ARTICLE 2

A review of exposure assessment methods for epidemiological studies of health effects related to industrially contaminated sites

Gerard Hoek,[1] Andrea Ranzi,[2] Ilir Alimehmeti,[3] Elena-Roxana Ardeleanu,[4] Juan P. Arrebola,[5-7] Paula Ávila,[8] Carla Candeias,[9,10] Ann Colles,[11] Gloria Cerasela Crişan,[4] Sarah Dack,[12] Zoltán Demeter,[13] Lucia Fazzo,[14] Tine Fierens,[11] Benjamin Flückiger,[15,16] Stephanie Gaengler,[17] Otto Hänninen,[18] Hedi Harzia,[19] Rupert Hough,[20] Barna Laszlo Iantovics,[21] Olga-Ioanna Kalantzi,[22] Spyros P. Karakitsios,[23,24] Konstantinos C. Makris,[17] Piedad Martin-Olmedo,[25] Elena Nechita,[4] Thomai Nicoli,[26] Hans Orru,[27] Roberto Pasetto,[14] Francisco Miguel Pérez-Carrascosa,[5,7] Diogo Pestana,[28,29] Fernando Rocha,[10] Dimosthenis A. Sarigiannis,[23,24,30] João Paulo Teixeira,[9] Christos Tsadilas,[26] Visa Tasic,[31] Lorenzo Vaccari,[2,32] Ivano Iavarone,[14] Kees de Hoogh[15,16]

[1] Institute for Risk Assessment Sciences, Utrecht University (The Netherlands)
[2] Environmental Health Reference Centre, Regional Agency for Prevention, Environment and Energy of Emilia-Romagna, Modena (Italy)
[3] Occupational Health Department, Faculty of Medicine, University of Medicine, Tirana (Albania)
[4] "Vasile Alecsandri" University of Bacău (Romania)
[5] Instituto de Investigación Biosanitaria de Granada (ibs. GRANADA), University of Granada (Spain)
[6] CIBER de Epidemiología y Salud Pública (CIBERESP), Madrid (Spain)
[7] Oncology Unit, Virgen de las Nieves University Hospital, Granada (Spain)
[8] National Laboratory of Energy and Geology (LNEG), Amadora (Portugal)
[9] EpiUnit, Public Health Institute, University of Porto (Portugal)
[10] GeoBioTec, Geosciences Department, University of Aveiro, Santiago Campus (Portugal)
[11] Sustainable Health, Flemish Institute for Technological Research (VITO), Boeretang (Belgium)
[12] Environmental Hazards and Emergencies Department, Centre for Radiation, Chemical and Environmental Hazards, Public Health England, London (UK)
[13] National Public Health Institute, Budapest (Hungary)
[14] Unit of Environmental and Social Epidemiology, Department of Environment and Health, Italian National Health Institute (ISS), Rome (Italy)
[15] Swiss Tropical and Public Health Institute, Basel (Switzerland)
[16] University of Basel, Basel (Switzerland)
[17] Water and Health Laboratory, Cyprus International Institute for Environmental and Public Health, Cyprus University of Technology, Limssol (Cyprus)
[18] Department Public Health Solutions, National Institute for Health and Welfare, Helsinki (Finland)
[19] Department of Environmental Health, Estonian Health Board, Tallinn (Estonia)
[20] James Hutton Institute, Craigiebuckler, Aberdeen, Scotland (UK)
[21] "Petru Maior" University of Târgu Mureş (Romania)
[22] Department of Environment, University of the Aegean, Mytilene (Greece)
[23] Department of Chemical Engineering, Environmental Engineering Laboratory, Aristotle University of Thessaloniki (Greece)
[24] HERACLES Research Center on the Exposome and Health, Center for Interdisciplinary Research and Innovation, Balkan Center, Thessaloniki (Greece)
[25] Escuela Andaluza de Salud Pública, Granada (Spain)
[26] Hellenic Agricultural Organization, General Directorship of Agricultural Research, Institute of Industrial and Forage Crops, Larissa (Greece)
[27] Institute of Family Medicine and Public Health, University of Tartu (Estonia)
[28] Center for Health Technology and Services Research (CINTESIS), Porto (Portugal)
[29] Nutrition&Metabolism, NOVA Medical School, Faculdade de Ciências Médicas, Universidade Nova de Lisboa (Portugal)
[30] University School for Advanced Study (IUSS), Pavia (Italy)
[31] Department for Industrial Informatics, Mining and Metallurgy Institute Bor (Serbia)
[32] Department of Engineering "Enzo Ferrari", University of Modena and Reggio Emilia (Italy)

Corresponding author: Gerard Hoek; g.hoek@uu.nl

ABSTRACT

BACKGROUND: this paper is based upon work from COST Action ICSHNet. Health risks related to living close to industrially contaminated sites (ICSs) are a public concern. Toxicology-based risk assessment of single contaminants is the main approach to assess health risks, but epidemiological studies which investigate the relationships between exposure and health directly in the affected population have contributed important evidence. Limitations in exposure assessment have substantially contributed to uncertainty about associations found in epidemiological studies.

OBJECTIVES: to examine exposure assessment methods that have been used in epidemiological studies on ICSs and to provide recommendations for improved exposure assessment in epidemiological studies by comparing exposure assessment methods in epidemiological studies and risk assessments.

METHODS: after defining the multi-media framework of exposure related to ICSs, we discussed selected multi-media models applied in Europe. We provided an overview of exposure assessment in 54 epidemiological studies from a systematic review of hazardous waste sites; a systematic review of 41 epidemiological studies on incinerators and 52 additional studies on ICSs and health identified for this review.

RESULTS: we identified 10 multi-media models used in Europe primarily for risk assessment. Recent models incorporated estimation of internal biomarker levels. Predictions of the models differ particularly for the routes 'indoor air inhalation' and 'vegetable consumption'. Virtually all of the 54 hazardous waste studies used proximity indicators of exposure, based on municipality or zip code of residence (28 studies) or distance to a contaminated site (25 studies). One study used human biomonitoring. In virtually all epidemiological studies, actual land use was ignored. In the 52 additional studies on contaminated sites, proximity indicators were applied in 39 studies, air pollution dispersion modelling in 6 studies, and human biomonitoring in 9 studies. Exposure assessment in epidemiological studies on incinerators included indicators (presence of source in municipality and distance to the incinerator) and air dispersion modelling. Environmental multi-media modelling methods were not applied in any of the three groups of studies.

CONCLUSIONS: recommendations for refined exposure assessment in epidemiological studies included the use of more sophisticated exposure metrics instead of simple proximity indicators where feasible, as distance from a source results in misclassification of exposure as it ignores key determinants of environmental fate and transport, source characteristics, land use, and human consumption behaviour. More validation studies using personal exposure or human biomonitoring are needed to assess misclassification of exposure. Exposure assessment should take more advantage of the detailed multi-media exposure assessment procedures developed for risk assessment. The use of indicators can be substantially improved by linking definition of zones of exposure to existing knowledge of extent of dispersion. Studies should incorporate more often land use and individual behaviour.

Keywords: industrially contaminated sites, exposure assessment, dispersion modelling, biomonitoring, epidemiology

KEYPOINTS

What is already known

- **Health risks related to living close to industrially contaminated sites (ICSs) are a public concern.**
- **Risk assessment of single contaminants is the main approach to assess health risks, but epidemiological studies have contributed important evidence.**
- **Limitations in exposure assessment have substantially contributed to uncertainty about associations found in epidemiological studies.**

What this paper adds

- **We conducted a review to examine exposure assessment methods used in epidemiological studies of ICSs in comparison with risk assessment.**
- **The majority of studies used proximity indicators of exposure; air pollution dispersion modelling, soil monitoring, and human biomonitoring have been used in a small number of epidemiological studies.**
- **Detailed multi-media environmental modelling methods, such as those used for regulatory risk assessment, were not applied.**
- **Recommendations for refined exposure assessment in epidemiological studies were developed, including taking more advantage of the procedures developed for risk assessment, improvement of proximity indicators and the need for validation studies using personal exposure or human biomonitoring to assess misclassification of exposure.**

INTRODUCTION

Health risks for the general population residing near industrially contaminated sites (ICSs) are a public concern[1-5] At the Sixth Ministerial Conference on Environment and Health held in Ostrava in June 2017, waste and contaminated sites were declared one of the seven priority areas for the European environmental policy agenda.[6] Local soil contamination in 2011 was estimated for 2.5 million potentially contaminated sites in the 39 Countries reporting to the European Environment Agency (EEA).[7] EEA estimated that 342,000 of these sites were highly likely contaminated.[7,8] Waste disposal and treatment, and industrial and commercial activities were the two major sources of soil contamination, together responsible for about 70% of the contaminated sites.[7] A comprehensive analysis of research and policies related to contaminated land can be found in a recent book.[2]

The environmental performance of European industry has improved in the last decades. However, the sector has still a significant role in causing pollution to air, water, and soil, as well as generation of waste:[9] between 2008 and 2012, the cost of damage to health and the environment from air pollution from the 14,000 most polluting facilities in Europe was estimated at between 329 billion and 1,053 billion euros and 50% of the costs occurred as a result of emissions from just 147 facilities (1% of these facilities).

The need of a European response to the environmental health issues posed by contaminated sites was originally raised in the framework of two technical meetings organized by the World Health Organization.[10]

Industrially contaminated sites have been defined as: "Areas hosting or having hosted industrial human activities which have produced or might produce directly or indirectly (waste disposals) chemical contamination of soil, surface or ground-water, air, food-chain, and resulting or being able to result in human health impacts".[1] The definition encompasses more settings than the EEA definition, which is limited to contaminated soil.[8] ICSs include a wide diversity of settings, such as (municipal and industrial) waste landfills, large industrial complexes (steel factories, petrochemical industries), waste incinerators, harbour areas, and mining and quarrying extraction activities operating in the past and/or still in operation. An illustration of the diversity can be found in the 44 national priority contaminated sites identified in Italy and studied in the Italian SENTIERI project.[11] Industrial agriculture can be included in the definition as well, bringing in pesticide exposures.

A first common feature of an ICS is that multiple environmental media (air, water, soil, and food-chain) are typically affected. The main emission of a source can be directly to the soil (leaking drums on a landfill), to outdoor air (incinerators, steel factories), to water or a combination of these three. Subsequently, other environmental media may be affected by transport processes, such as deposition of airborne metals on soil or volatilization of soil contaminants, such as benzene into indoor and outdoor air. **A second common feature** is that a cocktail of exposure to multiple chemicals is typically observed. Frequently occurring chemicals around ICSs include heavy metals (e.g., arsenic, cadmium, lead, chromium), volatile organic components (VOC, such as benzene, toluene), polycyclic aromatic hydrocarbons (PAH, such as Benzo(a)pyrene), dioxins, mineral oil, chlorinated hydrocarbons (CHC, such as trichlorethene and polychlorinated biphenyls – PCBs), and pesticides.[8] Concern about potential health effects of contaminated sites currently mainly focuses on populations living close to a site, as it has been estimated that the impact on the overall population is limited.[3]

Two main approaches have been used to assess health risks of ICSs: risk assessment and epidemiology.[1] **The first approach** is based on risk assessment comparing measured or modelled human intake of specific chemicals with typically toxicologically based guidelines for pollutant doses. The risk assessment methodology is the main approach to determine health risks of specific sites in practice and has the advantage that it estimates exposure, so lengthy and expensive public participation is not required. This is particularly useful for sites that are not (currently) populated. To make such predictions, detailed modelling is required, which in many cases cannot be validated. In many European Countries and in the USA, detailed procedures for risk assessment have been developed.[1,3,12] The Public Health Assessment approach designed by the US Agency for Toxic Substances and Disease Registry (ATSDR) supplements risk assessment with population health data and incorporates public participation.[13] The focus of these assessments is on specific sites and the population living near that site.

The second approach involves epidemiological studies that investigate the relationships between exposure and health directly in the affected population. Epidemiological studies may address some of the limitations of typical risk assessment, including the single pollutant based assessment in the common multi-pollutant context of ICSs; the interaction between chemical and non-chemical stressors; the reliance on toxicological data requiring the use of somewhat arbitrary safety factors. The notion that below a certain intake value no (adverse) health effects occur is also questionable, as has been demonstrated extensively for outdoor air pollution.[14] Limitations of epidemiological studies around specific contaminated sites, including often small population size, have been discussed.[15] Epidemiological studies of ICSs can be distinguished into:

- studies that describe health profiles of populations living in an ICS using routinely available data at area level;
- studies that analyse associations between ICS exposures and health outcomes using individual level studies to test a-priori hypotheses;
- surveillance studies of temporal patterns of population health.[1]

Because of the typical complex multi-pollutant, multi-media exposure setting of contaminated sites, assessment of human exposure to pollutants has been challenging, both for risk assessment[3] and epidemiological studies. In a recent systematic review of health effects of hazardous waste, limitations in exposure assessment were listed as a major issue in reliably assessing health risks of hazardous waste.[16] The need for improvement of exposure assessment was also identified in a review of epidemiological studies of major industrial areas.[17] To our knowledge, no recent comprehensive review of exposure assessment relevant for epidemiological studies of ICSs has been published. In 1991, a review by the National Research Council of US studies of hazardous waste sites was published; it included recommendations for improved exposure assessment.[18] Recommendations stated that exposure assessment needs to take into account all possible media and must try to include direct methods (personal exposure monitoring) and indirect methods (micro-environmental monitoring and mathematical models).

OBJECTIVES

The aim of this review is to examine exposure assessment methods for epidemiological studies of industrially contaminated sites. We compared exposure assessment in epidemiological studies and site-specific and screening risk assessments. The goal of this comparison is to provide recommendations for further development of exposure assessment methods for epidemiological studies to enable more informative epidemiological studies. The review was prepared in the framework of the COST Action Industrially Contaminated Sites and Health Network (ICSHNet) (https://www.icshnet.eu/).

METHODS

We started with defining a conceptual framework of human exposure related to contaminated sites. Then, we discussed in some detail selected regulatory multi-media models applied in specific European Countries to assess soil contamination supplemented with recently-developed multi-media research tools where these illustrate new developments in exposure assessment. We specifically assessed multi-media exposure assessment methods starting from contaminated soil, because this is an important category of ICS. We next provided an overview of the type of study design and exposure assessment in three groups of epidemiological studies of contaminated sites. First, we evaluated 54 studies included in a recent systematic review of health effects of hazardous waste[16] and expanded the evaluation of exposure assessment methods compared to the original review. We further include results of a 2013 systematic review of exposure assessment approaches of 41 epidemiological studies on incinerators.[19] Finally, we performed a systematic search in PubMed using the search terms: (contaminated OR polluted) (area* OR site* OR facilit* OR communit* OR factory OR factories*) health epidemiology industrial, so identifying an additional 52 studies (from 582 abstracts). We performed the additional search to expand the scope of studies beyond waste and incinerators. We do not claim that our search found all studies, as the literature is very large and different search terms result in different sets of studies. The main purpose of the review is to discuss principles of methods, not a quantitative overview of methods of exposure assessment methods. We did not include studies of radiation from nuclear power plants. We further excluded studies of generic contamination without a specific local source (e.g., on arsenic in groundwater). We only included studies in the English, Italian, and Dutch language (the vast majority was in English). Based on these assessments, we formulate a series of recommendations for refined exposure assessment in epidemiological studies of ICSs.

CONCEPTUAL FRAMEWORK OF EXPOSURE

There are a number of conceptual frameworks for exposure assessment: some have been adopted by regulatory authorities, while others have been used primarily for research activities. For example, a conceptual framework for exposure assessment for Public Health Assessments has been provided by ATSDR.[13] Figure 1 illustrates the ATSDR framework with drums serving as an example of a source for initially soil contamination, followed by contamination of other environmental media. Figure 2 depicts the exposure framework related to studies performed to assess human exposure and health risks related to a Portuguese mining area. Figure S1 (see on-line supplementary material) shows the framework in an early report of the US National Research Council (NRC).[18]

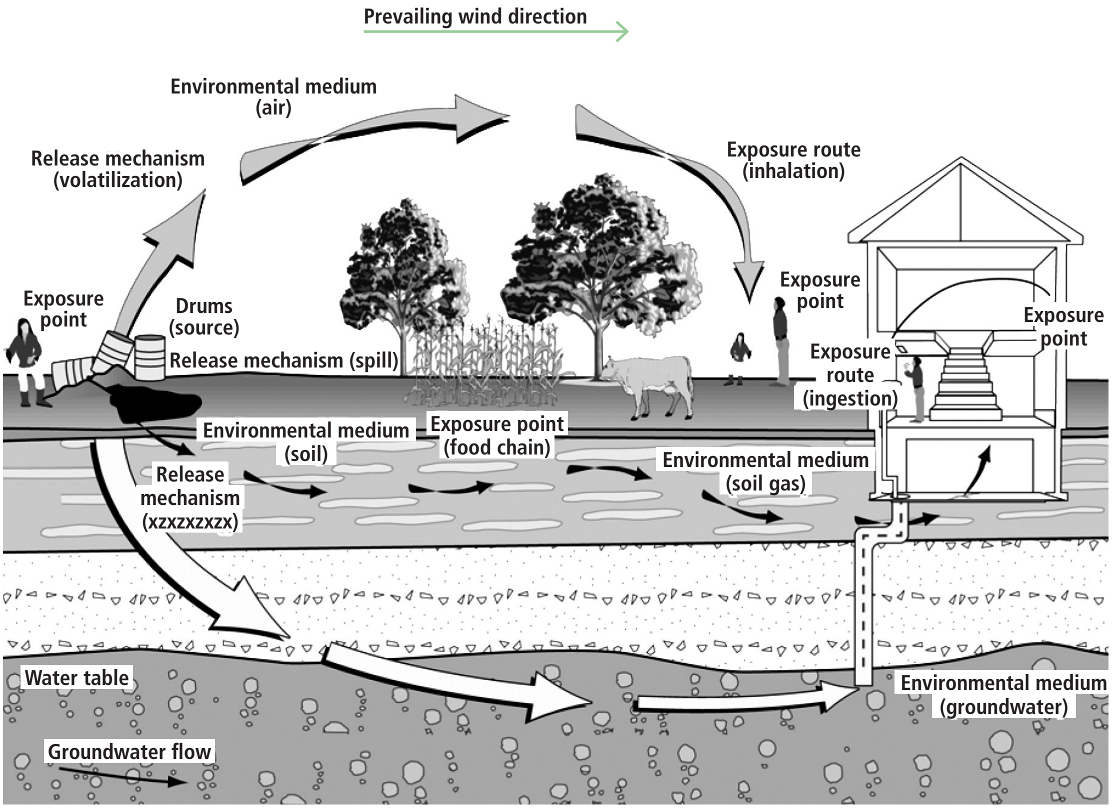

Figure 1. Framework for human exposure of contaminated sites. **Source:** Public Health Assessment Guidance Manual (2005 Update).[13]

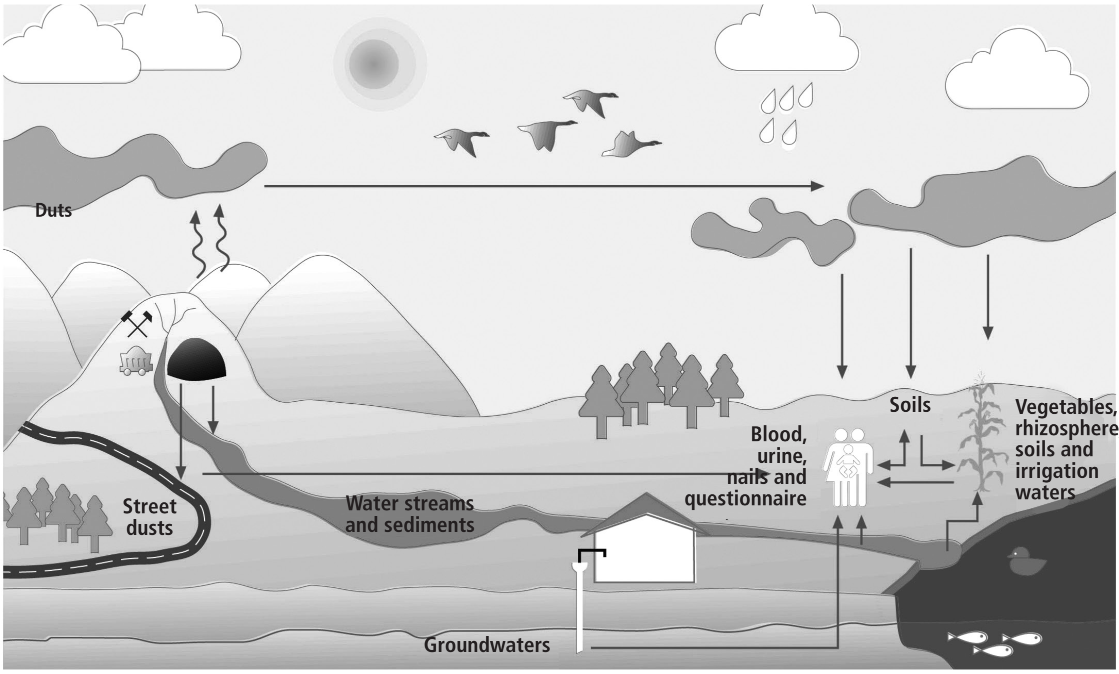

Figure 2. Exposure pathways of the Portuguese Panasqueira mining area. **Source:** Candeias 2013.[50]

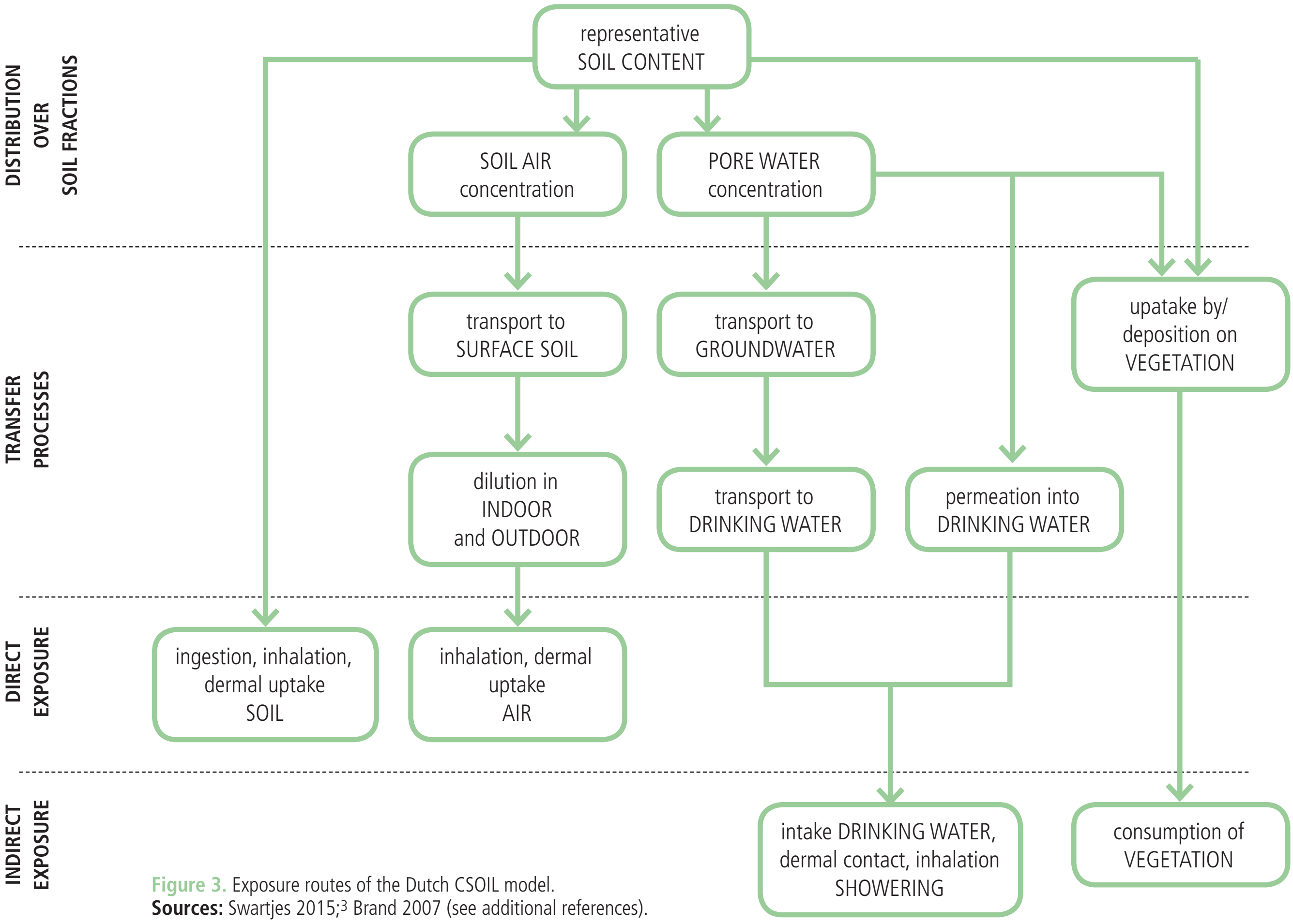

Figure 3. Exposure routes of the Dutch CSOIL model.
Sources: Swartjes 2015;[3] Brand 2007 (see additional references).

Similar frameworks form the basis of European models, such as CSOIL, S-Risk and CLEA (figure 3). These frameworks illustrate the multi-media exposures. In the setting of contaminated soil, the distinction between exposure and concentration in the environment[20] is critically important. Exposure requires contact of humans with pollutants in the environment. Therefore, exposure is determined by the interaction between environmental contamination and human receptors. When focused on soil, the human exposure of a population living near a site depends on the following groups of factors:

- type of site, affecting the specific pollutant and magnitude of contamination;
- macro-level factors such as topography, hydrology, and meteorology that influence fate and transport of pollutants;
- soil properties including pH, organic carbon content, ground water flows;
- pollutant properties, including solubility, vapour pressure, reactivity;
- mechanisms for transformation and transport of pollutants between environmental medias;
- use of the soil, such as growth of vegetables for consumption;
- intake factors such as inhalation rate, consumption of locally grown vegetables

Soil ingestion, vegetable consumption, and vapour inhalation are often the most important pathways,[3] but this depends critically on the contaminant.

EXPOSURE ASSESSMENT BY MULTI-MEDIA MODELS FOR RISK ASSESSMENT

Exposure assessment methods for human health risk assessment of contaminated land have recently been reviewed.[3] In the review, both monitoring and modelling of human exposure is discussed. In this section, we focus on modelling methods.

A comparison of exposure models used in different EU Countries for screening risk assessment has been published by the Joint Research Centre on the basis of input of a large group of national experts.[21] Carlon and co-workers reported substantial differences in model predictions, especially related to the choice of which receptors needed to be protected and which exposure pathways were included. Particularly, the inclusion of 'indoor air exposure' and 'consumption of home-grown vegetables' had an important impact on total human exposure estimates.[21] For the risk calculations, the inclusion of background pollution from sources other than the contaminated site (e.g., smoking for Cd) contributed to differences in risk estimation. A comparison of model predictions from 7 European models, including CSOIL and CLEA, showed two orders of magnitude differences in calculated total exposure in a series of scenarios.[22] The differences were particularly large for the exposure pathways 'indoor air inhalation' and 'consumption of contaminated vegetables'.[22] For more mobile and volatile components, differences between models were largest.

Table 1 lists multi-media modelling methods applied in different Countries for risk assessment purposes identified within the COST Action. A detailed description of the models can be found in the on-line supplementary material. The table does not cover all European models, e.g., of the 7 models evaluated by Carlon,[21] only CSOIL and CLEA are included. This table includes mostly models that are applied in soil regulatory frameworks, but also three research models used for human exposure and risk assessment (Hough model, Merlin-EXPO, and INTEGRA), where the Hough model has been applied in regulatory settings. Figure 3 shows the exposure routes taken into account by the Dutch CSOIL model as an example. The CSOIL model starts with representative concentrations of the pollutant in the soil and then models the distribution of a pollutant over the different soil phases (solid, water, air), transfer to contact media, and finally exposure to humans. The model assesses contamination of different environmental media, including soil, water, indoor and outdoor air, and uptake by vegetation. The model specifies different exposure scenarios related to the use of the land, with residential land use with garden as the default.

Differences between models

The models focus on exposure of local populations and not on the contribution of the collection of ICSs to overall contamination of the environment. The models use similar frameworks, but differ in the level of detail included in the model. Contamination of ground water is not included in the models, except for S-Risk, Risknet, and RBCA. In CSOIL and S-Risk, leaching of contaminants in water pipelines is included. The level of detail of characterizing the food exposure pathway differs, with the HOUGH model being the most detailed one. The food pathway often includes only vegetables and not animals. S-Risk, Merlin, and INTEGRA also include animals in the food pathway. The Merlin Expo and INTEGRA models include physiologically-based pharmacokinetic (PBPK) modelling of contaminant levels in target tissues in the human body, whereas the other models are limited to calculate intake. In view of the application in epidemiology, an important difference among models is that some allow user-defined input values, whereas others do not. Some models can be used for site-specific and generic assessments. We did not repeat

MODEL	PURPOSE	PRINCIPLE	CONSIDERED EXPOSURE ROUTES	INPUT	SCENARIOS FOR LAND USE	OUTPUT	REFERENCE*
CSOIL (the Netherlands)	Characterization of human risk in screening risk assessment of soil. Derivation of soil reference values.	Starting from soil concentration the distribution over soil solid, water and air phase is calculated. Via a set of equations via an air, water, crop, and ground water module pollutant intake is calculated.	Inhalation of indoor and outdoor air (gas, particles); ingestion of soil, food, drinking water; dermal contact with contaminated soil particles and showering.	Soil concentration; scenarios for land use; site and soil properties; physico-chemical distribution constants; intake parameters such as inhalation rate.	Default residential with garden; six other.	Concentration in contact media of individual pollutants, dose, risk.	Brand 2007
CLEA v1.071 (UK)	Selected as 'supporting initiative' [primarily] for land regeneration by UK EA. While other models are available, it is easier to gain agreement from regulators if CLEA is used.	A deterministic source-pathway-receptor model using concentrations of contaminants in soil as the source term with estimates made of uptake into plants, gaseous emissions (including ingress into buildings), as well as direct exposure to soil. CLEA does not include groundwater, but can be used generically or site-specific.	Ten exposure pathways are considered including; direct and indirect ingestion of soil and dust ingestion via contaminants incorporated into crops and ingestion via soil adhered to vegetables and fruit, inhalation of dust indoors/outdoors. Ingestion of vapours indoors/outdoors, dermal contact with soil.	Default values and land use scenarios enable CLEA to be run with only soil concentrations, or back calculated for clean-up values. Users can add their own site-specific data and most default values (including exposure factors) can be modified including basic soil chemical parameters (pH, organic C) and relative soil bioavailability, as well as building parameters and amount of vegetables consumed.	A large number of land use scenarios representing minimal and low risk, 11 different building types and 9 different soil types, that can be run for residential, commercial, allotments and public open space. Many can be user-defined.	Concentrations of contaminant in model compartments. Assessment criteria for soil, modelled exposure by pathway, ratio of exposure to criteria values.	Jeffries 2009
Atlantic RBCA (Canadian used in UK in conjunction with CLEA)	Risk assessment of petroleum contaminated soil.	Starting with concentrations in soil, the distribution over solid, liquid, and gaseous phases in soil is estimated and used as the basis for simulating a variety of exposure pathways. RBCA is a tiered model that can be used generically or site-specific.	Ingestion via groundwater and food production, inhalation from gaseous ingress into buildings, dermal exposure. (The ground water pathway, which is not included in CLEA, is why RBCA is widely adopted in the UK).	Default values and land use scenarios enable RBCA to be run with only soil concentrations, however all sensitive parameters can be user defined.	Four land use scenarios available (agricultural, commercial, residential, industrial).	Risk estimates for a number of petroleum hydrocarbons; clean-up values based on a backwards calculation.	RBCA 2012
HOUGH Model	Research model used to underpin a number of large generalized risk assessments including the use of organic wastes in agriculture.	Starting with soil concentrations, estimates exposure to a range of inorganic and organic contaminants via various food-chain related exposure pathways. Originally deterministic, Version 3 (Stubberfield 2018) of the model utilizes a Bayesian framework.	Ingestion via food crops, milk and meat products, direct ingestion of soil, inhalation of dusts and vapour. Exposure via groundwater is not included.	The model can be run with contaminant concentrations in soil, soil pH and organic content. All parameters, including exposure factors and receptor characteristics can be user-defined.	Agriculture, residential with small-scale food production (gardens, allotments).	Risk estimates for defined receptors (including critical receptors) based on comparing modelled exposure to critical values.	Hough 2002; Stubberfield 2018
RISKNET (Italy)	Characterization of human risk in screening risk assessment. Derivation of threshold concentrations to have an acceptable risk.	Starting from soil concentration greater than the threshold of potential contamination pollutants pathway is modelled in soil, groundwater and air. Intake is calculated using exposure indicators and concentrations at point of exposure.	From top soil: inhalation of indoor and outdoor air (gas, particles); ingestion of soil, dermal contact with contaminated soil particles, leaching in groundwater. From deep soil: inhalation of indoor and outdoor gases, leaching in groundwater. From groundwater: inhalation of indoor and outdoor gases.	Soil concentration; scenarios for land use; site and soil properties.	Residential, industrial.	Carcinogenic risk and hazard index (also cumulative). Threshold concentrations to have an acceptable risk.	http://www.reconnet.net
S-Risk (Belgium)	Calculation of generic or site-specific human health-based screening levels and prediction of human health risks at contaminated sites.	Starting with concentrations in soil, the distribution over solid, liquid and gaseous phases in soil is estimated and used as the basis for simulating a variety of exposure pathways. S-Risk is a tiered model that can be used generically or site-specific.	Oral intake of soil and indoor settled dust particles; intake of vegetables; intake of animal products (i.e., meat, milk and eggs); intake of water (i.e., drinking-water and/or ground water). Inhalation outdoor and indoor vapour contaminants; inhalation outdoor and indoor particles; inhalation of vapour during showering. Dermal exposure: absorption from soil and settled dust particles; absorption from water during bathing and showering.	Soil concentration is mandatory; concentrations in groundwater, food, dust and air are optional. Default model parameters (e.g., soil properties) can be modified if necessary.	Agricultural, residential (without garden, with garden or with vegetable garden), day recreation (indoor or outdoor), holiday resort, industry (light or heavy).	Concentrations in contact media, exposure results, risk indices, remediation values.	https://www.s-risk.be/
POPs Toolkit	Provide basic information for managing contaminated sites with persistent organic pollutants (POPs) and other hazardous chemical substances using a human-health risk assessment process.	Starting with tools for site prioritization for risk assessment and field sampling procedures, the human health risk assessment (HQs for non-carcinogens and incremental lifetime cancer risk (ILCRs) for carcinogens) can be calculated and as result risk management tools or policies can be applied.	Accidental soil ingestion, water ingestion, food ingestion, inhalation of contaminated particles and dermal contact with contaminated soil.	Concentration of contaminant in soils/drinking water/particles in the air, (accidental) soil/water/food ingestion rate for adult, absorption factor for the gastrointestinal tract/skin, surface area of exposed skin, soil loading to exposed skin, time of exposure, body weight of receptor, life expectancy (not used for non-carcinogens).	Not specified.	Hazard Quotient, Incremental Lifetime Cancer Risk, total dose.	http://www.popstoolkit.com/
RAIS - The Risk Assessment Information System (USA but used in Europe)	Web-based system to disseminate risk tools on chemical and radionuclides (separately) and supply information for risk assessment activities.	Offers essential tools and information for chronic and sub-chronic exposure risk.	Soil, sediments and air (outdoor and indoor) by ingestion, dermal contact and inhalation. Tap water and surface water by ingestion and dermal contact. Consumption of fish and farm produced products.	Soil, sediments, water and air concentration; scenarios for land; site, soil, air properties; physico-chemical distribution constants; intake parameters such as inhalation rate Humans characterization.	Residential, recreation, and workers (indoor, outdoor, composite, excavation, construction, and agriculture).	Non-carcinogenic and carcinogenic risk.	
MERLIN	Estimation of contaminants concentration in human tissues and organs.	Contaminants concentrations from food, drinks, soil, water and air are collected (there is also the possibility to model the contaminant pathway). Then a PBPK model estimates concentrations in human (individual or population) tissues from the intake.	Inhalation of indoor and outdoor air (gas, particles); ingestion of soil, food, drinking water.	Concentrations in environmental matrices, Matrix physical parameters, exposure indices, PBPK model parameters (toxicokinetic parameters and characteristics of population).		Concentration in human tissues and organs. Concentration in urine is also achievable.	http://merlin-expo.eu
INTEGRA	Multi-route, multi-pathway and internal exposure assessment.	Starting from environmental releases or environmental media concentrations, exposure through multiple pathway and routes for various age and gender groups external and internal exposure are estimated. Exposure is also calculated backwards from HBM data.	Inhalation of indoor and outdoor air (gas, particles); - Dietary ingestion (food, water, beverages) Non-dietary ingestion (soil, house dust, object to mouth Dermal: contact with consumer materials and cosmetics, rubbing off dust from surfaces, showering.	Release rate in various environmental media, environmental media concentrations, physicochemical properties, toxicokinetic properties.	Industrial, agricultural, urban.	Concentration in various environmental media, intake rate from various pathways and routes, internal dose in target tissues, expected biomarker levels.	Sarigiannis 2016

All models, except MERLIN-EXPO and INTEGRA, are multi-media models starting from contaminated land. MERLIN-EXPO and INTEGRA were included as they have been applied to assess exposure due to contaminated land.
*Some references can be found in the list "Additional references".

Table 1. Selected multi-media exposure modelling tools applied in Europe for human risk assessment.

the detailed quantitative comparison between models and model predictions made by the experts in 2007.[21,22] We suspect that the differences between models are still applicable. Input parameters of the models differ substantially, including especially compound-specific properties, human characteristics, and parameters describing physicochemical transfer processes.[3]

Particularly, modelling of indoor air concentrations and consumption of locally grown contaminated food has considerable uncertainty.[3] Problems for assessment of exposure through vegetable consumption include the lack of data on locally grown vegetables and particularly the calculation of the concentration in plants. Despite large efforts to model speciation in the soil, uptake by roots and transport within the plant, reliable estimates of metals in plants are rarely achieved. Organic components can be better modelled.[3] A tiered approach has been proposed to assess health risks of consumption of vegetables grown on cadmium contaminated soil.[23] The approach starts with establishing whether vegetables are locally grown, then applies generic and site-specific modelling tools, and ends with measurements of contaminant levels if health risks are judged to be possible.[23] Modelling of indoor air concentrations from contaminated groundwater or soil is highly uncertain. A validation study documented several orders of magnitude difference between modelled and measured concentrations.[3] Measurements of concentrations in indoor air are often highly variable and affected by other indoor sources. Reliable validation requires repeated measurements.

EXPOSURE ASSESSMENT IN EPIDEMIOLOGICAL STUDIES

Exposure assessment in epidemiological studies may deviate from that in risk assessment. Distance to specific landfill sites may be useful in epidemiology, but not in risk assessment. Figure 4 shows a general typology linked to the causal chain from source to intake by humans, addressing both modelling and monitoring at different levels. Figure S3 (see on-line supplementary material) shows a typology focused on contaminated sites, including a qualification of the performance.

Epidemiological studies on contaminated sites have extensively used **ecological study designs** to assess potential health effects.[16,24] This implies that the health status of populations exposed to contaminated sites is compared with the health status of reference populations not exposed to contaminated sites using (small) area-level data. No individual level data on health, confounders and exposure are used. In this design, exposure assessment cannot be refined as no individual data are used. Fewer individual level studies, such as cohort, case-control and cross-sectional studies, have been conducted. In these study designs, more detailed exposure assessment is feasible. Examples are an individual cohort study based on administrative data on landfill sites in the Lazio Region (Central Italy)[25] and a multisite study on residents near incinerators in the Emilia-Romagna Region (Northern Italy).[26]

Table 2 lists the frequency of application of exposure assessment methods in order of increasing complexity for three groups of epidemiological studies: hazardous waste sites, incinerators, and the additionally identified general ICS studies. Figure S4 (see on-line supplementary material) shows which environmental media have been characterized in epidemiological studies. Tables S1 and S2 (see on-line supplementary material) present the exposure assessment of individual epidemiological studies of ICSs on hazardous waste in the systematic review by Fazzo[16] and

METHOD	METRICS	NUMBER OF STUDIES APPLYING METHOD FOR		
		Hazardous waste studies (No. 54)*	Contaminated sites studies (No. 52)**	Incinerator studies (No. 41)***
Proximity indicators	Distance to a site from GIS Residence in municipality with an ICS	53, of which: • 25 distance • 28 municipality	39, of which: • 13 distance • 26 municipality	30, of which: • 19 distance • 11 municipal presence
Environmental modelling	Dispersion model for air pollution multi-media models	0	6^	11 (for air)
Environmental monitoring	Contaminants in soil, air, water, food	0	2	0
Personal exposure assessment	Direct (monitoring) or indirect (integrating time activity with environmental monitoring)	0	0	0
Biota monitoring	Hg in fish; Metals in lichens, pine needles, mosses indoors, outdoors	0	0	0
Human biomonitoring	Pb in blood, Cd in urine, hair	1	9	0

* Studies in systematic review,16 details in table S1 including references.[16]
** Additional studies identified for the current review, details in table S2 including references.
*** Studies identified in a systematic review of incinerator studies.[19]
^ All air pollution dispersion modelling.

Table 2. Methods of exposure assessment in selected epidemiological studies of contaminated sites.

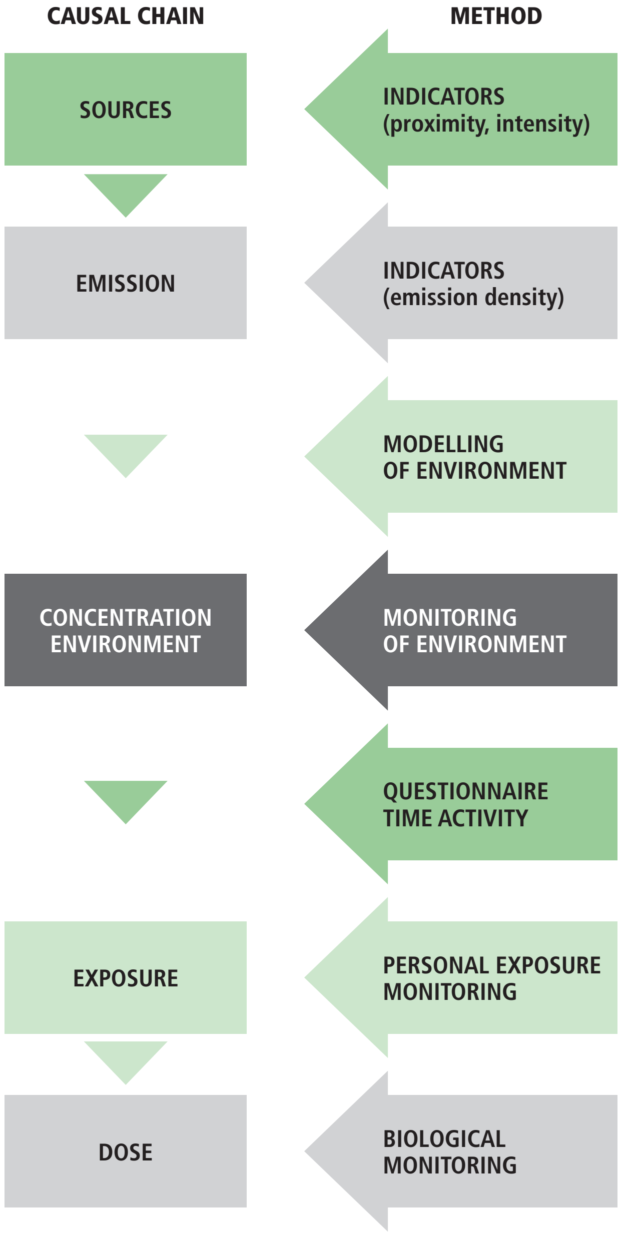

Figure 4. Exposure assessment methods in environmental epidemiology.

on contaminated sites in general. For references of the individual incinerator studies, we refer to the review by Cordioli,[19] to which we did not add additional evaluation.

Virtually, all of hazardous waste studies (53 out of 54) have used indicators of exposure, based on municipality or zip code of residence (28 studies) or distance to a contaminated site (25 studies). A limited number of studies reported monitoring data to support exposure status (figures S4). Detailed environmental modelling methods, such as those used for regulatory risk assessment, were not applied, possibly because of a lack of input data, particularly the soil contents of contaminants. One study in 32 11-13-year-old children used human biomonitoring (metals in hair) to link to intelligence quotient (IQ).[27] In virtually all epidemiological studies, the actual land use tends to be ignored, while it is an important component of exposure assessment in screening and site-specific risk assessment.

The 52 additional studies covered a wide range of ICSs and major pollutants from multiple Countries, including major industrial facilities, asbestos ore, industrial accidents (table S2). In the 52 additional studies on contaminated sites, proximity indicators were applied in 39 studies. Biomonitoring was used in 9 studies; 6 studies air pollution dispersion modelling; 1 study directly used measured metal pollution in soil in the epidemiological analysis.[28] A series of studies from Spain used data from the European Pollutant Release and Transfer Register (EPRTR)[29] to identify industrial sites with specific contaminants. In these ecological studies, distance to the industrial sites was used as exposure indicator.[30-32] Although monitoring was infrequently used directly, many studies included environmental monitoring to support that significant contamination occurred. We did not include studies that assessed specific industrial pollutants without mentioning a specific contaminated site. An example of this large group of studies is a recent study on persistent organic pollutants (POPs).[33] Two studies on Libby Montana asbestos-contaminated ore exposure used a questionnaire to identify activities with potential asbestos exposure. All other studies did not include time activity patterns, such as the place where people work, typically because of a lack of available data.

Exposure assessment in epidemiological studies on incinerators included indicators (qualitative and distance to the incinerator) and air dispersion modelling.[19] While the use of air dispersion modelling can be seen as an improvement on simply only using indicators of exposure, none of the studies used multi-media models or monitoring data in the epidemiological analysis. Furthermore, the studies differed in the level of detail of the residential information (address, full postal code or municipality/crude postal code). Given the reliance on location of residence as an indicator of exposure, the level of uncertainty associated with the metric used to describe location of residence (e.g., 6-figure postal code *vs.* 4-figure postal code) could well have a significant influence on levels of exposure misclassification.

Exposure indicators

The use of simple indicators of exposure, such as residence in municipality with an ICS, is linked to the (typically small) area design of most studies with no available information on individuals. Exposure indicators do not provide a quantitative measure of specific pollutants, in contrast to risk assessment where estimates of exposure are typically derived from modelled or measured concentrations of contaminants in various environmental media. Studies substantially differ in what indicators of exposure have been used. Distance to a site/incinerator – especially when calculated from residential addresses – is a better indicator than the simple presence/absence of a site in a municipality.[19] Discussion of exposure assessment and consistency of findings can further be found in a review of epidemiological studies using proximity to environmental hazards including ICSs.[34]

The degree of misclassification related to the use of indicators of exposure is often not documented in the studies. Two studies in the UK and Italy, respectively, compared distance to incinerators with dispersion model calculations using ADMS-urban.[19,35] Assuming that dispersion models provide a better assessment of exposure, both studies documented significant exposure misclassification, particularly when distance is used as a categorical variable which is common in epidemiological studies.[35] Both studies showed substantial anisotropy, that is concentration patterns are not well described by simple concentric circles, related to prevalent wind directions and terrain. The misclassification is probably even more severe for industrial sites with higher stacks than incinerators. Mohan et al.[36] evaluated different methodologies to assess exposures to atmospheric pollutants from a landfill site in epidemiological studies and concluded that dispersion modelling would be an improvement on basic proxies like distance. However, there is significant scope to improve indicators of exposure using simple rule-based approaches that take into account, e.g., prevailing wind and/or topographical features. Regardless, more methodological work on characterizing misclassification of exposure is needed. Errors in exposure assessment by using simple proxies might have a strong Berkson error component, which leads to loss of precision, but not bias when applied in epidemiological studies.[37]

Although the majority of studies used indicators of exposure in the statistical analysis of relationships with health, data on environmental contamination or human biomonitoring based on previous studies was available in a limited number of papers. For example, in the studies of contaminated sites in Ferrara (Emilia-Romagna Region, Northern Italy) and Love Canal (New York State, USA), the analysed exposure measure was based on indicator variables, but in both studies environmental monitoring data was available to document significant environmental levels of specific contaminants.[38,39] A limitation is that often environmental data are available only for the exposed population, but not for the reference population. An exception is a study related to an oil field waste site in New Mexico, documenting significant differences in environmental and human biomarker levels between exposed and control towns.[40]

Epidemiological studies have refined exposure assessment by incorporating the type of hazardous waste site in the analysis, using data on sources or contaminant levels in the soil or other media.[41-43] Duration of residence has been incorporated as another refinement.[38]

Advantages of indicators include the ease of obtaining the information. Additionally, distance to the source characterizes multiple exposure pathways and pollutants compared to measuring a specific pollutant in a specific medium. Conceptually, this has advantages over traditional risk assessment that tends to deal with one pollutant at a time rather than treating the exposure as a mixture.

The use of exposure indicators would benefit from better linking with known dispersion patterns based on models or measurements. Both studies on contaminated land and incinerators have used very different distance categories to label an area as exposed.[19] A recent review of 77 epidemiological studies of air pollution around major industrial facilities illustrated that distance to the source was used in the majority of studies and that the distance categories were very different.[17] Studies should further attempt to include validation sub-studies to assess validity. As an example, human biomonitoring documented that the exposure surrogates based upon distance around the Love Canal site were related to measured chlorobenzene levels in serum.[44]

Environmental modelling

Except for dispersion modelling of air pollution around incinerators,[19] environmental modelling is not often used in epidemiological studies. A study conducted around a waste landfill site in Italy used dispersion modelling of hydrogen sulfide (H_2S) to improve exposure assessment based on distance to a site only.[25] A study in the Rome Longitudinal Cohort used air dispersion modelling to assess residential exposure from an incinerator, landfill, and refinery in the epidemiological analysis.[45] A validation study in France indicated dispersion modelling as a reliable proxy for dioxin exposure from a point source.[46] The detailed multi-media models used in risk assessment have not been applied in epidemiological studies of hazardous waste, incinerators, and contaminated sites in general.

Environmental monitoring

Environmental monitoring has been used only in one study as a direct measure of exposure in the epidemiological analysis. In a Swedish study, cadmium (Cd) and lead (Pb) in soil near glasswork plants were used to assess individual exposure.[28] As stated in the section on indicators, environmental monitoring has been extensively used to document that relevant exposure occurs, for example in studies in Love Canal (USA) and Priolo (Sicily Region, Southern Italy).[39,47] This status is very different from the epidemiological literature on outdoor air pollution where monitoring has been extensively applied.

There is a large literature of environmental monitoring around contaminated sites, typically related to risk assessment.[3] We take as an example a study in Portugal on a mining area with over 100 years of exploration, where researchers monitored soils, stream sediments and superficial waters, road dusts, biota, vegetables, drinking and irrigation waters on the impacted site and in control areas.[48-52] The geochemistry signature of the mining works is markedly visible in all analysed media, including vegetables and water for direct human consumption. In parallel, human biomonitoring (urine, blood, hair, and nail samples) surveillance was performed.[53] The populations of the studied 4 villages are strongly dependent on the mine, but also on the use of soil (agriculture) and water (drinking, irrigation and recreation). Figure 2 shows potential exposure pathways related to contamination from the mine.

Personal exposure monitoring

Personal exposure monitoring (PEM) has not been applied in the reviewed epidemiological studies of ICSs. We did not consider studies of radiation related to nuclear power plants. **Direct monitoring** is difficult to conceptualize, except for air pollution exposure assessment. Settings that would lend themselves to PEM include incinerators[19] and contaminated land, where indoor air contamination is an important pathway. PEM is often labour intensive and thus expensive. Currently, PEM may therefore be applied only in relatively small populations, but with the development of larger scale application of low-cost sensors may become feasible in the near future. In studies with physiological endpoints requiring a relatively small population, PEM could be a direct exposure metric. PEM could additionally be used as a validation tool for easier-to-obtain exposure metrics, as is common in air pollution exposure assessment.

Indirect personal exposure assessment by linking measurements in relevant environmental media (e.g., home, drinking water, soil, food) with individual time activity patterns has also not been applied. Except for a study on asbestos,[54,55] data on individual behaviour of subjects or actual land use has not been considered.

Human biomonitoring

Ten studies have used human biomonitoring (HBM), of which one on hazardous waste, directly in the epidemiological analysis. A study of the Tar creek Superfund site reported on the association between hair levels of manganese (Mn), arsenic (As), and Cd and neuropsychological test scores of 32 11-13-year-old children.[27] Two papers assessing a Portuguese mining area reported associations between As, Mn, and Pb in toenails and blood with genotoxic and immunological markers of 122 subjects.[56,57] A study in 129 children aged 3-13 years in two exposed (smelter) and one control town in Bulgaria reported haematological effects in relation to Pb and Cd in blood.[58] In a cohort study of 242 children living in three towns at different distance to a contaminated water national priority site, mercury (Hg) in hair was associated with neuropsychological endpoints.[59] These studies are smaller studies using physiological endpoints instead of morbidity and mortality.

HBM may additionally be used for validation of easier-to-measure exposure metrics. Exposure surrogates based upon distance around the Love Canal site were related to measured chlorobenzene levels in serum.[44] HBM provides the most direct documentation of actual population exposure related to a specific contaminated site. In the complex setting of ICSs, an attractive feature is that HBM integrates exposure from different exposure pathways, which may otherwise be difficult to assess. HBM further takes into account time activity of subjects. Depending on the biomarker, HBM reflects longer term exposure compared to environmental monitoring which is affected by short-term variations.[3] Repeated environmental sampling is needed to obtain an average exposure in indoor air, for example.

Potential problems with the interpretation of HBM data include that measured biomarkers levels may be affected by other sources, e.g., smoking. Because HBM data do not distinguish between sources of exposure, the data may be of limited use for risk management. HBM can be expensive both in sampling collection and analysis and, therefore, sometimes is feasible only in limited population sizes. Measurements of heavy metals in urine are not expensive and sampling urine is also relatively easy to perform. Because HBM is an integrated measurement, HBM may limit the need for measurements in different environmental compartments, depending on whether exposure assessment is for an epidemiological study or for practical risk assessment. The physico-chemical and pharmaco-kinetic characteristics of the contaminants influence the target analite as well as the biological matrix in which it is expected to be found; e.g., organochlorine pesticides are highly lipophilic and persistent chemicals that are expected to be found in fatty compartments, such as adipose tissue, but also in serum, although levels in the two matrices might have different biological meanings.[60] Given the rapid metabolism of organophosphate pesticides, biomonitoring programmes commonly target dialkyl phosphate metabolites instead of the parent compound.

An issue is how to use information available for a sample to assess individual exposure of the whole population. A common design in risk assessment is to select the most susceptible or vulnerable group as a study population. If the most susceptible group is safe, then other population groups will be safe too. One possibility for epidemiological studies is to derive a predictive empirical model that is developed based upon measured biomarkers in a sample of the population and important exposure related predictor variables. Willmore[61] have developed a linear regression model for measured blood lead levels (BLLs) in children in relation to proximity to a lead smelter. Residential distance to the smelter, log of residential soil lead concentration, and child's age were statistically significant factors for predicting elevated BLLs in children living near a North Lake Macquarie lead smelter.[61] A Polish study developed a regression model for Pb and Cd in blood in children and local industrial and traffic and individual lifestyle.[62] Three studies in Southern Spain developed models for human adipose tissue PCBs and hexachlorobenzene and serum organochlorine concentrations.[63-65] The review is prepared in the framework of the COST action on Industrially Contaminated Sites and Health Network (ICSHNet) (https://www.icshnet.eu/).

POTENTIAL APPLICATION OF MULTI-MEDIA EXPOSURE ASSESSMENT MODELS IN EPIDEMIOLOGICAL STUDIES

Application of the models has shown the relative contribution of different exposure routes to the total intake for key pollutants. This knowledge could be used in epidemiological studies to inform the choice of better proxies of exposure.

The direct application of the models in exposure assessment in epidemiology seems a promising improvement for epidemiological studies as the models can be used with default values and thus do not require detailed input data that may not be readily available for epidemiological studies. One requirement is the availability of soil monitoring data, which is often available as a motivation to start a health investigation. The INTEGRA model is able to estimate soil concentrations starting from emissions in other media (e.g., air) and to estimate the complete food chain (including vegetation, meat, dairy products, and fish) residues. Most models allow the user to adapt input values to tailor the assessment for site-specific assessment. A limitation is the large differences in model predictions.[22] Most models were designed to provide population risks and may not be useful to assess differences in individual exposure of subjects living in the same neighbourhood. The models may therefore be most useful for studies of multiple sites, where assessment of a group average exposure may be useful. Merlin-Expo and INTEGRA have been applied to assess individual exposure. These tools use a PBPK model to assess contaminant levels in the body and could represent an option to improve full-chain exposure assessment in epidemiological studies. Two studies in Belgium documented realistic agreement between modelled and measured Pb and As levels in blood, though with a low correlation of individual levels.[66,67]

EVALUATION AND RECOMMENDATIONS

Epidemiological studies have mostly used simple indicators of exposure, such as residence in a municipality with an ICS or distance to an incinerator, in the epidemiological analysis without actual modelling or monitoring of specific pollutants. Air dispersion models have been applied especially in incinerator studies. The more sophisticated deterministic multi-media models used in screening risk assessment of contaminated sites have not been applied in epidemiological studies so far. A few typically smaller studies of physiological health endpoints have applied human biomonitoring to assess exposure.

Based on the discussion in the previous sections, we formulate recommendations for potential improvement of exposure assessment in epidemiological studies of ICSs. We note that there are more purposes of exposure assessment than application in epidemiological studies, exposure assessment alone may be sufficient to result in policy decisions. Here we focus our discussion to epidemiological studies (see last section). To decide which is the optimal exposure assessment method depends on the design of the epidemiological study. Key features include type of health effects (chronic, acute), population size, single or multiple sites, and – last but not least – budgetary constraints.

Epidemiological studies using administrative health data at the area level and indicators of exposure, despite their limitations, represent a useful first approach to highlight priority areas and generate hypotheses. Epidemiological studies using administrative health data using geographic information system (GIS) could be improved by using individual data rather than area data, allowing more detailed exposure (and confounder) assessment. This development has already occurred in studies of health effects of air pollution using administrative data on mortality, morbidity, and cancer.[25,46,68,69] We further assert that studies using physiological health endpoints in addition to clinically manifest morbidity/mortality would be extremely useful as they can be conducted in smaller populations and thus allow more detailed exposure assessment.

The following recommendations were developed:

1. Proximity indicators will be applied in future despite its limitations. The application of indicators of exposure can be improved by using:

- continuous distance based metrics instead of presence/absence of an ICS in a municipality or other administrative unit;
- using residential address instead of municipality of residence to improve individual exposure assessment;
- knowledge on spatial extent of contamination to make less arbitrary choices when categories of distance to a contaminated site are used.

2. Epidemiological studies should make more use of land use data (GIS overlay with residential data) to account for differences in population including use of land.

3. More validation of exposure assessment methods is needed to allow assessment of misclassification of exposure. This applies to indicators of exposure, but also to modelled and measured environmental exposures. We recommend smaller validation studies using personal exposure monitoring or human biomonitoring to assess the validity of exposure metrics. Both exposed and reference populations need to be included, which is currently often not the case.

4. Methodological work of the impact of exposure measurement error on estimated health risks is needed, similar to work done in epidemiological studies of outdoor air pollution.

5. Epidemiological studies should consider using more extensively the multi-media exposure assessment models used in risk assessment, either directly or indirectly to better define the main potential exposure routes for different pollutants.

6. For the 'air inhalation' route around large point sources such as incinerators, dispersion modelling is preferable compared to using distance as a proxy.

7. The food exposure pathway is difficult to model. Additional work is needed, including characterization of the fraction of locally produced food and contamination in various foods. Monitoring is often the most practicable approach to more accurately characterizing exposures via the food chain, but limits investigation to a minimal number of potentially harmful agents.

8. Indoor air inhalation pathway is difficult to characterize both by modelling and monitoring. Additional work is needed, particularly important for semi-volatile compounds.

9. As exposure to contaminants from ICSs is often correlated in space with other environmental sources such as motorized traffic, inclusion of other sources in the analysis will increase the validity of the study.

10. Human biomonitoring and personal exposure monitoring should be considered particularly in well selected study populations assessing both exposure and physiological health endpoints. Human biomonitoring has the advantage to result in integrated measurement of all exposure routes.

11. The use of internal dosimetry models can provide further insights regarding the actual biologically effective dose that reaches the tissues. In addition, route- and age-dependent bioavailability differences are accounted for, providing a more refined metric for the effective dose than external exposure.

12. Application of various omics techniques may be useful to address the complex exposure pattern around an ICSs.[70] Wild[71] proposed the concept of the 'exposome' to more comprehensively assess human exposure to environmental stressors. Methods that have been proposed to assess the internal exposome include metabolomics, proteomics, adductomics.[72]

13. Contaminated sites include communities that have been exposed to excessive concentrations of hazardous substances and exposure assessment should consider the ethical dimension of the human health research that is conducted in the context of contaminated sites. An ethical analysis makes the rationale for decisions transparent and provides a basis for evaluating observed outcomes as a function of the rationale provided for past actions.

FINAL REMARKS

This paper is an original contribution aimed to address one of the main objectives of ICSHNet COST Action: the identification of suitable strategies, methods, and tools for exposure assessment in ICSs. The results will be used to develop Action guidance documents on how to deal with the complex environmental health scenarios of ICSs across Europe.

We hold there is an over-reliance on risk assessment in making decisions around management of ICSs. Epidemiological studies may provide useful information on actual population health risks of ICSs. Swartjes[3] noted that guideline values are typically stricter when epidemiological data is lacking and hence large safety factors are used. Management and remediation of ICSs is extremely costly, so some good epidemiological studies showing there is limited adverse health outcomes associated with an ICS could save a lot of money. The opposite may also occur, that is health effects may be detected in epidemiological studies where risk assessment modelling suggests no effect. Therefore, we need more and improved epidemiological studies of ICSs. Advantages of epidemiological studies include that health effect of the realistic mixture of contaminants is studied directly in humans. Interaction between chemical and non-chemical exposures (increased susceptibility due to social deprivation near an ICS) is taken into account in local studies. Epidemiological studies of a specific site also face intrinsic limits.[15] Issues include that the population size may not be large enough to detect small effects on morbidity and mortality. Exposures to an ICS may be correlated with other environmental exposures and, therefore, difficult to disentangle.[19,45] Adequate adjustment for potential confounders is another major issue.

Environmental health issues in ICSs often involve marked inequalities. These sites, being in general not attractive residential places, tend to be inhabited by people of lower socioeconomic level, and deprivation gradients are often seen around contaminated sites.[73] In ICSs, there is the concurrence of multiple residential and occupational contaminants, social disadvantages, and additional burden imposed at the individual level by unhealthy lifestyles.[73,74] Addressing exposure assessment strategies to different population subgroups can help in better characterizing the exposures and health scenarios in ICSs; to this purpose, an effort should be made to integrate, rather than to adjust for, information deriving from exposures experienced in ICSs by

- workers employed in the industrial activities, who are also part of the resident population);
- exposure profiles of residents not occupationally exposed, in particular women and elderly people;
- children, who are not occupationally exposed nor significantly exposed to other typical adult lifestyles, but who have some behaviours that could increase their exposure to specific pollutants (i.e., ingestion of soil contaminants).

This approach, when attainable, can help in identifying the sources of environmental contaminants. Moreover, this is per se of public health relevance as it could help in addressing inequalities in exposure to contaminants of toxicological concern, also in absence of direct information on local health impacts.

Conflict of interest disclosure: the Authors declare they have no conflict of interest.

REFERENCES AND NOTES

1. Pasetto R, Martin-Olmedo P, Martuzzi M, Iavarone I. Exploring available options in characterising the health impact of industrially contaminated sites. Ann Ist Super Sanita 2016;52(4):476-82.
2. Swartjes FA (ed). Dealing with Contaminated Sites. From Theory towards Practical Application. Springer 2011.
3. Swartjes FA. Human health risk assessment related to contaminated land: state of the art. Environ Geochem Health 2015;37(4):651-73.
4. Axelsson G, Stockfelt L, Andersson E, Gidlof-Gunnarsson A, Sallsten G, Barregard L. Annoyance and worry in a petrochemical industrial area – prevalence, time trends and risk indicators. Int J Environ Res Public Health 2013;10(4):1418-38.
5. Geelen LMJ, Souren AFMM, Jans HWA, Ragas AMJ. Air Pollution from Industry and Traffic: Perceived Risk and Affect in the Moerdijk Region, The Netherlands. Hum Ecol Risk Assess 2013;19(6):1644-63.
6. Declaration of the Sixth Ministerial Conference on Environment and Health. Available from: http://www.euro.who.int/en/media-centre/events/events/2017/06/sixth-ministerial-conference-on-environment-and-health/documentation/declaration-of-the-sixth-ministerial-conference-on-environment-and-health
7. van Liedekerke M, Prokop G, Rabl-Berger S, Kibblewhite M, Louwagie G. Progress in the Management of Contaminated Sites in Europe. Report EUR 26376. Luxembourg, Joint Research Centre, 2014. Available from: https://ec.europa.eu/jrc/en/publication/reference-reports/progress-management-contaminated-sites-europe
8. Panagos P, Van Liedekerke M, Yigini Y, Montanarella L. Contaminated sites in Europe: review of the current situation based on data collected through a European network. J Environ Public Health 2013;2013:158764.
9. European Environment Agency. SOER 2015 – The European environment – state and outlook 2015. Synthesis report. Copenhagen: EEA; 2015. Available from: www.eea.europa.eu/soer (last accessed: april 2018).
10. WHO Regional Office for Europe. Contaminated sites and health. Report of two WHO workshops. Syracuse, Italy, 18 November 2011; Catania, Italy, 21-22 June 2012. Copenhagen, WHO Regional Office for Europe, 2013. Available from: http://www.euro.who.int/__data/assets/pdf_file/0003/186240/e96843e.pdf?ua=1
11. Pirastu R, Pasetto R, Zona A, et al. The health profile of populations living in contaminated sites: SENTIERI approach. J Environ Public Health 2013;2013:939267.
12. US Environmental Protection Agency. Superfund Risk Assessment. 2018. Available from: https://www.epa.gov/risk/superfund-risk-assessment (last accessed: 21.04.2018).
13. Agency for Toxic Substances and Disease Registry. Public Health Assessment Guidance Manual (2005 Update). Available from: https://www.atsdr.cdc.gov/hac/PHAManual/toc.html (last accessed: 01.09.2016).
14. Di Q, Dominici F, Schwartz JD. Air Pollution and Mortality in the Medicare Population. N Engl J Med 2017;377(15):1498-99.
15. Savitz DA. Commentary: Response to Environmental Pollution: More Research May Not Be Needed. Epidemiology 2016;27(6):919-20.
16. Fazzo L, Minichilli F, Santoro M, et al. Hazardous waste and health impact: a systematic review of the scientific literature. Environ Health 2017;16(1):107.
17. Pascal M, Pascal L, Bidondo ML, et al. A review of the epidemiological methods used to investigate the health impacts of air pollution around major industrial areas. J Environ Public Health 2013;2013:737926.
18. National Research Council (US) Committee on Environmental Epidemiology. Environmental Epidemiology: Volume 1: Public Health and Hazardous Wastes. Washington (DC): National Academies Press (US); 1991.
19. Cordioli M, Ranzi A, De Leo GA, Lauriola P. A review of exposure assessment methods in epidemiological studies on incinerators. J Environ Public Health 2013;2013:129470.
20. Zartarian VG, Ott WR, Duan N. A quantitative definition of exposure and related concepts. J Expo Anal Environ Epidemiol 1997;7(4):411-37.
21. Claudio Carlon (ed). Derivation methods of soil screening values in Europe. A review and evaluation of national procedures towards harmonisation. Ispra: Joint Research Centre; 2007. Available from: https://esdac.jrc.ec.europa.eu/ESDB_Archive/eusoils_docs/other/EUR22805.pdf
22. Swartjes FA. Insight into the variation in calculated human exposure to soil contaminants using seven different European models. Integr Environ Assess Manag 2007;3(3):322-32.
23. Swartjes FA, Versluijs KW, Otte PF. A tiered approach for the human health risk assessment for consumption of vegetables from with cadmium-contaminated land in urban areas. Environ Res 2013;126:223-31.
24. De Sario M, Pasetto R, Vecchi S, et al. A scoping review of the epidemiological methods used to investigate the health effects of industrially contaminated sites. Epidemiol Prev 2018;42(5-6) Suppl 1:59-68.
25. Mataloni F, Badaloni C, Golini MN, et al. Morbidity and mortality of people who live close to municipal waste landfills: a multisite cohort study. Int J Epidemiol 2016;45(3):806-15.
26. Candela S, Ranzi A, Bonvicini L, et al. Air pollution from incinerators and reproductive outcomes: a multisite study. Epidemiology 2013;24(6):863-70.
27. Wright RO, Amarasiriwardena C, Woolf AD, Jim R, Bellinger DC. Neuropsychological correlates of hair arsenic, manganese, and cadmium levels in school-age children residing near a hazardous waste site. Neurotoxicology 2006;27(2):210-16.
28. Nyqvist F, Helmfrid I, Augustsson A, Wingren G. Increased Cancer Incidence in the Local Population Around Metal-Contaminated Glassworks Sites. J Occup Environ Med 2017;59(5):e84-90.
29. European Pollutant Release and Transfer Register. Available from: http://prtr.ec.europa.eu/#/home
30. López-Abente G, García-Pérez J, Fernández-Navarro P, Boldo E, Ramis R. Colorectal cancer mortality and industrial pollution in Spain. BMC Public Health 2012;12:589.
31. Cirera L, Cirarda F, Palència L, et al. Mortality due to haematological cancer in cities close to petroleum refineries in Spain. Environ Sci Pollut Res Int 2013;20(1):591-96.
32. Fernández-Navarro P, García-Pérez J, Ramis R, Boldo E, López-Abente G. Proximity to mining industry and cancer mortality. Sci Total Environ 2012;435-436:66-73.
33. Mustieles V, Fernández MF, Martin-Olmedo P, et al. Human adipose tissue levels of persistent organic pollutants and metabolic syndrome components: Combining a

cross-sectional with a 10-year longitudinal study using a multi-pollutant approach. Environ Int 2017;104:48-57.

34. Brender JD, Maantay JA, Chakraborty J. Residential proximity to environmental hazards and adverse health outcomes. Am J Public Health 2011;101 Suppl 1:S37-52.
35. Ashworth DC, Fuller GW, Toledano MB, et al. Comparative assessment of particulate air pollution exposure from municipal solid waste incinerator emissions. J Environ Public Health 2013,2013:560342.
36. Mohan R, Leonardi GS, Robins A, et al. Evaluation of methodologies for exposure assessment to atmospheric pollutants from a landfill site. J Air Waste Manag Assoc 2009;59(4):490-501.
37. Armstrong BG. Effect of measurement error on epidemiological studies of environmental and occupational exposures. Occup Environ Med 1998;55(10):651-56.
38. Pasetto R, Ranzi A, De Togni A, et al. Cohort study of residents of a district with soil and groundwater industrial waste contamination. Ann Ist Super Sanita 2013;49(4):354-57.
39. Gensburg Lenore J, Pantea C, Kielb C, Fitzgerald E, Stark A, Kim N. Cancer incidence among former Love Canal residents. Environ Health Perspect 2009;117(8):1265-71.
40. Dahlgren J, Takhar H, Anderson-Mahoney P, Kotlerman J, Tarr J, Warshaw R. Cluster of systemic lupus erythematosus (SLE) associated with an oil field waste site: a cross sectional study. Environ Health 2007;6:8.
41. Benedetti M, Zona A, Beccaloni E, Carere M, Comba P. Incidence of Breast, Prostate, Testicular, and Thyroid Cancer in Italian Contaminated Sites with Presence of Substances with Endocrine Disrupting Properties. Int J Environ Res Public Health 2017;14(4):E355.
42. Fazzo L, Minichilli F, Pirastu R, et al. A meta-analysis of mortality data in Italian contaminated sites with industrial waste landfills or illegal dumps. Ann Ist Super Sanita 2014;50(3):278-85.
43. Lu X, Lessner L, Carpenter DO. Association between hospital discharge rate for female breast cancer and residence in a zip code containing hazardous waste sites. Environ Res 2014;134:375-81.
44. Kielb CL, Pantea CI, Gensburg LJ, et al. Concentrations of selected organochlorines and chlorobenzenes in the serum of former Love Canal residents, Niagara Falls, New York. Environ Res 2010;110(3):220-25.
45. Ancona C, Badaloni C, Mataloni F, et al. Mortality and morbidity in a population exposed to multiple sources of air pollution: A retrospective cohort study using air dispersion models. Environ Res 2015;137:467-74.
46. Floret N, Viel JF, Lucot E, et al. Dispersion modeling as a dioxin exposure indicator in the vicinity of a municipal solid waste incinerator: a validation study. Environ Sci Technol 2006;40(7):2149-55.
47. Fazzo L, Carere M, Tisano F, et al. Cancer incidence in Priolo, Sicily: a spatial approach for estimation of industrial air pollution impact. Geospat Health 2016;11(1):320.
48. Candeias C, Ferreira da Silva E, Ávila PF, Teixeira JP. Identifying Sources and Assessing Potential Risk of Exposure to Heavy Metals and Hazardous Materials in Mining Areas: The Case Study of Panasqueira Mine (Central Portugal) as an Example. Geosciences 2014;4(4):240-68.
49. Candeias C, Ávila PF, Ferreira da Silva E, Ferreira A, Salgueiro R, Teixeira JP. Acid mine drainage from the Panasqueira mine and its influence on Zêzere river (Central Portugal). J Afr Earth Sci 2013;99(2):705-12.
50. Candeias C, Ávila PF, Ferreira da Silva E, Teixeira JP. Integrated approach to assess the environmental impact of mining activities: estimation of the spatial distribution of soil contamination (Panasqueira mining area, Central Portugal). Environ Monit Assess 2015;187:135.
51. Candeias C, Ávila PF, Ferreira da Silva E, Ferreira A, Durães N, Teixeira JP. Water-Rock Interaction and Geochemical Processes in Surface Waters Influenced by Tailings Impoundments: Impact and Threats to the Ecosystems and Human Health in Rural Communities (Panasqueira Mine, Central Portugal). Water Air Soil Pollut 2015;226(2):23.
52. Ávila PF, Ferreira da Silva E, Candeias C. Health risk assessment through consumption of vegetables rich in heavy metals: the case study of the surrounding villages from Panasqueira mine, Central Portugal. Environ Geochem Health 2017;39(3):565-89.
53. Coelho P, Costa S, Costa C, et al. Biomonitoring of several toxic metal(loid)s in different biological matrices from environmentally and occupationally exposed populations from Panasqueira mine area, Portugal. Environ Geochem Health 2014; 36(2):255-69.
54. Horton DK, Bove F, Kapil V. Select mortality and cancer incidence among residents in various U.S. communities that received asbestos-contaminated vermiculite ore from Libby, Montana. Inhal Toxicol 2008;20(8):767-75.
55. Ryan PH, Rice CH, Lockey JE, et al. Childhood exposure to Libby amphibole asbestos and respiratory health in young adults. Environ Res 2017;158:470-79.
56. Coelho P, García-Lestón J, Costa S, et al. Genotoxic effect of exposure to metal(loid)s. A molecular epidemiology survey of populations living and working in Panasqueira mine area, Portugal. Environ Int 2013t;60:163-70.
57. Coelho P, García-Lestón J, Costa S, et al. Immunological alterations in individuals exposed to metal(loid)s in the Panasqueira mining area, Central Portugal. Sci Total Environ 2014;475:1-7.
58. Fischer AB, Georgieva R, Nikolova V, et al. Health risk for children from lead and cadmium near a non-ferrous smelter in Bulgaria. Int J Hyg Environ Health 2003; 206(1):25-38.
59. Deroma L, Parpinel M, Tognin V, et al. Neuropsychological assessment at school-age and prenatal low-level exposure to mercury through fish consumption in an Italian birth cohort living near a contaminated site. Int J Hyg Environ Health 2013;216(4):486-93.
60. Artacho-Cordón F, Fernández-Rodríguez M, Garde C, et al. Serum and adipose tissue as matrices for assessment of exposure to persistent organic pollutants in breast cancer patients. Environ Res 2015;142:633-43.
61. Willmore A, Sladden T, Bates L, Dalton CB. Use of a geographic information system to track smelter-related lead exposures in children: North Lake Macquarie, Australia, 1991-2002. Int J Health Geogr 2006;5:30.
62. Kowalska M, Kulka E, Jarosz W, Kowalski M. The determinants of lead and cadmium blood levels for preschool children from industrially contaminated sites in Poland. Int J Occup Med Environ Health 2018;31(3):351-59.
63. Arrebola JP, Martin-Olmedo P, Fernandez MF, et al. Predictors of concentrations of hexachlorobenzene in human adipose tissue: a multivariate analysis by gender in Southern Spain. Environ Int 2009;35(1):27-32.
64. Arrebola JP, Fernandez MF, Porta M, et al. Multivariate models to predict human adipose tissue PCB concentrations in Southern Spain. Environ Int 2010;36(7):705-13.
65. González-Alzaga, Lacasaña M, Hernández AF, et al. Serum concentrations of organochlorine compounds and predictors of exposure in children living in agricultural communities from South-Eastern Spain. Environ Pollut 2018;237:685-94.
66. Fierens T, van Holderbeke M, Standaert A, et al. Multimedia & PBPK modelling with MERLIN-Expo versus biomonitoring for assessing Pb exposure of pre-school children in a residential setting. Sci Total Environ 2016;568:785-93.
67. van Holderbeke M, Fierens T, Standaert A, et al. Assessing multimedia/multipathway exposures to inorganic arsenic at population and individual level using MERLIN-Expo. Sci Total Environ 2016;568:794-802.
68. Benedetti M, De Santis M, Manno V, et al. Spatial distribution of kidney disease in the contaminated site of Taranto (Italy). Am J Ind Med 2017;60(12):1088-99.
69. Makris KC, Voniatis M. Brain cancer cluster investigation around a factory emitting dichloromethane. Eur J Public Health 2018;28(2):338-43.
70. Sarigiannis DA, Karakitsios S. Addressing complexity of health impact assessment in industrially contaminated sites via the exposome paradigm. Epidemiol Prev 2018;42(5-6) Suppl 1:37-48.
71. Wild CP. Complementing the genome with an "exposome" : the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev 2005;14(8):1847-50.
72. Wild CP. The exposome: from concept to utility. Int J Epidemiol 2012;41(1):24-32.
73. Viel JF, Hägi M, Upegui E, Laurian L. Environmental justice in a French industrial region: are polluting industrial facilities equally distributed? Health Place 2011;17(1):257-62.
74. Martuzzi M, Mitis F, Forastiere F. Inequalities, inequities, environmental justice in waste management and health. Eur J Public Health 2010;20(1):21-26.

ADDITIONAL REFERENCES

- Ancona C, Mataloni F, Badaloni C, et al. Residential cohort approach in industrial contaminated sites: the ERAS Lazio project. Epidemiol Prev 2014;38(2) Suppl 1:158-61.
- Barry V, Winquist A, Steenland K. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. Environ Health Perspect 2013;121(11-12):1313-18.
- Binazzi, GdL SENTIERI-ReNaM. SENTIERI – Epidemiological study of residents in national priority contaminated sites: incidence of mesothelioma. Epidemiol Prev 2016;40(5) Suppl1:1-116.
- Binazzi A, Marinaccio A, Corfiati M, et al. Mesothelioma incidence and asbestos exposure in Italian national priority contaminated sites. Scand J Work Environ Health 2017;43(6):550-59.
- Brand E, Otte PF, Lijzen JPA. CSOIL 2000: an exposure model for human risk assessment of soil contamination. A model description. RIVM report 711701054/2007. 2007. Available from: https://www.rivm.nl/dsresource?objectid=b1300413-2fb6-4c18-a383-32c921f6e592&type=org&disposition=inline
- Candeias C, Melo R, Ávila PF, Ferreira da Silva E, Salgueiro R, Teixeira JP. Heavy metal pollution in mine-soil-plant system in S. Francisco de Assis – Panasqueira mine (Portugal). Applied Geochemistry 2014;44:12-26.
- Candeias C. Modelling the Impact of Panasqueira Mine in the Ecosystems and Human Health: A Multidisciplinary Approach. Ph.D. Thesis, University of Aveiro and University of Porto, Aveiro, Portugal, 2013.

- Cernigliaro A, Tavormina E, Dardanoni G, Scondotto S. Reproductive health in high environmental risk areas in Sicily Region (Southern Italy) in the period 2007-2013. Epidemiol Prev 2016;40(3-4):197-204.
- Chang JW, Chen HL, Su HJ, Liao PC, Guo HR, Lee CC. Dioxin exposure and insulin resistance in Taiwanese living near a highly-contaminated area. Epidemiology 2010;21(1):56-61.
- Davies BE, White HM. Trace elements in vegetables grown on soils contaminated by base metal mining. J Plant Nutr 1981;3(1-4):387-96.
- European Envioronment Agency. The application of models under the European Union's Air Quality Directive: A technical reference guide. EEA Technical Report No 10/2011. Copenhagen, EEA, 2011. Available from: https://www.eea.europa.eu/publications/fairmode
- Elliott P, Briggs D, Morris S, et al. Risk of adverse birth outcomes in populations living near landfill sites. BMJ 2001;323(7309):363-68.
- Eizaguirre-García D, Rodríguez-Andrés C, Watt GC, Hole D. A study of leukaemia in Glasgow in connection with chromium-contaminated land. J Public Health Med 1999; 21(4):435-38.
- Eizaguirre-García D, Rodríguez-Andrés C, Watt GC. Congenital anomalies in Glasgow between 1982 and 1989 and chromium waste. J Public Health Med 2000;22(1):54-58.
- Fantini F, Porta D, Fano V, et al. Epidemiologic studies on the health status of the population living in the Sacco River Valley. Epidemiol Prev 2012;36(5) Suppl 4:44-52.
- Fazzo L, Puglisi F, Pellegrino A, et al. Mortality and morbidity cohort study of residents in the neighbourhood of Milazzo industrial area (Sicily). Epidemiol Prev 2010;34(3):80-86.
- Forand SP, Lewis-Michl EL, Gomez MI. Adverse birth outcomes and maternal exposure to trichloroethylene and tetrachloroethylene through soil vapor intrusion in New York State. Environ Health Perspect 2012;120(4):616-21.
- Granslo JT, Bråtveit M, Hollund BE, Lygre SH, Svanes C, Moen BE. A follow-up study of airway symptoms and lung function among residents and workers 5.5 years after an oil tank explosion. BMC Pulm Med 2017;17(1):18.
- Helmfrid I, Berglund M, Löfman O, Wingren G. Health effects and exposure to polychlorinated biphenyls (PCBs) and metals in a contaminated community. Environ Int 2012;44:53-58.
- Herbarth O, Franck U, Krumbiegel P, Rehwagen M, Rolle-Kampczyk U, Weiss H. Noninvasive assessment of liver detoxification capacity of children, observed in children from heavily polluted industrial and clean control areas, together with assessments of air pollution and chloro-organic body burden. Environ Toxicol 2004;19(2):103-08.
- Hough R. Applying Models of Trace Metal Transfer to Risk Assessment. PhD Thesis, University of Nottingham, UK, 2002.
- Hough RL, Booth P, Avery LM, et al. Risk assessment of the use of PAS100 green composts in sheep and cattle production in Scotland. Waste Manage 2012;32(1):117-30.
- Iavarone I. Industrially contaminated sites and health network. In: Pasetto R, Iavarone I (ed). First Plenary Conference. Industrially Contaminated Sites and Health Network (ICSHNet, COST Action IS1408). Istituto Superiore di Sanità. Rome, October 1-2, 2015. Proceedings. Rapporti ISTISAN 16/27. Roma: Istituto Superiore di Sanità; 2016; pp 3-5; 6-8. Available from: http://old.iss.it/binary/publ/cont/16_27_web.pdf
- Jeffries J. Using science to create a better place. CLEA software (Version 1.05) Handbook. Better Regulation Science Programme. Science Report: SC050021/SR4. Bristol, UK Environment Agency, 2009.
- Kerger BD, Butler WJ, Paustenbach DJ, Zhang J, Li S. Cancer mortality in Chinese populations surrounding an alloy plant with chromium smelting operations. J Toxicol Environ Health A 2009;72(5):329-44.
- Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. Int J Epidemiol 2016;45(6):1866-86.
- Lee LJ, Chung CW, Ma YC, et al. Increased mortality odds ratio of male liver cancer in a community contaminated by chlorinated hydrocarbons in groundwater. Occup Environ Med 2003;60(5):364-69.
- Lin MC, Yu HS, Tsai SS, et al. Adverse pregnancy outcome in a petrochemical polluted area in Taiwan. J Toxicol Environ Health A 2001;63(8):565-74.
- Linos A, Petralias A, Christophi CA, et al. Oral ingestion of hexavalent chromium through drinking water and cancer mortality in an industrial area of Greece – an ecological study. Environ Health 2011;10:50.
- Lijzen J, Rikken, M. EUSES version 2.0. Bilthoven, Netherlands: RIVM; 2004.
- Marinaccio A, Binazzi A, Bonafede M, et al. Malignant mesothelioma due to non-occupational asbestos exposure from the Italian national surveillance system (ReNaM): epidemiology and public health issues. Occup Environ Med 2015;72(9):648-55.
- Mayan ON, Gomes MJ, Henriques A, Silva S, Begonha A. Health survey among people living near an abandoned mine. A case study: Jales mine, Portugal. Environ Monit Assess 2006;123(1-3):31-40.
- Parodi S, Santi I, Casella C, et al. Risk of leukaemia and residential exposure to air pollution in an industrial area in Northern Italy: a case-control study. Int J Environ Health Res 2015;25(4):393-404.
- Parodi S, Santi I, Marani E, et al. Risk of non-Hodgkin's lymphoma and residential exposure to air pollution in an industrial area in northern Italy: a case-control study. Arch Environ Occup Health 2014;69(3):139-47.
- Pascal L, Pascal M, Stempfelet M, Goria S, Declercq C. Ecological study on hospitalizations for cancer, cardiovascular, and respiratory diseases in the industrial area of Etang-de-Berre in the South of France. J Environ Public Health 2013;2013:328737.
- Pesatori AC, Baccarelli A, Consonni D, et al. Aryl hydrocarbon receptor-interacting protein and pituitary adenomas: a population-based study on subjects exposed to dioxin after the Seveso, Italy, accident. Eur J Endocrinol 2008;159(6):699-703.
- Pirastu R, Zona A, Ancona C, et al. Mortality results in SENTIERI Project. Epidemiol Prev 2011;35(5-6) Suppl 4:29-152.
- Pirastu R, Comba P, Iavarone I, et al. Environment and health in contaminated sites: the case of Taranto. J Environ Public Health 2013;2013:753719.
- Ranzi A, Ancona C, Angelini P, et al. Health impact assessment of policies for municipal solid waste management: findings of the SESPIR Project. Epidemiol Prev 2014;38(5):313-22.
- Atlantic Risk-Based Corrective Action. Atlantic RBCA (Risk-Based Corrective Action) for Petroleum Impacted Sites in Atlantic Canada. Version 3, User Guidance. July 2012. Available from: http://esdat.net/Environmental%20Standards/Canada/Atlantic_Petroleum_Impacted_Sites/ATLANTIC_RBCA_User_Guidance_v3_July_2012doc_final.pdf
- Ribeiro TS, Carvalho DP, Guimarães MT, et al. Prevalence of hypertension and its associated factors in contaminated areas of the Santos-São Vicente Estuarine region and Bertioga, Brazil: 2006-2009. Environ Sci Pollut Res Int 2016;23(19):19387-96.
- Rodríguez-Barranco M, Lacasaña M, Gil F, et al. Cadmium exposure and neuropsychological development in school children in southwestern Spain. Environ Res 2014;134:66-73.
- Rusconi F, Catelan D, Accetta G, et al. Asthma symptoms, lung function, and markers of oxidative stress and inflammation in children exposed to oil refinery pollution. J Asthma 2011;48(1):84-90.
- Santoro M, Minichilli F, Pierini A, et al. Congenital Anomalies in Contaminated Sites: A Multisite Study in Italy. Int J Environ Res Public Health 2017;14(3):E240.
- Sarigiannis D, Gotti A, Karakitsios S, Kontoroupis P, Nikolaki S. P-234: Intera Platform A Tool for Mechanistic Risk Assessment of Indoor Air Pollutants. Epidemiology 2012;23(5S):P-234.
- Sarigiannis D, Karakitsios S, Gotti A, Handakas E, Papadaki K. INTEGRA: Advancing risk assessment using internal dosimetry metrics. Toxicology Letters 2015;238(2): S110-11.
- Sarigiannis D, Karakitsios S, Gotti A, et al. Integra: From global scale contamination to tissue dose. Proceedings - 7th International Congress on Environmental Modelling and Software: Bold Visions for Environmental Modeling, iEMSs 2014;2:1001-08.
- Sarigiannis DA. Assessing the impact of hazardous waste on children's health: The exposome paradigm. Environ Res 2017;158:531-41.
- Sarigiannis DA, Karakitsios SP, Handakas E, Simou K, Solomou E, Gotti A. Integrated exposure and risk characterization of bisphenol-A in Europe. Food Chem Toxicol 2016;98(Pt B):134-47.
- Savitz DA, Stein CR, Elston B, et al. Relationship of perfluorooctanoic acid exposure to pregnancy outcome based on birth records in the mid-Ohio Valley. Environ Health Perspect 2012;120(8):1201-07.
- Smith-Sivertsen T, Bykov V, Melbye H, Tchachtchine V, Selnes A, Lund E. Sulphur dioxide exposure and lung function in a Norwegian and Russian population living close to a nickel smelter. Int J Circumpolar Health 2001;60(3):342-59.
- Stubberfield J. The Health Benefits and Risks of Growing Your Own Produce in an Urban Environment. Ph.D. Thesis, University of Nottingham, UK, 2018.
- Swartjes FA, Rutgers M, Lijzen JP, et al. State of the art of contaminated site management in The Netherlands: policy framework and risk assessment tools. Sci Total Environ 2012;427-428:1-10.
- Vinikoor LC, Larson TC, Bateson TF, Birnbaum L. Exposure to asbestos-containing vermiculite ore and respiratory symptoms among individuals who were children while the mine was active in Libby, Montana. Environ Health Perspect 2010;118(7):1033-38.
- Warner M, Eskenazi B, Mocarelli P, et al. Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. Environ Health Perspect 2002; 110(7):625-28.
- Weinhouse C, Ortiz EJ, Berky AJ, et al. Hair Mercury Level is Associated with Anemia and Micronutrient Status in Children Living Near Artisanal and Small-Scale Gold Mining in the Peruvian Amazon. Am J Trop Med Hyg 2017;97(6):1886-97.
- Zani C, Donato F, Magoni M, et al. Polychlorinated Biphenyls, Glycaemia and Diabetes in a Population Living in a Highly Polychlorinated Biphenyls-Polluted Area in Northern Italy: a Cross-sectional and Cohort Study. J Public Health Res 2013;2(1): 2-8.