RASSEGNE E ARTICOLI

Methods and data needs to assess health impacts of chemicals in industrial contaminated sites

Metodi e dati necessari per la valutazione di impatto sulla salute delle sostanze chimiche nei siti industriali contaminati

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ABSTRACT

BACKGROUND: human exposure to mixtures of chemicals of toxicological interest, typically found in industrial contaminated sites (ICSs), has been associated with a broad range of different health outcomes. Deprived population groups endure most of the burden of disease and premature death associated to the exposure to those pollutants. Characterising the impacts on health of an ICS is a challenging process. Currently the two main methodological approaches used are Human Health Risk Assessment (HHRA) and Environmental Epidemiological (EE) studies.

OBJECTIVES: review existing guidance and scientific evidence for HHRA and EE studies applied to contaminated sites that orientate in selecting the most suitable methodological approach for characterising health impacts in ICSs according to the site characteristics, and the availability of environmental, health and sociodemographic data.

RESULTS: HHRA has evolved into a more holistic approach, placing more emphasis in planning, community involvement and adapting the dimension of the assessment to the problem formulation and to the availability of resources. Many different HHRA guidelines for contaminated sites has been published worldwide, and although they share a similar framework, the scientific evidence used for deriving reference values and the variet of policy options can result in a wide variability of health risk estimates. This paper condenses different options with the recommendations to use those tools, default values for environmental and exposure levels and toxicological reference values that most suit to the population and characteristics of the ICSs under evaluation.

CONCLUSIONS: the suitability to use one or another approach to assess the impact of ICSs on health depends on the availability of data, cost-benefit aspects and the kind of problem that needs to be answered. Risk assessment based on toxicological data can be very rapid and cheap, providing direct informa-

WHAT IS ALREADY KNOWN

- **Chemical pollutants from ICSs represent a persistent environmental burden of past and current unsustainable practices and, a large public health problem worldwide, but especially in low and middle-income Countries.**
- **There is an urgent need to identify the most suitable interventions aimed at prevention in affected communities, to facilitate a better social and economic development, while minimising population exposure to harmful compounds associated with an ICS.**

WHAT THIS ARTICLE ADDS

- **Different methodological approaches for characterising the impact on health of ICSs have been reviewed and the main critical issues highlighted.**
- **Information derived from an accurate exposure assessment (EA) is determinant for adopting preventive public health measures but also for defining additional health research. EA is a crucial step useful for both approaches (risk based and epidemiological studies).**
- **Epidemiological analytical studies can be informative and very useful for quantifying dose-response relationships directly in the affected ICSs resident populations; quantitative risk assessment offers a more rapid, low-cost approach to assessing the potential impact.**

tion when the intervention to protect the health of population is urgent and no suitable dose-response functions are available from epidemiological studies. Conducting EE studies provide a deeper insight into the problem of the exposure to industrial pollutants that do not require extrapolation from data obtained from toxicological studies or other population, addressing the community concern's more directly. Complementing the results obtained from different approaches, including those from public health surveillance systems, might provide an efficient and complete response to the impact of ICSs.

Keywords: industrially contaminated sites, human health risk assessment, environmental epidemiology, exposure assessment, chemicals

RIASSUNTO

INTRODUZIONE: l'esposizione umana a mix di sostanze chimiche di interesse tossicologico, tipicamente presenti nei siti industriali contaminati (ICS), è stata associata a una vasta gamma di esiti sanitari. I gruppi di popolazione deprivati sopportano gran parte del carico di malattie e morti premature associate all'esposizione a tali inquinanti. Caratterizzare l'impatto sulla salute dei siti industriali contaminati costituisce, dunque, una sfida importante. Al momento attuale i due principali approcci metodologici utilizzati sono: la valutazione del rischio per la salute umana (HHRA) e gli studi di epidemiologia ambientale (EE)

OBIETTIVI: effettuare una revisione dell'evidenza scientifica e delle raccomandazioni diposnibili per HHRA e gli studi EE riguardanti i siti contaminati al fine di orientare la selezione degli approcci metodologici più idonei per la caratterizzazione degli impatti sulla salute negli ICS secondo le caratteristiche del sito e sulla base della disponibilità di dati ambientali, sociodemografici e sanitari.

RISULTATI: HHRA si è evoluto in un approccio più olistico, dando particolare enfasi alle fasi di pianificazione, coinvolgimento delle comunità e adattando la dimensione del processo valutativo a quella della formulazione del problema e della disponibilità di risorse. Nel mondo sono state pubblicate molte linee guida per l'HHRA riguardanti i siti contaminati e, sebbene abbiano caratteristiche analoghe, l'evidenza scientifica usata per derivare i valori di riferimento e le diverse opzioni di politica sanitaria (scenari) possono portare a una grande variabilità di stime di rischio/impatto sanitario. Il presente articolo integra le diverse opzioni e raccomandazioni disponibili al fine di individuare gli strumenti di valutazione, i valori standard ambientali, i valori di riferimento l'esposizione e quelli tossicologici che meglio rispondono alle caratteristiche della popolazione e del sito industriale oggetto di indagine.

CONCLUSIONI: L'appropriatezza di un approccio piuttosto che di un altro nella valutazione dell'impatto di un ICS sulla salute dipende dalla disponibilità di dati, dal rapporto costi-benefici e dal tipo di problema a cui si vuole dare risposta. Il processo di valutazione del rischio basato su dati tossicologici può essere rapido ed economico, e offrire informazioni dirette quando l'intervento per tutelare la salute della popolazione è urgente e gli studi epidemiologici non forniscono funzioni dose-risposta utilizzabili. Condurre studi EE può dare una visione più approfondita del problema dell'esposizione a inquinanti industriali, affrontando in modo più diretto le preoccupazioni della comunità considerata, senza la necessità di estrapolare i dati da studi tossicologici o da altri contesti. Integrare i risultati ottenuti da diversi approcci valutativi, , inclusi quelli prodotti da sistemi di sorveglianza della salute pubblica, può offrire una risposta più efficace e completa al tema dell'impatto dei degli ICS.

Parole chiave: siti industriali contaminanti, valutazione del rischio per la salute, epidemiologia ambientale, valutazione dell'esposizione, sostanze chimiche

INTRODUCTION

Pollution is the leading environmental cause of disease and premature deaths in the world today.[1] According to the World Health Organization (WHO), almost 1.5 million deaths per year in the WHO European Region are attributable to environmental risks that could be avoided.[2]

The expansion of industry and progress of chemical technology have significantly improved the world's standard of living. However, the sector has also played a relevant role in the degradation and contamination of the environment. A recent report published by the Joint Research Centre on the *Status of local soil contamination in Europe*,[3] reveals the possible existence in all 28 EU Member States of around 2.8 million sites where polluting activities took or are taking place, affecting soil, with more than 650,000 sites identified and registered in national and/or regional inventories. Industrial activity is also responsible for a large pollution of sediments, ambient air and water (surface and ground water), as well as in the generation of waste.[4] The European population living close to contaminated sites is significant, with an estimated density of 5.7 contaminated sites per 10,000 inhabitants, based on soil contamination data.[5]

WHO provided a general operational definition of contaminated sites, based on a public health perspective, as "areas hosting or having hosted human activities which have produced or might produce environmental contamination of soil, surface or groundwater, air, and food chain, resulting or being able to result in human health impacts".[6] This operational definition, restricted to contamination generated by industrial activity (including waste), was adopted by the COST Action on *Industrially Contaminated Sites and Health Network* (ICSHNet) (https://www.icshnet.eu/) launched in 2015.

A recent comprehensive systematic literature search identified 655 epidemiological studies investigating the health of residents living nearby industrial contaminated sites (ICSs).[7] It shows that industrial pollution and accidental spills are associated with increased cancer incidence (leukaemia, mesothelioma, thyroid, lung, brain, renal, stom-

ach, bladder, soft-tissue sarcoma, skin), respiratory diseases, adverse birth outcomes, and premature mortality, amongst other harmful effects. Research conducted in India, Indonesia and the Philippines suggests that exposure to toxic pollutants from ICSs may be equally or more harmful to human health than certain infectious diseases like malaria, accounting for up 828,722 DALYs (Disability-adjusted Life Years) among the 8,629,750 persons posed at risk in the 373 ICSs of the three Countries.[8] Particularly relevant is the expected detrimental impact of ICSs on children's health, for whom the WHO has estimated that as much as 33% of the global burden of disease, is attributable to environmental risk factors, versus the 24% for the adult population.[9] A recent study, focused on the environmental burden of childhood disease in the 28 Countries of the EU, proved that the seven selected risk factors (PM_{10}, $PM_{2.5}$, ozone, second-hand smoke, dampness, lead, and formaldehyde) were responsible in overall for around 211,000 DALYs annually in children.[10]

Children living in poor and socially deprived regions are most severely affected as they have limited access to healthy housing, clean air and water, healthy eating pattern, sanitation services, health care or education. Special concern raises the exposure of children to hazardous chemicals classes such as heavy metals, persistent organic pollutants (POPs), pesticides and air contaminants. Heavy metals and lipophilic POPs cross the placenta, and favour transfer into breast milk, usually the primary source of food for infants. Heavy metals and POPs are known to interfere with the normal growth and development of children.[9]

These findings show that chemical pollutants from ICSs represent a persistent environmental burden of past and current unsustainable practices and a large public health problem worldwide, but especially in low and middle-income Countries.[11,12]

Characterising the impacts on health of ICSs is a challenging process, with many elements that need to be taken into account as described by Iavarone and Pasetto.[13]

As part of the main goals of the ICSHNet, this paper aims to review the state of the art regarding the two main current methodological approaches for characterising the health impacts of chemicals in ICSs: risk based approach and epidemiological studies.[14] Special attention has been paid to those aspects that can orientate public health practitioners on choosing the most suitable option according to the site characteristics and the availability of environmental, health, and sociodemographic data. Although there are aspects in the proposed methodological steps common to all population subgroups, the review is focused mainly on people residing close to an ICS, and at a minor extent on people living there and working in the industrial premises, as occupational exposure and health is much broadly regulated and under control.

STRATEGIES FOR CHARACTERISING THE IMPACT ON HEALTH OF ICSs

HUMAN HEALTH RISK ASSESSMENT APPROACH (HHRA)

Generally speaking, HHRA focusses and builds on the quantitative estimation of the probability of the occurrence of disease as a function of dosage of exposure to a given agent, typically a chemical one. The classical four step framework of risk assessment[15,16] (i.e., **1.** hazard identification; **2.** dose-response assessment; **3.** exposure assessment, and **4.** risk characterisation) has recently been reformulated into a more holistic approach, placing more emphasis in key elements such as planning and scoping, problem formulation, and improving public, stakeholders and community involvement. A final step has also been added to connect the purpose for which HHRA was conducted with the conclusions, and its strengths/limitations.[17,18]

A recent review conducted by Xiong et al. (2018),[19] showed that 90% of the total identified published studies conducted in ICSs for quantifying impacts on health (No. 92), used the framework approach of HHRA, either by calculating the hazard quotient for non-cancer endpoints (25%) or by estimating the probability excess risk of cancer (65%).

HHRA is an iterative process in which data gaps are identified and addressed, and key stages are successively refined. The scope of the HHRA (i.e., the level of effort) and the number of iterations will depend on the complexity of the site, the overall goals of the assessment, the extent of available data, timeframe and the results or outcomes of the initial steps.[20] Health Canada proposes the following three levels of details and complexity of HHRA attending to the data demand:[18]

A. screening-level risk assessment: it is mostly a qualitative approach used to identify whether sources, relevant exposure pathways, and exposed population may exist. Alternatively, it may also include comparison of environmental concentrations with relevant numerical criteria to assess whether potential risks might be anticipated to be significant, or to establish a relative risk ranking among the contaminants, sites, or potential exposed population subgroups;

b. preliminary quantitative risk assessment (PQRA) commonly carried out based on relatively limited site information to provide an approximate, but conservative (worst-case scenario) estimate of potential human health risk;

c. detailed quantitative risk assessment (DQRA) implies a more comprehensive site characterisation and a more representative or site-specific exposure characterisation. DQRA should be conducted only when the benefits for reducing uncertainty in the estimates risk for supporting decision-making and related communication strategies compensate the costs and resources needed to collect additional data.

The U.S. Environment Protection Agency (U.S. EPA) has done extensive work in risk assessment. The report entitled *Framework for Human health Risk Assessment to Inform Decision Making*[17] provides a detailed list of guidance and manuals that EPA has developed for different topics since 1983. This updated guidance also incorporates the recommendations issued in 2009 by the National Research Council (NRC)[21] on the original design of risk assessment, and the opportunities for improving its utility. A comprehensive set of links to EPA free access publications and tools is also available at EPA's Risk Assessment Portal (http://www.epa.gov/risk/) or more specifically for HHRA at EPA ExpoBox (https://www.epa.gov/expobox). The general output of the process applied by US EPA, especially as part of site remedial investigations, refers to numeric estimate of theoretical risk, focusing on current and potential future exposures and considering all contaminated media regardless if exposures are occurring or are likely to occur. By design, it generally uses standard (default) protective exposure assumptions when evaluating site risk. The US Agency for Toxic Substances and Disease Registry (ATSDR) also developed a procedure called Public Health Assessment (PHA) that incorporates similar steps of the DQRA process, but differing from the US EPA approach by focusing more closely on site-specific exposure conditions regarding past, present or future polluting activities affecting particular communities.[22] In addition to environmental and exposure data, PHA also incorporates specific community health concerns, and any available health effects data (toxicological, epidemiological, medical, and health outcome data) to provide a site-specific evaluation, and identify appropriate public health actions such as: medical monitoring, health education, health studies and/or health surveillance and substance-specific research.[22]

A wide variety of other guidance on how to conduct HHRA in contaminated sites is offered by different international, national, and regional health and environmental agencies (some examples in Table 1S, online supplementary material). Many European Countries have either their own models, or screening values derived by their models to highlight when intervention is needed or the possibility of an unacceptable risk may occur. Examples of these are the UK Contaminated Land Exposure Assessment model (CLEA)[23,24] and the Dutch CSOIL model.[25]

A slightly different approach used for HHRA considers this process as the systematic evaluation of changes in the population health resulting from modifying the distribution of population exposure to a risk factor or a group of risk factors.[26,27] The so-called **comparative quantification of health risk assessment** involves calculating the population attributable risk, or where multi-level data are available, potential impact fraction, defined as the proportion of future burden of disease or injury that could be avoidable if current or future exposure levels to a risk factor or group of risk factors are reduced to hypothetical scenarios. Maldonado and Greenland (2002)[28] and Murray et al. (2003)[26] refer to those scenarios as counterfactual, and they imply a reduction in the distribution of a risk factor in the population to a theoretical minimum level (zero or as low as possible), or to a better achievable level (i.e., by 5%, 10%, 20% or 30%). This is a population-based approach, which aims at assessing changes in the specific studied population, using epidemiological methods and evidences. Concentration-response functions (CRFs), derived from epidemiological studies, are periodically revised by WHO working groups.[29] Available CRFs is restricted to some pollutants, with problems in generalising evidences to particular exposure situations, such as those arising in ICSs.

A recent work by Hänninen et al.[30] proposed a unified population approach to environmental burden of disease, providing formulas for both epidemiological and toxicological dose-response functions.

ENVIRONMENTAL EPIDEMIOLOGICAL STUDIES

Environmental epidemiological studies (EE) are used to identify and quantify associations between exposure to environmental factors and the health effects, and/or to assess the health profile of populations living in contaminated sites.

In the context of ICSs, descriptive epidemiological studies (e.g., ecological studies, community health assessments, etc.) are able to generate aetiological hypotheses by describing how much the occurrence of health outcomes in populations and subgroups of population residing in a geographic (small) contaminated area differs from that of suitable reference populations.

When the aim is to assess and quantify associations between environmental exposures and health effects, analytical epidemiological studies represent the most suitable approach as they allow verifying aetiological hypotheses by providing exposure-response relationships linking health effects and exposures to environmental hazardous chemicals accounting for the contribution of other possible risk factors like occupational exposures, socio economic and lifestyles factors.

A very recent literature review focused on the type of EE studies conducted in ICSs,[7] showed that most of available studies are descriptive (32.5%), cross-sectional (16.3%), or narrative review (14.8%), while analytical studies – case-control and cohort studies (9.6% and 8.4%, respectively) are much less represented.

Descriptive and analytical studies mainly differ by design, being based on aggregate data the first, and on individual data the latter, though they are not entirely mutually exclusive.[7]

Epidemiological studies have different aims respect to HHRA, and also different needs. Recently, Savitz has ad-

dressed this aspect, analysing in particular the choice between epidemiological studies and HHRA, with pro and cons.[31]
A third option is represented by the epidemiological surveillance that aims at monitoring the evolving patterns of the population health status.[12,14] Epidemiological surveillance (or public health surveillance) is based on an ongoing collection, integration, analysis and interpretation of data. It plays a key role in identifying harmful aspects and providing information for remediation. It can represent a useful tool of investigation when there is not a robust evidence of harmful effects of considered pollution, and/or when exposure data and scenario are not fully available and understood.[12]
In Countries where health information systems are established, the epidemiological surveillance of populations residing close to an ICS can represent an informative low cost approach to increase knowledge about the impact of industrial emissions.[31] In this context, the Italian SENTIERI study, based on the a priori identification of the health effects expected to be associated to the industrial activities, represents an example of epidemiological surveillance system used to monitor the health profile of populations living in contaminated sites of national concern for remediation. This kind of approach allows verifying the efficacy of preventive clean-up measures aimed at reducing the relevant exposures in the target populations.[32,33]

BACKGROUND INFORMATION FOR SITE DESCRIPTION

A first step, common to HHRA and EE studies, is to gather information about the nature, magnitude, and extent of contamination of a site and for identifying potentially exposed populations. This phase is well documented in many national and regional guidance documents and publications for categorising the soil contamination level and related human health risks,[16,34,35] but not widely available and well known in the context of public health. In summary, the main elements are:

- key geographic and geo-morphological data, and other features of the site (name and address or geographic location, map showing the distance from the site to the closest residence or potential future residence, physical hazards such as stacked drums, accessible chemical products, etc. that may constitute a public health concern);
- current and past activities conducted at the site, including industrial process description and associated waste generation, and dates of specific site operations or spills. These practices would allow for identifying a list of priority potential hazards released to the environment;
- previous and ongoing remediation activities or other risk management strategies implemented previously in the site;
- information on land use and natural resources at and near the site, including if possible mapping site conditions, the proximity to population areas, location of special vulnerable groups (schools, green parks, hospitals, residence for elderly people, among others), and information referring to uses of water, agricultural areas, and potentially affected biota;
- available environmental sampling data, indicating concentration of contaminants in water, soil, air, and food chain (biota), not only on-site but also that naturally occurring as a background concentration. It is also important to register the dates when samples were collected and analysed, and information about sampling representativeness and analysis methods used;
- demographic information in order to define size, characteristics, locations (distance and direction), and possible susceptibility of known population subgroups related to the site. In this respect, it is important to gather information on age, gender distribution, ethnicity, socioeconomic status, and occupational activities, if possible;
- main properties of the hazardous substances of potential concern related to current and past activities conducted at the site. It is important to identify, the health effects potentially related to the contaminants based on already available toxicological and/or epidemiological studies, and data on toxic-kinetic information that allows defining the main mechanism for the chemical to enter the human body and to exert their adverse effects in target tissues and organs. In that respect, it is worth mentioning the systematic literature review conducted under the SENTIERI project, where multi-outcome health effects were identified related to many chemicals or mixtures encountered in national priority contaminated sites in Italy;[33]
- health data recorded through local, regional and/or national information systems that may reveal whether people living or working near an ICS are experiencing adverse health effects at a rate higher than would be expected to occur if the exposure/s of interest was/were not present.

DATA NEEDED FOR CHARACTERISING HUMAN EXPOSURE

Critical to the process of characterising the potential impacts on health is the evaluation of exposure, defined as the contact of an individual with a pollutant for specific duration of time.[36,37] Conducting an accurate and complete exposure assessment (EA) represents the basis to define the magnitude of the problem in terms of identifying the potentially affected population, and the nature and extent of environmental contamination at and around the site.

QUANTITATIVE EXPOSURE ASSESSMENT

Quantitative EA can be conducted by either direct dose assessment (biomonitoring), or by indirect methods (environmental monitoring, modelling, and questionnaires).

Although direct measures of exposure are considered the best approach for assessing the effect of a specific substance on the target population, indirect measures have greater utility for linking population health to specific pollution emission sources.[37,38] Indirect exposure methods may also be preferable in epidemiological studies if larger study populations are included. These methods have rapidly evolved in the last years, especially due to the increasing use of Geographical Information Systems (GIS) and computer models to simulate atmospheric dispersion[20,38,39] and soil/water interaction and flow.[40]

BIOMONITORING

Biomonitoring directly reflects the total body burden or biological effect resulting from exposure to environmental contaminants, their metabolites, or early markers of health effects, in body tissues or other biological specimens (such as blood, urine, hair, nail).[41,42] Biomonitoring therefore allows integrating different sources of contamination, routes of exposures (ingestion, inhalation, dermal absorption) and environmental media (air, soil, water and food-chain contaminants). Biomonitoring also allows direct assessment of the distribution of risk factors in the population, incorporating individual variability in exposures, as well as the differential ability to metabolise and to transform chemicals into the body tissues. In general, biomonitoring results in an estimate of cumulative exposures from a past period, ranging from hours (exhaled breath) to years (nails).[20] Biomonitoring weaknesses include its technical difficulty, high costs, frequent lack of a reference value for the contaminant concentration in bodily material, and a difficulty to inform about future exposures.[20,41] Biomonitoring cannot generally reveal exposure sources, routes, or duration of exposure, so environmental monitoring remains crucial for the development of targeted policy actions.[9,42] A recent publication by Colles et al. (2019, in press)[43] recorded some lessons learnt from biomonitoring studies conducted in ICSs from five European Countries.

INDIRECT QUANTIFICATION OF EXPOSURE ASSESSMENT

One of the most accurate procedures for indirect exposure assessment involves identifying potential exposure pathways, defined as the course that the contaminant takes from its source to the portal of entry to the human body.[9,18] This includes characterising the following five components:[16,18,22]

1 source of contamination;
2 affected environmental media (i.e., water, soil, air, food chain) and fate and transport of pollutants between media;
3 exposure point or area where people get in contact with contaminants (e.g., drinking water well, residential yard);
4 mechanism for the chemical to enter the human body by one or a combination of exposure routes (by ingestion, inhalation, or dermal contact);
5 potentially exposed population (e.g., residents, children, workers).

In undertaking indirect EA, it is necessary to account for the potential exposure by all possible pathways, considering the different population subgroups and factors such as age, behaviours, occupation and activity patterns that may affect exposure and vulnerability to contaminants. For example, children may have increased vulnerability to some types of toxin but may also have greater exposure because of greater hand to mouth contact and mouthing behaviours.[22,34,44,45] In this case, description of exposure pathways would need to account for all possible exposures resulting from ingestion, inhalation or dermal contact with soil contaminants.[9,22,35] The occupational exposure pathway may involve workers that, at the same time, are residents of the affected area, and this double exposure needs to be addressed. The analysis of occupational exposure pathway requires some specific considerations and references values that are out of the scope of this article more focused on residents of ICSs.

Complete exposure pathways are those where all five elements reported above are clearly identified. Potentially exposure pathways imply that some uncertainty exists about some of those elements, and further information is needed. If the EA concludes that nobody is exposed, then no further evaluation is required. It would be convenient, nonetheless, to explain the rationale for excluding any likely exposure, and communicate the conclusions to the affected stakeholders (e.g., citizens, policy makers) in a comprehensive and transparent way at the earliest possible, as the perceived risk can lead to stress and ill-health. The next step is to quantify the magnitude, frequency, duration and time pattern of contact with a contaminant for each of the identified complete exposure pathway.[9,16-18,22]

Data needed about sources, affected environmental media, exposure points and populations can be collected through the review of site background information previously described. However, additional site-specific information is normally required to better define the fate and transport of contaminants in the environment, such as local geologic, topographic, and climatic conditions. This information is crucial for drawing the most complete exposure model that comprises all potential pathways.[16,18,22] ATSDR and US EPA provide wide guidelines and information about environmental data needed for conducting exposure assessment in contaminated sites[16,22,46]

In order to characterise the exposure model, the following elements are necessary to be considered: data from environmental sampling including the background concentrations, modelling, and exposure factors.

Data from environmental sampling are essential inputs

for accurate EA since they are often direct measurements of exposure point concentrations. In many cases, different agencies or stakeholders might have generated these data for purposes other than public health evaluations.
Collecting information about the sampling strategies and the validity of the sampling and analytical methods that support available environmental data is therefore important for public health applications.[18,22,47,48] Information about this can be found in several EU regulations that address methods for identifying a number of chemicals in soil, water, air, and foodstuff (e.g., Regulation 333/2007).[49] Still, the best source of information for assessing the validity of environmental sampling and analytical data is from the experts responsible for collecting and reviewing that data. These individuals often can give insights on the strengths and weaknesses of environmental sampling projects.[22] Promoting partnership between experts from different disciplines (e.g., environment, public health, analytical chemistry, and geology) is critical for a successful evaluation of health impacts of ICSs.[12] Public health experts should acknowledge the uncertainty level of environmental sampling data for estimating exposure point concentrations and evaluate if public health conclusions can be drawn from such datasets, or indicate whether additional sampling is required.

Understanding the contributions from **background concentrations** in the environment – defined either as naturally occurring ambient levels of substances (e.g., arsenic due to the local geologic conditions), or anthropogenic levels of substances which are not related to site industrial emissions (e.g., benzene in ambient air due to city's motor vehicle traffic) – is an important element of the EA analysis. In general, site-specific background data are more reliable but data for the region, state, or nation might also be applied[22] (e.g., in the UK, background air pollution maps are available than can be consulted as a source of information, as well as background levels of certain soil contaminants). Background concentrations need to be considered in the final calculations of the potentially exposure dose (see any chapter on exposure assessment from any of the guidance proposed in Table S1). However, background concentrations are also useful in a first stage to analyse the nature of the contamination and the validity of the data collected. If concentrations of environmental samples are consistently lower than background concentrations, there is a possibility of bias in the sampling approach conducted or in the selected background levels. If valid and representative sampling data are consistent with background concentrations, this could mean that there is no source significantly contributing to the contamination of the environmental media of concern.[20,22]
Unfortunately, environmental sampling data, even validated, might be limited to very specific locations and/or time frames. In such circumstances, **models or statistical tools** have been proved useful in estimating the nature and extent of contamination for other areas or time.[20,23-25,39,50] For example, past exposures can be modelled from available historical sampling data for a particular area. Models are also applied to assess levels of contamination by interpolating among observed values, to forecast the fate and transport of environmental contaminants in various media (e.g., air, groundwater, surface water, and soil), or to illustrate the contamination trends based on statistical analyses of data. A broad range of models and statistical tools are available to estimate levels of environmental contamination (see Table S2, online supplementary material). Hoek et al. (2018)[39] conducted a critical review of models most frequently used in the context of ICSs in several Countries within the ISCHNet, most of them in the framework of soil regulation.
All models represent a simplification of actual environmental conditions. For this reason, when using modelled data, it is important to review and specify the assumptions and uncertainties inherent to the model for formulating public health statements. Reviewing modelling studies requires interdisciplinary work, with experts from different sectors.

Exposure factors are factors related to human behaviour, and other characteristics that are able to affect the individual's exposure to a contaminant. For example, a child's exposure to air contaminants through inhalation is determined by factors such as the duration of time spent in different indoor and outdoor locations, and the child's breathing rate during the exposure period.[9] The main exposure factors affecting indirect quantitative EA are:[16,20,22]

- substance concentrations at the exposure point, obtained by environmental monitoring or modelling as described above. Different guidance documents provide recommendations on how to use this data, if as maximum concentration, or average or geometric media, etc.[16,22,51]
- intake rate, defined as the amount of a polluted environmental media to which a person is exposed during a specified period of time (e.g., amount of water or food ingested on a daily basis). It is also important to consider the bioavailability factor, which is the amount of a substance absorbed into a person's body, expressed as a percent of the total amount of a substance ingested, inhaled, or dermal-contacted that actually enters the bloodstream. For screening purposes, and as a worst scenario, the bioavailability factor is typically assumed to be one (i.e., all is bioavailable), but more accurate data can be obtained revising the toxicology of the harmful substances present at the site. Data on bioavailability can also be obtained from Denys et al (2012)[52] and Hamilton et al (2015).[53]

■ body weight, as people with lower body weights will receive a relatively higher dose of the substance than people with higher body weights.
■ exposure factor, derived by considering the following elements:
• frequency of exposure expressed as the average likely number of days in a year in which exposure occurs. The total dose of a substance can cause different toxic effects depending on whether the dose is administered as a high short dose or a lower long term dose;
• exposure duration, length of time a population has been exposed to site contaminants. This information can be estimated examining the site background information, ranging from acute effects (24 h/14 days), via sub-chronic (up to 90 days) to chronic (considerably more than 90 days). The phrases 'acute exposure' and 'chronic exposure' are also often used in the meaning of single exposure and repeated exposure, respectively;
• time of exposure used to express exposure in terms of an average daily dose that can be compared to health guidelines and toxicity study results. For non-carcinogenic substances, this parameter normally equates to the exposure duration (e.g., for a child exposed to a contaminant in a playground for 3 years, the time exposure would be 365 days/year x 3 years). For carcinogenic effects, doses are generally estimated by calculating an average daily dose during a lifetime (assumed by default to be 70 years[22,54] (e.g., time input parameter for carcinogenic effects would be expressed as 365 days/year x 70 years). This approach for carcinogens assumes that a high dose received during a short period is the same as a corresponding low dose during a lifetime.[54] As with all assumptions, it may not be applicable in all situations.

Accurate indirect quantitative EA would require gathering information for exposure factors tailored to the site populations of each ICS, obtained by conducting *ad hoc* questionnaires or from national or regional health population surveys. When selecting appropriate data, it is necessary to consider possible subpopulations or conditions that may affect EA, such as gender, age, health status, occupation, cultural practices, climate, site activities, season, region, or urbanization level. Some agencies have provided some standard default values (see Table 1) that can also be used, but potential bias (under- or over-estimation) might probably affect the final EA. The uncertainty associated to the use of default values needs to be reflected on the final report.
In quantitative EA, the outputs are expressed numerically, either in deterministic or probabilistic terms. The first approach provides a point estimate of exposure or dose from single value input variables, while the probabilistic one replaces point estimates with probability density distributions for each input parameters (i.e., median estimate, 95th percentile estimate, etc.). In this way, probabilistic approaches provide a better understanding of the variability of the exposure pattern observed within the affected population, but they are not easy to apply. Disadvantages stems from the little information normally available to create a probability distribution for many of the input variables (e.g., variability in individual habits), and the greater level of complexity required in the calculation process.[9,18,20,35]

QUALITATIVE EXPOSURE ASSESSMENT: INDICATORS

In the review conducted by Hoek et al. (2018),[39] the method more broadly applied for EA in epidemiological studies conducted in ICSs is based on a qualitative indication of proximity to industrial activities using the residence of affected people as a reference. Hoek et al (2018)[39] reviewed a total of 147 studies, 54 referring to hazardous waste sites previously analysed by Fazzo et al. (2017),[55] 41 to incinerators studies evaluated by Cordioli et al. (2013),[38] and another 52 additional studies corresponding to different type of ICSs identified by Hoek's research team. From that total number, 122 studies defined exposure either by the presence/absence of a source or the presumed delimitation of the ICS boundaries based on the compilation of historical data (53%), or by different metrics for distance, both in a continuous scale and by defining concentric areas around the site with arbitraries radios (47%). Only 12% of total studies used environmental modelling (mostly focussing on the air exposure pathway), 1% environmental monitoring and 7% biomonitoring. A very similar proportion among methods for exposure was identified in the review of data used in epidemiology surveillance studies in ICSs conducted by Martin-Olmedo et al. (2018).[12]
Distance is considered a good indicator for exposure as contamination from a source (e.g., chimney) is generally expected to decrease with distance. However, the assumption of homogeneous dispersion of contaminants can lead to errors, as local environment characteristics (e.g., meteorology, topography etc.) and the type of source can markedly affect how emissions disperse and are deposited.[12,38]
The use of residence as a proxy for exposure location is common practice in environmental epidemiology. Cordioli et al. (2013)[38] proposed to use geocoding as the most precise approach for determining residence position in comparison to full postcode or census block. Promoting maximum disaggregation of data is recommended in order to maximise information and minimise differential ecological bias. Cordioli et al. (2013)[38] also suggested taking into consideration temporal variability in exposure. This variability can be associated to both changes in source emissions over time or to residential mobility

REFERENCE/TITLE	SHORT DESCRIPTION	SOURCE*
US ATSDR. Public Health. Assessment Guidance Manual.	This appendix describes in detail the equations and methods used when estimating doses of exposure throughout different exposure routes, using default exposure parameters (e.g., exposure rates and durations). However, ATSDR recommends using more realistic exposure estimates if possible to reflect site-specific exposure conditions.	Appendix G: https://www.atsdr.cdc.gov/hac/phamanual/pdfs/phagm_final1-27-05.pdf
US EPA. Exposure Handbook (updated). US Environmental Protection Agency, Washington, DC, EPA/600/R-09/052F. Washington, DC, 2011.	Defaults values adopted and used at US Superfund sites. The latest edition of the Exposure Factors Handbook was released in 2011, but since October 2017, EPA has begun to release chapter updates individually. This new process allows risk assessors to get the latest information as new data becomes available.	https://www.epa.gov/expobox/about-exposure-factors-handbook.
Nordic Council of Ministers. Existing Default Values and Recommendations for Exposure Assessment. A Nordic Exposure Group Project 2011.	Report providing an overview of default exposure factors to be used by authorities during the process of assessing exposure to both adults and children in relation to REACH, and to contribute towards a further harmonisation of exposure assessments. The parameters addressed in this report are: body weight, body surface areas, Inhalation rates, Ingestion of drinking water, Intake of food, Ingestion of soil and dust, Non-dietary ingestion factors, Lifetime expectancy, Activity factors, Consumer products. Main EU, US and WHO sources of non-chemical-specific exposure factors are revised.	http://norden.diva-portal.org/smash/get/diva2:702615/FULLTEXT01.pdf
European Commission. ExpoFacts: the European Exposure Factors Sourcebook.	ExpoFacts is a collection of statistics and references aimed at being a tool for environmental exposure analysis and risk assessment, similar to the U.S. EPA Exposure Factors Sourcebook but with European data. ExpoFacts database contains data from 31 European Countries on important exposure factors such as housing conditions, consumption of food and beverages, and time use in different microenvironments.	https://ec.europa.eu/jrc/en/expofacts/expofacts-database
EFSA. Guidance on selected default values to be used by the EFSA Scientific Committee, Scientific Panels and Units in the absence of actual measured data. EFSA Journal 2012;10(3):2579.	Scientific rationale for a number of default values to be used in a harmonised way across EFSA Scientific Committee, Scientific Panels and Units; it also harmonises the rules for rounding derived values, such as health-based guidance values.	https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2012.2579
UK Environment Agency. The Updated technical background to the CLEA model (Science Report Final SC050021/SR3).	Provides the alogrithms for the UK risk assessment model, and with them the Country specific defaults for such things as housing stock, exposure duration and body weight.	https://webarchive.nationalarchives.gov.uk/20140328153908 http://www.environment-agency.gov.uk/static/documents/Research/CLEA_Report_-_final.pdf

* Last accessed: 22.03.2019.

Table 1. Sources of information for default values of non-chemical exposure factors for conducting exposure assessment in ICS.
Tabella 1. Fonti di informazione per i valori di riferimento per i fattori di esposizione non chimici per effettuare la valutazione di esposizione in un ICS.

of the population. In this sense, those authors suggested to calculate cumulative exposure, that is, the sum of the annual exposure concentration over the exposure duration. In future studies, efforts should be developed in reconstructing residential histories and variability in sources' emission (quantity, direction and movement into the breathing zone/deposition onto soil) over time, at least as a sensitivity analysis for the environmental modelling.

DATA NEEDED FOR CHARACTERISING IMPACTS ON HEALTH

ENVIRONMENTAL REFERENCE VALUES

In general, Environmental References Values (ERVs) are defined as concentrations of a substance present in an environmental media (e.g., in water, soil, and air) to which humans may be exposed during a certain time without experiencing adverse health effects. They are normally derived from toxicological references values (TRVs) for specific exposure routes, assuming high estimates of exposure point concentrations (approaching 90th percentile) and default conservative exposure factors related to the Country/region where they are proposed. Other criteria such as being "technically achievable" or "politically acceptable" are also considered when defining these factors.[22]

ERVs represent a very useful tool for screening all contaminants of potential concern found in potential or complete exposure pathways that require further investigation on a site.[16,18,22,34] In this way, it would be reasonable to consider that contaminants the concentrations of which in an exposure contact point are equal or below to relevant ERVs for that media are unlikely to pose a significant harmful effect. However, the opposite circumstances (contaminant concentration > ERV) does not imply

that adverse health effects might occur. In those cases, it is necessary to calculate the exposure dose for site-specific conditions, and compare it with specific TRVs.[22]
Different European Regulations record ERVs for a wide range of substances that might be present in drinking water, air and some foodstuff. In each case, the ERV takes a different name, e.g., "limit value" for air quality standards, or "parametric values", in drinking water. Several environmental or health agencies such as ATSDR, US EPA, Australia and the Netherlands have also derived ERVs for different environmental media, adjusted to their national or local conditions. Assessors should ensure to use the most appropriate and up-to date ERVs. The ERVs use for screening purposes should be consistent with conditions at or near the site, especially in terms of time frame (i.e., acute, sub-chronic or chronic) and population exposed (e.g., adults, children).[17,22,35] Table 2 show a list of potential sources to consult ERVs.

TOXICOLOGICAL REFERENCE VALUES (TRVS)

In the HHRA approach, all contaminants identified in complete exposure pathways, with a concentration higher than the background and higher than an ERV, and those for which no ERVs are available, need to be further investigated. At this stage, the exposure dose (mathematical estimation of the amount of a contaminant encountered in the environment per unit of body weight and time), calculated under site-specific conditions, is compared to TRVs or health guidelines. Calculations of the exposure dose can be found in any of the HHRA guidelines in Supplementary material.
For the purpose of HHRA, the potential health effects associated to harmful substances are categorised as non-carcinogenic or carcinogenic. For substances with non-carcinogenic effect, it is defined a threshold exposure dose below which it is not probable that harmful effect occurs. These health-based guidance values for human exposure are derived from epidemiological or, more frequently, from experimental studies with animal or in vitro tests that are largely available in the literature.[16,22] The identification of the critical effects and the analysis of dose-response relationship allow the extrapolation of such data to TRVs that protect the whole population including the most susceptible ones.
In the case of carcinogenic substances, it is assumed that no safe threshold dose can be ensured for avoiding an alteration in the genetic material in the human body. However, this established linear relation between exposure and excess of cancer risk is currently under debate since cancer normally occurs through a multi-step process and DNA repair mechanisms are able to cope, with low levels of DNA damage.[20,54] The US EPA provides guidance to develop quantitative cancer risk estimates, also using the benchmark dose approach.[54,56,57] The TRVs used for estimating cancer risk are either the unit risk (i.e., excess of cancer per unit of concentration), or the slope cancer factor (i.e., excess of cancer per unit of exposure dose).
In the European Union, another approach is followed to consider possible safety concerns arising from the presence in the environment of substances which are both genotoxic (which may damage DNA) and carcinogenic: the Margin of Exposure approach (MoE).[58] The MoE is a ratio of two factors: the dose at which a small but measurable adverse effect is first observed and the level of exposure to the substance considered. The dose of reference is commonly a benchmark dose, estimated with best fitting techniques of the experimental results on animal or, more rarely, epidemiological data. In the case of genotoxic carcinogens, the BMDL10 is used, which is the lower limit of the confidence interval of the benchmark dose associated with an increase in tumors of 10%

MoE = BMDL10/Exposure

It has been proposed, based on practical and scientific consideration, that an MoE of 10,000 or higher, if it is based on the BMDL10 from an animal study, would be of low concern from a public health point of view and might be considered as a low priority for risk management actions.
We are aware that for many substances present in the environment there are little or no toxicological/epidemiological evidence available. In this respect, it is worth mentioning the so-called Threshold of Toxicological Concern (TTC) approach, meant for assessing qualitatively the risk of low-level substances in the environment.[59,60]
It is very important to note that each TRVs, for both non-carcinogenic or carcinogenic effects, are defined for specific route of exposure (oral, dermal or inhalation), specific health effects, and time of exposure (acute, subchronic or chronic).
The coupled role of epidemiology and toxicology in risk assessment of environmental agents is obvious. Only the intersection of the datasets of both disciplines would permit straightforward conclusions with regard to a causal relationship between environmental agents and health effects.
Table 3 provides information on several databases with TRVs and guidance for the derivations of those critical exposure values.

HEALTH DATA

The availability of health information systems might be particularly valuable in assessing the health impact of ICSs especially when health monitoring covers a wide range of health outcomes and events (mortality and morbidity data) and address population subgroups (children, pregnant women, elderly people, ethnic minorities)[7].
However, site-specific health data are not always available

ENVIRONMENTAL REFERENCE VALUES		
MEDIA	**DESCRIPTION**	**SOURCE****
Soil*	RSL tables provide comparison values for residential and commercial/industrial exposures to soil, air, and tapwater (drinking water) to be applied at Superfund sites. The proposed values are risk-based screening levels, calculated using the latest toxicity values, default exposure assumptions and physical and chemical properties, and a calculator where USA default parameters can be changed to reflect site-specific risks.	US EPA. Regional screening levels (RSL): https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables
	A review and evaluation of national procedures towards harmonisation Soil Screening Values (SVs) are quality standards that are used to regulate contaminated sites. Derivation methods of SVs have scientific and political bases; they differ from Country to Country, and SVs numerical values vary consequently.	Joint Research Centre-European Soil Data Centre (ESDAC). Derivation methods of soil screening values in Europe. A review and evaluation of national procedures towards harmonisation (2007): https://esdac.jrc.ec.europa.eu/content/derivation-methods-soil-screening-values-europe-review-and-evaluation-national-procedures
	This technical report outlines a risk-based methodology for deriving soil contaminant concentrations protective of human health.	New Zealand Ministry for the Environment (2011). Methodology for Deriving Standards for Contaminants in Soil to Protect Human Health: http://www.mfe.govt.nz/publications/hazards/methodology-deriving-standards-contaminants-soil-protect-human-health
	Intervention Values for when to carry out further works.	The Netherlands Rijkswaterstaat (the Ministry of infrastructure and Water Environment)
Air	WHO guidelines that provide a basis for setting standards or limit values for air pollutants.	WHO air quality guidelines for Europe: http://www.euro.who.int/en/health-topics/environment-and-health/air-quality
	Air quality standards according to EU legislation: Directive 2008/50/EC on ambient air quality and cleaner air for Europe; Directive 2004/107/EC of the European Parliament and of the Council relating to arsenic, cadmium, mercury, nickel and polycyclic aromatic hydrocarbons in ambient air (Fourth Daughter Directive); Directive 2015/1480/EC of 28 August 2015 amending several annexes to Directives 2004/107/EC and 2008/50/EC of the European Parliament and of the Council laying down the rules concerning reference methods, data validation and location of sampling points for the assessment of ambient air quality; Commission Implementing Decision 2011/850/EU: Commission Implementing Decision of 12 December 2011 laying down rules for Directives 2004/107/EC and 2008/50/EC of the European Parliament and of the Council as regards the reciprocal exchange of information and reporting on ambient air quality (notified under document C(2011) 9068).	http://ec.europa.eu/environment/air/quality/standards.htm
Water	GDWQ of WHO covers a broad range of chemicals that can affect drinking-water quality. For many of these chemicals, guideline values (ERVs) are derived.	World Health Organization's (WHO) Guidelines for drinking-water quality (GDWQ): https://www.who.int/water_sanitation_health/water-quality/guidelines/chemicals/en/
	Water quality standards according to EU legislation: Annex I of the Drinking Water Directive (Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption), amended by Commission Directive (EU) 2015/1787 of 6 October 2015; Water Framework Directive (WFD, 2000/60/EC), and its 'daughter Directives': Groundwater Directive (GWD, 2006/118/EC) and Environmental Quality Standards Directive (EQSD, 2008/105/EC) .	Policies of the European Commission: water: http://ec.europa.eu/environment/water/index_en.htm
Foodstuff	EU legislation on contaminants in food are laid down in Council Regulation 315/93/EEC; Regulation (EC) No 1881/2006: Established maximum levels for contaminants in food; Regulation (EC) No 396/2005: Established maximum residue levels for pesticides in food; Regulation (EC) No 470/2009: Established procedures for the setting of Maximum Residue Limits (MRLs) for veterinary medicines in food.	EU legislation of contaminants in foodstuff: https://ec.europa.eu/food/safety/chemical_safety/vet_med_residues/legislation_en

*No specific legislation for soil has been approached at the EU level, so there is no harmonised ERVs for contaminants in soil at the EU.
**Last accessed: 22.03.2019.

Table 2. Sources of information for environmental reference values (ERVs).
Tabella 2. Fonti di informazione per i valori di riferimento ambientale (ERV).

or are of insufficient quality to enable us to link health outcomes with site-related exposures. Moreover, particularly in small areas, the number of people likely to be affected might be too small to be detected.
The morbidity can be studied through many health outcomes sources. One available source is represented by administrative health databases (from hospital based health information systems) that collect clinical information (e.g., hospital admission and discharge records) which can be used for epidemiological purposes, though created for other purposes. These types of data allow the calculation of disease prevalence, but rarely disease incidence. Examples of these data source are: hospital discharge databases including inpatient, outpatient and A&E attendances, primary care (e.g., Family doctors, dental, pharmacy, telephone helplines).
Disease registries are organized systems that collect clinical and other data on a specific disease or on a specific group of diseases. These kind of registries, very useful as data sources in epidemiological studies, are population-based registries that collect all cases of a specific disease diagnosed in the entire population residing in a well-defined geographic area and time period. For these purposes, multiple sources on health information are used. This type of registers ensures a very high quality of data especially in terms of accuracy and completeness. Disease registries usually allow calculating the incidence of health outcomes. Important disease registries used in epidemiological study are the cancer registries (International Agency for Research of Cancer (IARC), International Association of Cancer Registries (IACR), and European Network of Cancer Registries (ENCR)). Furthermore, ad hoc health surveys can be useful particularly for investigating outcomes inherited health behaviour.
The birth certificates database (or birth registries) represents another very useful data source to study early adverse health effects (e.g., low birth weight, preterm births, small for gestational age,). Birth registries collect information both on the new-born and on the mother (pregnancy). Amongst the birth outcomes, the risk from congenital anomalies in contaminated sites has been recently assessed.[61, 62] The best data source to investigate the congenital anomalies is the EUROCAT registry, the European network of population-based registries for the epidemiologic surveillance of congenital anomalies.[63]
Mortality data, a very common data source used in epidemiological studies, are usually collected at local, regional and national level, usually available or long time periods, and they ensure a high standard of data quality in many Countries.
Morbidity and mortality data are classified and coded in all the Countries using the International Classification of the Disease (ICD). Mortality data can be extracted by Vital Statistics databases or by regional/national mortality registries. The latter generally collect more detailed information.
European, National or Regional Statistical Institutions provide routine health indicators that are public. The main limitation is that these health indicators are usually related to a very large area whereas ICSs are generally represented by small areas.
The data usage in an epidemiological study depends on several factors: commitment of the study, available resources, availability of data with different levels of aggregation, data protection, and study design.

CONCLUSIONS

In this study, the state of the art regarding different methodological approaches for characterising the impact on health of ICSs have been reviewed, and the main critical issues highlighted. The suitability to use one or another approach – HHRA or EE studies – depends on the availability of data, cost-benefit and the type of problem that needs to be answered.
In any case, the first step should include identification of: **i)** environmental pollution source/s, **ii)** main type of hazardous substances involved and **iii)** most probable exposure conceptual model, delimiting the potential/complete routes of exposure. Information derived from an accurate exposure assessment (EA) is determinant for assessing the consequent health impact, for adopting preventive public health measures as well as for defining additional health research.[31] In this sense, the results from the EA can support risk managers in identifying the best approach for assessing the health impact of ICSs and implement the best suitable preventive action through remediation activities. Results from EA have been better integrated in the HHRA approach, but it is equally useful for setting up more effective epidemiological and surveillance studies. In those cases, EA would allow identifying the most relevant chemicals affecting people, discriminate between exposed and non-exposed population, and, in some cases, even to accurately assess exposure at individual level.[20,31]
Quantitative risk assessment, especially following the preliminary approach (PQRA) based on toxicological scientific evidence, can be conducted quite quickly at modest expense, providing direct information on the urgency of intervention to protect the health of population, remediate exposure, or identifying appropriate public health actions such as medical monitoring, health education, and/or health surveillance and substance-specific research.[22]
The estimates obtained out of it would inform if the population might be or not at risk of being affected by non-carcinogenic or carcinogenic health effects, but does not quantify the number of health events (in terms for mor-

TOXICOLOGICAL REFERENCE VALUES		
TRV	**DESCRIPTION**	**SOURCE***
TDI	**Tolerable daily intake:** amount of a contaminant, expressed on a body weight basis (e.g., mg kg-1 bw day-1), that can be ingested daily over a lifetime without appreciable health risk. Proposed in the 1970s by the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA), as an extension for contaminants of the acceptable daily intake (ADI) originally developed for setting standards for dietary safety of food additives. Refers only to non-carcinogenic effects.	World Health Organization – various sources including: http://www.inchem.org/ http://jecfa.ilsi.org/index.htm
PTWI	**Provisional tolerable weekly intake:** similar to TDI, but reflects averaged exposure over longer period than a single day. The term "provisional" for contaminants, whether referring to daily or weekly intake, refers to certain uncertainty in the data available.	World Health Organization – various sources including: http://www.inchem.org/ http://jecfa.ilsi.org/index.htm
RfD	**Reference dose:** an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive groups) that is likely to be without an appreciable risk of non-carcinogenic effects during a lifetime. It covers all exposure routes. **Reference concentration (RfC)**, equivalent to the RfD, but based on inhalation and is defined as a concentration in air.	United State Environmental Protection Agency-Integrated Risk Information System (EPA-IRIS): https://www.epa.gov/iris
MRL	**Minimal Risk levels:** an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure. Derivate for oral and inhalation exposure and different duration of exposure (chronic, intermediate – up to one year –, and acute exposure.	US Agency for Toxic Substances and Disease Registry: https://www.atsdr.cdc.gov/mrls/mrllist.asp
BMD or BMC	**Benchmark dose or benchmark concentration:** a dose or a concentration of a chemical that produces a predetermined change in response rate of an adverse effect (called the benchmark response, BMR) compared to background.	United State Environmental protection Agency-Benchmark Dose Tools: https://www.epa.gov/bmds
MPR	**Maximum Permissible Risk:** amount of a substance (usually a chemical substance) that any human individual can be exposed to daily during full lifetime without significant health risk. It covers mainly oral and in-halation exposure but if necessary, also dermal exposure, and non-carcinogenic and carcinogenic risks.	Netherlands National Institute of Public Health and the Environment: http://www.rivm.nl/bibliotheek/rapporten/711701025.pdf
OSF or IUR	**Oral slope factor:** an estimate of the increased cancer risk from oral exposure to a dose of 1 mg/kg-day for a lifetime. The OSF can be multiplied by an estimate of lifetime exposure (in mg/kg-day) to estimate the lifetime cancer risk. **Inhalation unit risk (IUR):** an estimate of the increased cancer risk from inhalation exposure to a concentration of 1 µg/m^3 for a lifetime. The IUR can be multiplied by an estimate of lifetime exposure (in µg/m^3) to estimate the lifetime cancer risk.	United State Environmental protection Agency-Integrated Risk Information System (EPA-IRIS): https://www.epa.gov/iris
OTHER SOURCES OF INFORMATION FOR TOXICOLOGICAL INFORMATION AND TRVS		
The Office of Environmental Health Hazard Assessment (OEHHA) Chemical Database of the State of California (USA) is a searchable compilation of health hazard information including TRVs, ERVs, California public health goals, child-specific reference doses, Proposition 65 safe harbor numbers, soil-screening levels, and fish advisories.		California Environmental Protection Agency: http://www.oehha.ca.gov/risk/ChemicalDB/index.asp
ECB is the focal point for data and the assessment procedure on dangerous chemicals. It coordinates the EU risk assessment programmes covering the risks posed by existing substances and new substances to workers, consumers and the environment.		European Chemicals Bureau (ECB): https://echa.europa.eu/es/information-on-chemicals
Scientific Expert Panels of EFSA provides risk assessments on all matters linked to food and feed safety, including the presence of chemical contaminants in food.		European Food Safety Authority (EFSA): http://www.efsa.europa.eu/en/topics/topic/chemical-contaminants
IARC monographs are critical reviews of data on carcinogenicity for agents to which humans are known to be exposed. IARC classifies chemicals according to their carcinogenic potential, i.e., hazard, as indicated by the available data.		International Agency for Research on Cancer (IARC): https://monographs.iarc.fr/
ATSDR Toxicological profiles are a unique compilation of peer-reviewed toxicological information on a given hazardous substance. Each Tox Profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicological and epidemiological information on a substance.		US Agency for Toxic Substances and Disease Registry: https://www.atsdr.cdc.gov/toxprofiledocs/index.html
Chemical hazards compendium include information about **1.** general information on the chemical; **2.** toxicological overview of the compound; **3.** incident management focusing on information needed during chemical incidents, such as physicochemical properties, health effects and decontamination.		UK Chemical hazards compendium: https://www.gov.uk/government/collections/chemical-hazards-compendium
Hosted by the US National Library of Medicine, Toxnet is a collection of databases on toxicology, hazardous chemicals, environmental health, and toxic releases. These include IRIS, Toxline and the Hazardous Substances Data Bank (HSDB).		Toxicology Data Network (Toxnet): https://toxnet.nlm.nih.gov/

*Last accessed: 21.03.2019.

Table 3. Sources for toxicological reference values (TRVs) and toxicological profiles.
Tabella 3. Fonti dei valori di riferimento tossicologico (TRV) e profili tossicologici.

bidity and mortality) associated to such exposure. Although most of the models existing in different Countries for HHRA share a similar framework and approach, with many equations recognisably the same, the chosen scientific evidence and the local regulatory advice may vary, which can result in a wide variability of health risk estimates. This inconsistency stems primarily from the identification and selection of the way the affected population interact with the ICSs and their cultural and social conditions, such as their use of green space, TRVs but also policy choices.[18,20] A stronger harmonisation of HHRA tools and guidance worldwide should be encouraged in order to achieve a higher perception of justice (and a reduced sense of "outrage"), and health protection among citizens and stakeholders, and a better science integrity.[6,20] Swartjes described in his review a list of elements that should address this possible harmonisation process for HHRA in contaminated sites.[20] Savitz suggests complementing the results obtained from HHRA with public health surveillance data in order to provide a more efficient and complete response.[31]

The comparative quantification for health risk allows moving one-step forward characterising the burden of disease (number of health events) that would be avoided if exposure was reduced to the counterfactual values (safe or referent level). For applying this approach, it is necessary to gather a more detail information not always available, such as robust dose-response functions derived from epidemiological studies, availability of routinely health data, etc.

As Savitz described, EE studies are relevant for generating new scientific evidence and advance knowledge, such as getting a better understanding of the exposure-disease relationship, especially for novel chemicals (e.g., perfluorinated compounds). The information generated under this approach provides a direct answer tailored to the affected population, and normally induces more easily a governmental intervention for remediation and taking legal and administrative actions against the responsible entity of the problem. People from the affected communities also understand better the results generated by EE studies, being such results an important tool for running communication strategies and decreasing the anxiety of perceive risks.[31]

Analytical epidemiological studies are the most suitable to test aetiological hypothesis between environmental exposure and health effects. On the other hand, analytical epidemiological studies might be quite expensive and slow, and they are not able to give a prompt answer in situations where remediation activities cannot be further postponed. In these scenarios, if the health outcomes of interest are routinely available at little or no expense (e.g., birth outcomes registered at the site), then an informative study may be quite feasible. However, if assessing the health outcome requires clinical evaluation of each individual, the marginal contribution of the new research may be negligible.[31]

Moreover, several contaminants usually found in ICSs (heavy metals, dioxins, PCB, aromatic hydrocarbons, PM, and gaseous pollutants) are well known in term of toxicological effect, and information on associated human health risks and impacts are available from scientific literature or from previous assessments.[7] In such settings, especially in ICSs of low-income or less research-intensive Countries, health impact assessment can rely upon already available data/assessment rather than wait for findings of new local epidemiological studies.

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