to environmental pollutants and their health implications, since internal levels of a pollutant typically reflect the overall exposure from different sources of exposure and exposure pathways (44, 45). The studies are also a key aspect of promoting surveillance and prevention measures from potentially harmful exposures to chemicals in the population, and for tracking progress in reducing public exposure to environmental chemicals (46). The use of HBM in environmental health policy and research has advanced rapidly in Europe but there are major challenges ahead that should be addressed.

COST Action IS1408 provided support for collaboration between international HBM experts and academic researchers to strengthen HBM capacity in Europe and improve data comparability. The network also involved all management, governing and administrative functions necessary for managing remediation and response.

The positive experiences as well as the challenges described by the six European case studies detailed in this paper, have potential to help promote HBM as a tool for exposure assessment in ICSs and design efficient HBM studies to answer research question and/or policy questions.

In the long-term, preparing a European Human Biomonitoring Plan for ICS, which will advance the use of HBM in environmental health policy development and evaluation of exposure levels, would be advantageous.

4.1. Positive experiences

Positive experience 1: HBM in ICSs helps in setting priorities

The case studies discussed in this paper illustrate that using HBM in ICSs helped in setting priorities in multiple topics, enhancing delineation of the concerns and remediation possibilities specific for the ICS studied. The HBM results refined the knowledge about the pollutants of concern by identifying those exposure biomarkers that are elevated in the target population compared to control populations, reference values, or health-based guidance values (priorities in exposure of concern). Combining these biomarkers of exposure with health data, preferably from the same study subjects, also enabled identification of the main health concerns associated with the measured exposure levels (priorities in health effects of concern for e.g. monitoring purposes or provision of specialist healthcare resources), supporting the prioritisation of remediating actions (priorities for policy actions) and/or providing guidance to future research and development activities (priorities for further research). Combining the biomarkers of exposure with (early) biomarkers of health effects also supported development of preventative health policy.

Positive experience 2: children as study population reflect local pollution

Choosing children and/or pregnant/breastfeeding women as a study population means choosing vulnerable sub-groups whose bodies and organs are still developing. Children also provide a good representation of the local environmental pollution, since they are not occupationally exposed and spend most of their time in the neighbourhood of their residence. Children are also usually more exposed (at least in terms of dose) to environmental pollution because they eat, drink and breathe relatively more per unit body weight compared to adults.

Positive experience 3: questionnaire data are useful to fine tune results

Using well-designed questionnaires offered opportunities to control sources of variability (e.g. season, time spent outdoors), to identify other determinants of exposure (e.g. diet, smoking, traffic) and vulnerable sub-populations, such as specific age groups, gender and socioeconomic groups. Since HBM data reflect aggregated sources and routes of exposure, well-designed questionnaires provided more details on additional sources at the ICS (other than the targeted industry: e.g. heavy traffic because of the ICS activities), on exposure routes relevant for the ICS (e.g. locally grown food) and on other non-ICS related sources (e.g. smoking). This additional information will improve the study results and can allow more targeted remediating actions to reduce exposure and differentiate towards more vulnerable populations.

Positive experience 4: a well-considered choice of matrix or a combination of matrices depending on the research questions to answer

Biological matrices of interest strongly depend on the physico-chemical properties of the pollutants, but also on the type and duration of the exposure. In the ICS studies analysed in this paper, choice of sampling matrix enabled differentiating between past and recent exposure and associating ICS activity patterns with measured levels of biomarkers of exposure. Blood and urine are the most frequently used biological matrices to measure internal doses of pollutants in human subjects. Some biomarkers are significantly influenced by time between exposure and sampling and multiple samples taken at different time points are often required to correctly classify exposure (44, 47). Hence, there are limitations to the utilisation of some biomarkers in urine and serum as estimators of mid/long-term exposure, a crucial issue for the evaluation of associated health effects (48). In the Portuguese case study, additional biomarkers exposure were measured in finger- and toenails and in hair samples. These different matrices usually reflect different exposure time-windows (short and long-term exposure) for the same biomarker of exposure, and can be used independently or combined. Urine, nails and hair can be sampled in a non-invasive manner, whereas blood requires invasive sampling. Compared to hair, nails are less easily contaminated, especially toenails since they are less frequently exposed to ambient air, metallic objects and other contaminating sources, such as dyes (49). In regards to persistent organic pollutants (POPs), a status of equilibrium between serum and fatty compartments is frequently assumed under fasting conditions and/or lipid standardization of the concentrations, although this approach might not always be adequate (50). Two additional human sampling matrices which are interesting for measuring long-term exposure to POPs, but non-used in the case studies selected in this paper, are adipose tissue and human milk. Adipose tissue is considered the main reservoir of POPs and, therefore, an adequate estimator for the evaluation of the long-term exposure (51) as well as an important biological matrix in the development of chronic non-infectious diseases, e.g. cancer and metabolic syndrome (52-54). However, it is clearly a non-accessible matrix for most HBM studies especially in ICS areas where population size is often limited. Human milk is used by the WHO to monitor levels of POPs in the population, because the high lipid content of human milk makes it very suitable for POPs measurements (55, 56). Using human milk as a sampling matrix limits the eligible participants to breastfeeding mothers, which is not recommended in ICS settings with limited population sizes.

Positive experience 5: use local data for optimisation of the study design

Before setting-up an HBM study as part of monitoring potential exposures associated with an ICS, collecting available information on industrial activities, emissions, contaminant levels in environmental media, or using validated computer models to calculate dispersion of pollutants and collecting available health data all proved very useful when defining the study area, selecting appropriate biomarkers, exposed groups and other aspects of the study design. Since documented data are often fragmented or unavailable and researchers performing the study are not always familiar with the local area and history, involvement of local stakeholders from the beginning of the study can add valuable local knowledge to the project, improve the study design and ultimately the success of the study.

Positive experience 6: combining exposure makers with biomarkers of early effects can help in assessing early health damage

Measuring not only biomarkers of exposure, but biomarkers of early biological effects in the same study population as well is very useful for several purposes. First of all, combining biomarkers of exposure and effect in the same subjects allows to investigate associations between both, providing information on the potential health relevance of the actual exposure. Secondly, measuring biomarkers of early biological effects allows to develop preventive actions to improve residentsô health and quality of life before people get sick. Using these biomarkers of early biological effects also helps in avoiding long follow-up times waiting for severe health outcomes (57). A side note on this is that many early markers are not clinical markers, which can complicate interpretation at the level of the individual.

Positive experience 7: involving local stakeholders builds knowledge, confidence and shared responsibilities

Local stakeholders can also be very important for motivating residents within the vicinity of the ICS to participate in HBM studies and other research activities. This early involvement of stakeholders also helps to build confidence in the study results, to get support for remediating actions and to take on responsibilities for implementing these remediating actions when the study is completed. Local stakeholder participation should be incorporated in policy planning irrespective of the source encouraging this engagement, which could be due to state actions or bottom-up mobilization of communities (58).

Positive experience 8: communicating results serves awareness raising and agenda setting

When communicating modelled exposure risks, messages can become impersonal with a tendency to talk about theoretical constructs of populations and sub-populations. In this regard, there is a need for studies assessing the perception and attitudes of the general population towards the exposure (59), which can be of help inform e.g. HBM studies and public health interventions (60). Human biomonitoring measures indicators of exposure at individual-level within identified population groups and therefore makes the pollution personal (21, 36). A dialogical risk communication and reporting back study results to participants or the general population might result in larger attention and understanding by society of environmental health topics, creating opportunities for empowerment and awareness raising. This strategy should be carefully designed to meet the population´s requirements (61), particularly vulnerable groups, which frequently need tailored approaches to risk communication and remediation actions (62, 63).

4.2. Challenges in performing HBM in ICSs

In addition to sharing positive experiences, the WG2 discussions also revealed several encountered difficulties in using HBM for assessment of ICSs. The potential on successful development of the study can significantly be enhanced by taking these challenges into account before planning an HBM study in an ICS. In this section the challenges that most frequently emerged in the analysed case studies are identified and provided with solutions to tackle them.

Challenge 1: study populations of limited size obstruct convincing results
One of the major challenges when performing HBM in ICS is the size of the study population. Residential areas near ICS can be very limited in population size, making it difficult to recruit a sufficient number of participants for robust statistical analysis. For reliable biomarker reference values that characterise a population at least between 100 and 200 participants are needed (64). This issue also hampers the evaluation of exposure of vulnerable population sub-groups such as children, patients with chronic diseases, or pregnant women. This challenge might not always be possible to overcome. In case of limited number of residents near the ICS, attention should be paid to avoid strong triage in the eligible population to participate and research questions to be answered should not be overambitious.

Challenge 2: some sub-groups are difficult to recruit
Some population sub-groups, such as people with a low attained level of education, low family income or belonging to specific ethnic groups are often underrepresented in HBM studies because of difficulties in recruiting them. Although this is a general challenge for HBM studies and other types of research, ICS studies are even more challenged, as low income and socially deprived population sub-groups are likely to be a significant proportion of the population living in the vicinity of ICSs. This can be an obstruction to obtaining a representative study population or limits analytical capabilities such as exploration of sociodemographic determinants. A better knowledge of the barriers for participating in these studies specific for the locally targeted populations and help from the local community is very important in order to increase participation of these groups (65). This would also allow to better assess the potential unequal distribution of health impacts related to ICS within the population. Some of the case studies discussed in this paper, experienced working with children as study population as an advantage because they better reflect local environmental pollution compared to adults. However, recruiting children can also be challenging e.g. with respects to, getting ethical permission. A less invasive study design (e.g. urine, hair or nails as matrix, sampling in a comfortable and trusted environment, short questionnaires, etc.) can offer a solution.

Challenge 3: availability of validated and representative biomarkers
For all case studies discussed in this paper, validated and well-known biomarkers were at the disposal of the researchers, representative of the known environmental pollution associated with the ICS. However, progress of industry and technology generates new emerging chemicals, for some no validated biomarkers are yet available.

Challenge 4: the most suitable matrix of biomarker measurements can limit access of part of the residents to participate the study
The choice of matrix can also be a weakness, in case the ideal matrix for the temporal variation in exposure does not match with the choice of matrix to facilitate subject recruitment. Blood and adipose matrix (more informative for a medium-long term exposure) require an invasive sampling approach, which is not easily accepted by participant subjects in an HBM study, especially when children are involved. Choosing cord blood as a matrix implies only pregnant women can participate, strongly restricting the number of eligible participants. This restriction is even stronger when human milk is used as matrix, because this limits the eligible participants to women who gave birth and opt for breastfeeding their baby. The limiting effect of these matrices on recruitment is less, if the population size of residents living in the ICS is larger. When difficulties in recruitment can be expected, special attention should be paid to involvement of stakeholders, who can help with communicating the planned study and motivating residents for participation.

Challenge 5: relevance of the observed concentrations for health risks
Interpretation of the HBM results in terms of health risks is not always straight forward. For some biomarkers of exposure HBM health based guidance values for biological matrices are available such as the HBM-I and -II values from the German Human Biomonitoring Commission (41) or Biomonitoring equivalents (42). For many other compounds these guidance values do not yet exist or are still under discussion due to multiple or changing threshold values. Deciding whether the measured levels of biomarkers of exposure indicate the necessity of some form of public health intervention is often fraught with difficulty and uncertainty. Also, when personal results are communicated to the participants, not being able to inform about implications for peopleõs health with certainty can make the message very complex and difficult to understand. Linking biomarkers of exposure with measured biomarkers of effect by statistical analysis of exposure-effect associations can help inform the messaging around project findings.

Challenge 6: policy uptake of the results
In some of the case studies, policy uptake of the HBM results by the competent authorities to implement actions to reduce exposure of local residents was also experienced as a difficulty. In the Belgian case study, a participative approach was used, involving local stakeholders as well as representatives of the Flemish government throughout the entire study, working together with experts and researchers on policy uptake of the study results. To be able to achieve this, efforts are needed in open and transparent communication with all involved parties as well as willingness and mandates to participate are required from the authorities.

Challenge 7: how to deal with exposure to mixtures of pollutants?
Another challenge for current HBM research is that most of the studies deal with risks related to individual chemicals of interest. However, people (including those individuals residing close to ICS) are usually exposed to complex mixtures of pollutants, which might present synergistic interactions (66). Furthermore, exposure to chemicals of concern from a particular ICS might also interact with baseline exposures to other pollutants (e.g., organochlorine pesticides, metals), that are frequently found in the general population. In this regard, several statistical (67) and biological approaches have been proposed (68). There is not yet a good solution to deal with the total chemicalõs body burden.

5. Final conclusions and recommendations for HBM in European ICSs

Since human biomonitoring is becoming more frequently used for exposure assessment in ICSs all over Europe, a European protocol and guidance document for HBM in ICS would be useful. This could advance the use of HBM in local environmental health policy development and evaluation of exposure levels.

Based on the experiences of and the discussions with members of the working group ŒExposure assessmentô of the Industrially Contaminated Sites and Health Network (ICSHNet) COST Action, the following recommendations should be noted.

1) Study population of sufficient size: The study population should be of sufficient size to be representative for the area and to provide sufficient statistical power to draw conclusions. It has been shown that between 100 and 200 participants are needed at least to get reliable exposure distribution data.
2) When possible, avoid research triage in the study design: In case of small populations living in the affected area, we must be careful not limit the eligible population to

participate in the study too much by setting strict inclusion criteria (for example, to consider only pregnant women or a narrow age range), unless there is a very specific targeted study population.

3) Study design that correctly evaluates the exposure time-windows of interest: the periods when the industrial emissions occurred/still occur in relation to (a) the time when the HBM study is carried out, (b) the validity of the exposure biomarker as to integrate the relevant exposure routes and signal past or recent exposures, (c) the capacity of the biomarkers of effects, to capture the early effects of relevant exposures and (d) the time when the different health effects are expected to appear.
4) Smart choice of sampling matrix: A combination of sampling matrices (blood, urine, hair, nails, é) reflecting short- and long-term exposure should provide a more complete characterisation of the exposure and to allow comparison of measured biomarker levels with activity patterns of the ICS.
5) Use harmonized and validated questionnaires, spatial data and environmental monitoring/modelling to increase the utility of the study: Supplementing the biomarker measurement with questionnaire data widens the number of questions that the study can help inform, many of which are policy relevant. Questionnaire data can allow identification of additional sources in the ICS, of relevant routes of exposure for the ICS and of specific vulnerable sub-groups at the ICS. As stated by David Briggs (9): "What determines levels of exposure is consequently not just the distribution of pollution within the environment, but also human behaviours and lifestyles, and thus the sorts of exposure environments in which people spend their time. By the same token, exposure is not only an environmental process; it is also a social, demographic and economic one."
6) Combine biomarkers of exposure with biomarkers of (early) effects to get more information on the health relevance of the measured exposure
7) There is a strong need for a harmonized approach on advanced biomarkers and/or statistical techniques to deal with exposure to multiple compounds or mixtures.
8) Use a participatory approach: It is advised to actively involve authorities and local stakeholders from the beginning of the study to include local knowledge, gain local support and obtain commitments for policy uptake of the results.
9) Invest in communication of the study results: Communication of the study results to participants, public and stakeholders is a crucial part of an HBM project. When done well it promotes trust and mutual understanding. So, besides publishing the results in scientific articles it is important to present the results to people involved and offer them opportunities to discuss their results and their significance at an individual and collective level.
10) HBM also offers opportunities for monitoring exposure of residents near the ICS over time and contribute to evaluation of efficacy of exposure management efforts.

Depending on the type of biomarker measurements and the choice of study design, HBM studies can become expensive. In situations where limited resources are available, like in many low-income countries, other assessment methods might be more feasible.

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