A scoping review of the epidemiological methods used to investigate the health effects of industrially contaminated sites

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ABSTRACT

BACKGROUND: this paper is based upon work from COST Action ICSHNet. Industrial contaminated sites (ICSs) are of high concern since industrial plants have produced widespread contamination potentially affecting the health of local population.

OBJECTIVES: to assess the types of epidemiological designs applied in studies of health effects related to ICSs according to time periods, type of ICS, and geography.

METHODS: a literature search was conducted in Medline (OVID) through June 30th, 2018, using MeSH and customized terms, and no restrictions on publication year or language. We included all studies throughout the world where a potential contamination of industrial origin occurred, an epidemiological approach (including biomonitoring, HBM) was applied, and health outcomes or exposure biomarkers among residents were investigated. Data on publication year, geographical localization and ICS characterization, study design (systematic reviews, cohort, case-control, temporal changes, cross-sectional, ecological, descriptive – area-level, case-series, narrative reviews, and HBM), and health outcomes were extracted from the abstracts. To check the sensitivity of the main search strategy, a case-study on Italy was conducted applying an ad-hoc search.

RESULTS: from a literature search capturing 5,485 studies, 655 studies on resident populations were identified. The review includes more than 376 different ICSs, 86% from Europe, North America, and Asia combined, mostly dealing with nuclear sites and mining industries, waste and petrochemical activities. Most of the studies were descriptive (32.5%), cross-sectional (16.3%), or narrative review (14.8%), while analytical studies – case-control and cohort studies (9.6% and 8.4%, respectively) – were rarer; HBM were only 6.9%. A total of 235 studies, conducted mostly in Asia (34.5%), Europe (25.5%), and North America (22.3%), included children. The most frequently studied outcome was cancer (33.7%), followed by respiratory diseases (11.4%), and reproductive health (11.4%). The ad-hoc strategy greatly increased the number of detected papers (+122%).

CONCLUSIONS: future research should adopt the most valid and suitable study design, according to the area-specific social and environmental context, also in areas of the world which are less studied, but with very high environmental worries of the resident population suffering the industrial contamination. Involvement of local experts on ICSs and local inventories are recommended to improve the coverage of the present inventory.

Keywords: environmental epidemiology, industrially contaminated sites, residential exposure, study design

KEYPOINTS

What is already known

- **Industrially contaminated sites (ICSs) involving a variety of hazardous agents are found in almost all Countries of the world, as pollutants are intentionally or accidentally released into the environment.**
- **For the purpose of identifying studies referred to contaminated sites, there is the need to have a standard definition of the term 'contaminated site' or the adoption of common keywords related to 'contaminated sites', not available at the moment.**
- **Different approaches in environmental epidemiology have been used to study the health effects of ICSs on the local communities.**

What this paper adds

- **The present extensive literature search provided an inventory of 762 publications summarizing the effect of 376 different ICSs, with higher quality study designs increasing over time.**
- **To improve the sensitivity of search strategies, a collaboration with local experts is needed to identify local ICS names and inventories.**

INTRODUCTION

Areas contaminated by a variety of hazardous agents are found in almost all Countries of the world, as pollutants are – intentionally or accidentally – released into the environment either by active industrial sources or as residual toxic waste from past or current activities. Contaminated sites can be defined as "areas hosting or having hosted human activities which have produced or might produce environmental contamination of soil, surface or groundwater, air, food-chain, resulting or being able to result in human health impacts".[1] This operational definition, restricted to contamination raising from industrial emissions and waste of industrial origin, was adopted by the COST Action on Industrially Contaminated Sites and Health Network (ICSHNet) (https://www.icshnet.eu/). Among its main aims, ICSHNet has the collection, formulation, and dissemination of information and advice on industrially contaminated sites (ICSs), environment, and human health.

In recent years, networking, research initiatives, and literature on industrial contamination and health has increased, following the need to acquire evidence for risk management and policy actions.[2] In this perspective, many contaminated sites need to adequately address issues such as contamination-related health risks, the prioritization of efforts for remediation, the cost-effectiveness of actions promoting public health.

In current practice, the health impact of ICSs is evaluated using assessments falling in two broad types of approaches: risk assessment (RA) and environmental epidemiology (EE). RA is the process to estimate the toxicity of hazards, the nature and probability of adverse health effects in humans who may be exposed in contaminated environmental media; EE specially focuses on evaluating human health risks by direct observations of health status of human populations in relation to environmental exposures. In RA, risks are calculated based upon typically toxicologically-based dose-response relationships of single pollutants, whereas in EE health effects are directly observed in the population.

Epidemiological studies in ICS may have different aims:

- description of the health profile of residents;
- analysis of the causal associations between environmental exposures and health effects, to verify specific hypothesis (analytical or aetiological);
- planning the epidemiological surveillance.[3]

Study designs can be broadly classified into descriptive and analytic, even if the two categories are not entirely mutually exclusive. Typically, descriptive studies are most useful for generating hypotheses and analytic studies most useful for testing hypotheses, though each type of study can be used for both purposes. The body of literature is large and systematic reviews on the impact of ICSs are available.[4-9] Attempts of synthesis have been conducted,[2,3,10] but on limited types of industrial contamination. The objective of this scoping review was to perform a literature search of the epidemiological studies investigating the health of residents living nearby an ICS, with the aim of describing the applied study design, variation across Countries, time and type of industrial contamination, and the health outcomes investigated.

METHODS

CRITERIA FOR IDENTIFYING ELIGIBLE STUDIES

According to the Cochrane Effective Practice and Organization of Care Review Group guidelines on study design, randomized controlled trials (RCTs), systematic review, cohort and case-control studies are the most appropriate study designs for aetiological research in clinical medicine, public health, and health policy. However, in environmental (and occupational) epidemiology, other study designs can be also considered, especially when focusing on the potential health hazard or to assess the magnitude of risk. For example, a well-designed cross-sectional study, with detailed individual confounders information, may be as informative as a cohort study in many instances. Small-area approaches with mixed-design (exposure levels based on area-measured/modelled levels) sometimes provide more accurate information than analytical studies based on distance from the ICS as a proxy of individual exposure. Furthermore, the choice of different study designs depends also on feasibility aspects related to time, technical and financial resources which are context specific.

In our operational definition, studies examining the distribution of disease at geographical level (e.g., standardized mortality ratio – SMR, standardized incidence ratio – SIR studies) in defined populations living nearby ICSs were considered as **descriptive**. Descriptive studies do not formally evaluate the association between exposure and health outcomes. Studies analysing the hypothesized association among population groups rather than among individuals were classified as **ecological**. Studies examining, at individual level, the association of ICS exposure and disease prevalence were classified as **cross sectional** (e.g., surveys).[11] Time series studies, case-crossover, and panel studies were grouped as **temporal changes** studies. **Case-reports and narrative reviews** conducted on a specific ICS were considered as separate categories. As a high-quality evidence on a particular type of industrial contamination, we also considered systematic reviews on ICSs. Although human biomonitoring (HBM) is not an epidemiological study design, but a tool used to quantify

the body burden (internal dose) of ICS-related contaminants, HBM activities are increasingly being conducted in ICS settings, so we decided to include **HBM studies** as a separate category. Of course, **cohort and case-control studies** were considered. Commentaries or editorials were not considered; RA and health impact assessment (HIA) evaluations were excluded since they are not epidemiological studies.

We included all studies concerning areas throughout the world where a potential contamination of industrial origin occurred, and where study participants were represented by general population, including children, living nearby an ICS and, therefore, potentially exposed to contaminated soil, water, air, and food-chain. We decided a priori not to include studies dealing only on occupational exposures or studies including family members of workers. We included studies where indication of location of the ICS (at least the Country) and a clear identification of the type of industrial activity were available: mining, waste treatment or management (including urban waste landfills, hazardous waste sites, e-waste, incinerators, waste management plants), chemical, petrochemical and power plants, asbestos mining and processing, metallurgic plants and other types of industries, such as weapon industry, shipping, harbours. We did not include studies focusing on farming activities. Both persistent contamination due to the presence of industry and the contamination following an accident (e.g., the accident at Chernobyl nuclear plant in Ukraine occurred in 1986) were included. We retrieved information about the different health outcomes investigated in the studies on ICSs.

In this scoping review, all information was retrieved from the abstracts. Only location and type of ICS were searched in the full text if not available in the abstract.

SEARCH STRATEGY

A comprehensive systematic search for potential studies was conducted in Medline (OVID). The search considered publications from the earliest available date for each bibliographic database through June 30th, 2018. Search was conducted using generic search filters and modified filters designed to best address the specific investigated question. Searches included both medical subject headings (MeSH terms) and free-text terms related to the different types of industrial contamination. Specific search terms on the exposed population were added. We did not apply any language or publication date restrictions to the search. Studies on animals were excluded. Details of the search strategies are described in Appendix 1 (see on-line supplementary material).

DATA COLLECTION AND ANALYSIS OF THE IDENTIFIED STUDIES

Selection of studies

We imported and managed the results of the searches in the bibliographic software EndNote. The eligibility and relevance of the studies was assessed based on their titles and abstracts. Relevance and eligibility of the studies were assessed by two reviewers (MDS, CA) and differences in opinion at screening levels was resolved through discussions. Studies which clearly did not meet the inclusion criteria were excluded.

Data extraction and management

Data from the abstracts of the selected studies were extracted using a pre-designed data collection form. The review authors were not blinded to the names of the authors, institutions or journals of publication. Any disagreement was discussed and resolved by consensus with a third review author (SV). We extracted data on publication year, geographical localization of the ICS, type of study design (systematic reviews, cohort, case-control, temporal changes, descriptive, cross-sectional, ecological, case-series, narrative reviews, and HBM), site contamination following an accident, population, and health outcomes. Pregnancy outcomes were considered among the studies including children.

Since our aim was to classify the study design correctly following the above-mentioned categories, for a sample of 140 abstracts the classification was done by two review authors who revised 70 abstracts each. Disagreements were solved by panel discussion. Agreement between reviewers was evaluated using the kappa statistic proposed by Cohen[12] using the software STATA.[13]

Studies synthesis was presented and narratively described according to ICS type and by study design, describing also the outcomes and other study characteristics (children, industrial accident).

FOCUS ON THE ITALIAN ICSs

We decided to check the sensitivity of our search methodology to identify the whole body of evidence about ICSs in a specific Country by comparing the studies identified as previously described with those identified in PubMed by including the name of the main Italian ICSs (e.g., Seveso, Casale Monferrato, Gela) and by using the references reported in SENTIERI project,[14] the Italian epidemiological surveillance of the health status of populations living in National Priority Contaminated Sites,[15] and by EPIAMBNET, the Italian network of environmental epidemiologists who share their research on environment and health (https://reteambientesalute.epiprev.it/).

RESULTS

DESCRIPTION OF STUDIES

Results of the search

The literature search identified a total of 5,485 studies that potentially appeared to meet the inclusion criteria (624 additional studies resulted from the ad-hoc strategy in Italy); 4,856 papers were excluded on the basis of absence of key information in the title or in the abstract. Of the remaining studies, 491 were excluded on the basis of the reasons listed in the PRISMA flow diagram (figure 1). In total, 655 studies were judged to fulfil the inclusion criteria. Agreement between the two reviewers was good (k: 0.887 and 0.808). In total, 655 studies were judged to fulfil the inclusion criteria. Detailed information for each study can be consulted in an Excel sheet provided in Appendix 2 (see on-line supplementary material).

Included studies

■ **Study characteristics.** Figure 2 and 3 show the geographical distribution of the 655 selected studies by Country. The world map highlights that most studies were conducted in Asia or Europe (31.3% and 31.1%, respectively), followed by North America (24.3%). A comparatively smaller number of studies have been identified in Africa, Central and South America, Australia and New Zealand. The European region map suggests a greater

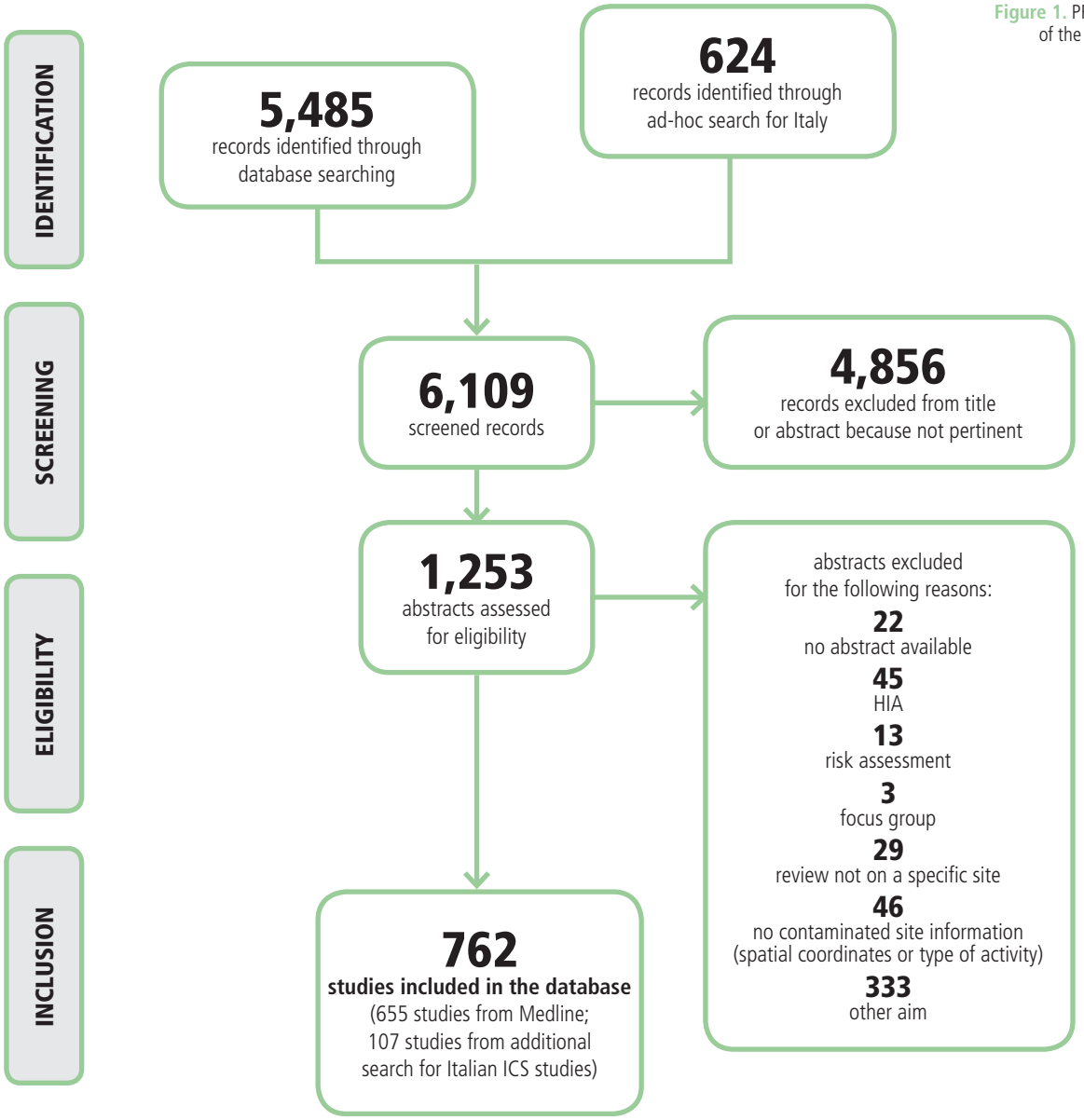

Figure 1. PRISMA flowchart of the literature search of ICS studies.

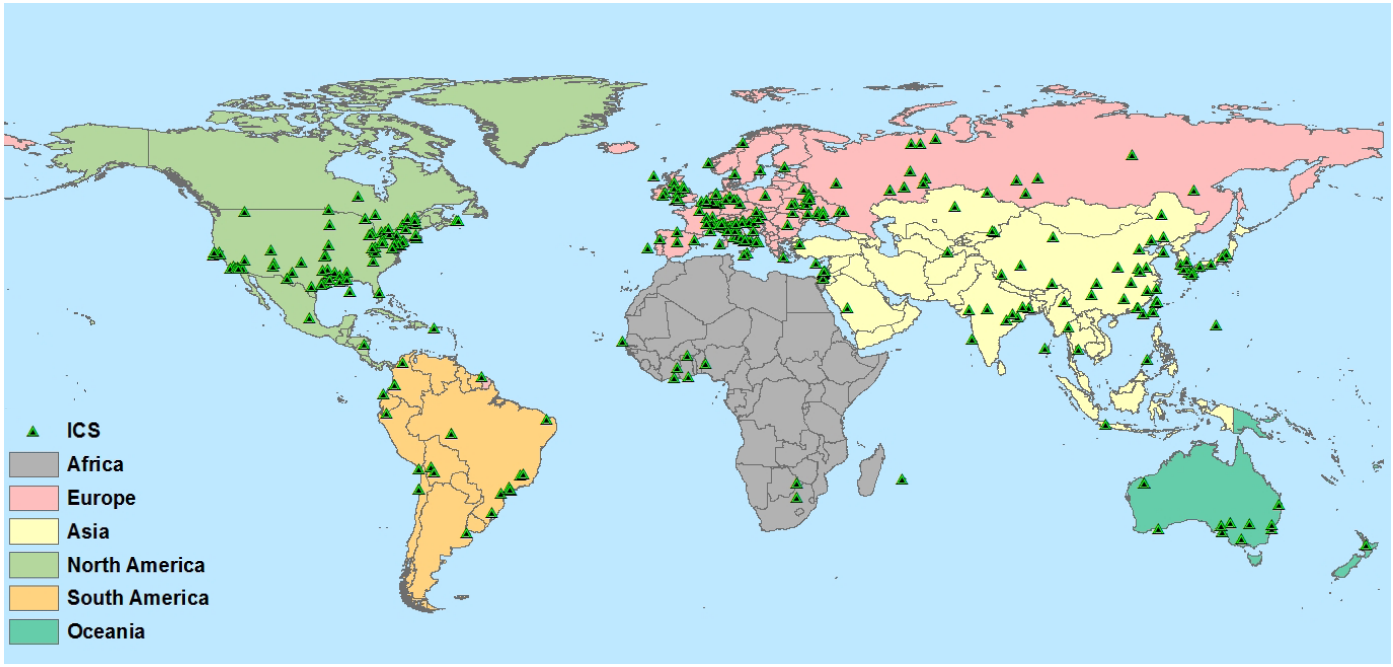

Figure 2. Geographic distribution of the identified ICSs (No. 376).

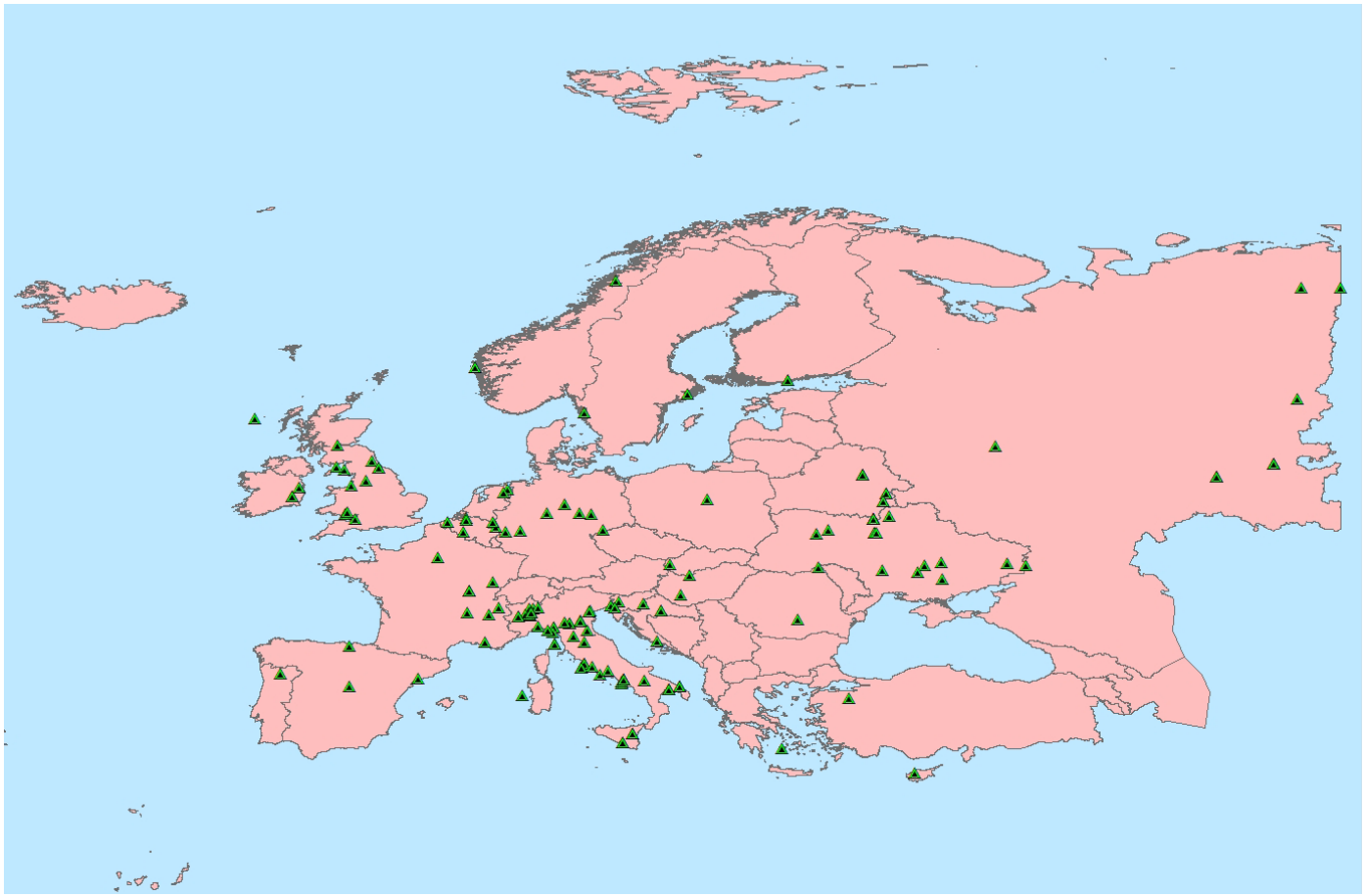

Figure 3. Geographic distribution of the ICSs in the European WHO region (No. 125).

STUDY DESIGN (No. OF STUDIES)	OUTCOME	CONTINENT (No. OF STUDIES)
Trial (No. 2) No study on industrial accidents, Adults only	• cardiovascular diseases	North America (No. 2)
Systematic review (No. 2) No study on industrial accidents, Adults only	• multiple outcomes	Europe (No. 1) North America (No. 1)
Cohort (No. 65) • 9 studies on industrial accidents (Three Mile Island, US; Fukushima, Japan; Chernobyl, Ukraine; Gulen, Norway; Minamata Bay, Japan) • 15 studies include children • 10 birth-cohort studies	• cancer (leukaemia, mesothelioma, thyroid, lung) • respiratory diseases, lung function • neurological diseases • reproductive health • skin diseases • cognitive performance, neurodevelopment • multiple outcomes	Asia (No. 16) Australia and New Zealand (No. 8) Central and South America (No. 2) Europe (No. 13) North America (No. 16)
Case-control (No. 63) • 3 studies on industrial accidents (Chernobyl, Ukraine) • 28 studies include children	• cancer (lymphoma, brain, breast, leukaemia, lung, mesothelioma, renal, soft-tissue sarcoma, stomach, thyroid, skin, bladder) • cardiovascular diseases • respiratory diseases • reproductive health • genetic/epigenetic changes	Asia (No. 12) Australia and New Zealand (No. 1) Central and South America (No. 2) Europe (No. 26) North America (No. 22)
Temporal changes (No. 19) • 4 studies on industrial accidents (Chernobyl, Ukraine; Fukushima, Japan; Three Mile Island, US) • 6 studies include children • 6 panel studies	• cancer (brain, leukaemia, thyroid, gastrointestinal) • cardiovascular diseases • respiratory diseases • reproductive health • cognitive development • psychological symptoms	Asia (No. 3) Australia and New Zealand (No. 1) Central and South America (No. 3) Europe (No. 9) North America (No. 3)
Descriptive (No. 213) • 7 studies on industrial accidents (Chernobyl, Ukraine; Fukushima, Japan; Three Mile Island, US; Seveso, Italy) • 63 studies include children • 16 studies used biomonitoring for individual exposure assessment	• cancer • cardiovascular diseases • respiratory diseases • neurological diseases • reproductive health • other diseases • multiple outcomes • genetic/epigenetic changes	Africa (No. 3) Asia (No. 50) Australia and New Zealand (No. 5) Central and South America (No. 8) Europe (No. 91) North America (No. 56)
Ecological (No. 23) • 4 studies on industrial accidents (Chernobyl, Ukraine; Fukushima, Japan; Three Mile Island, US) • 1 study used biomonitoring for individual exposure assessment • 9 studies include children	• cardiovascular • respiratory diseases • cancer (lung, bladder, digestive system, thyroid, lymphohaematopoietic) • perinatal mortality, pregnancy outcomes	Asia (No. 13) Central and South America (No. 2) Europe (No. 2) North America (No. 6)
Cross-sectional (No. 107) • 7 studies on industrial accidents (Chernobyl, Ukraine; Fukushima, Japan; Three Mile Island, US; Minamata Bay, Japan; St. Louis County, Missouri) • 21 studies used biomonitoring for individual exposure assessment • 51 studies include children	• pregnancy outcomes • genetic/epigenetic changes • cardiovascular disease • respiratory diseases, lung function • cognitive development • psychological symptoms • perceived risk	Africa (No. 8) Asia (No. 30) Australia and New Zealand (No. 5) Central and South America (No. 18) Europe (No. 23) North America (No. 23)
Narrative review (No. 97) • 26 studies on industrial accidents (Bhopal, India; Kyshtym, Russian Federation; Chernobyl, Ukraine; Fukushima, Japan; Nitro, US; Techa river, Russian Federation; Seveso, Italy; Minamata Bay, Japan) • 29 studies include children	• cancer (thyroid, bladder, breast, leukaemia, mesothelioma, skin, colorectal) • respiratory diseases, lung function • neurological diseases • reproductive health, congenital anomalies • growth • genetic/epigenetic changes	Africa (No. 2) Asia (No. 49) Australia and New Zealand (No. 1) Europe (No. 26) North America (No. 19)
Case-report (No. 19) • 8 studies on industrial accidents (Chernobyl, Ukraine; Three Mile Island, US) • 4 studies on children	• genetic/epigenetic changes • cancer (brain, breast, lung, mesothelioma, thyroid) • hypertension • neurological diseases • reproductive health • renal function	Asia (No. 10) Australia and New Zealand (No. 1) Europe (No. 6) North America (No. 2)
Biomonitoring (No. 45) • 1 study on industrial accidents (Texas City, US) • 21 studies include children		Africa (No. 3) Asia (No. 19) Australia and New Zealand (No. 4) Central and South America (No. 6) Europe (No. 7) North America (No. 6)

Table 1. Description of the ICS studies identified from the Medline search (No. 655), by study design, outcome, and continent.

number of papers on ICSs in Italy (37.3%), United Kingdom (10,6%), Spain (9.3%), France (6.8%), Germany (3.8%), and Ukraine (14.4%). Other Countries are less studied or not studied at all. Sixty-seven studies were conducted on industrial accidents. Table 1 shows that the number of studies increases over time, from less than 10 per year in the 1970-80s to 20-30 per year in the last decade.

Regarding the study population, 235 studies included children (these were both studies specifically on children or newborns and studies including several age groups). Those studies have been conducted mostly in Asia (34.5%), Europe (25.5%), and North America (22.3%); the study design adopted was mostly cross-sectional (26.8%), followed by narrative reviews (12.3) and case-control (11.9%); the most prevalent industrial contamination was related to nuclear, chemical plants, and mining sites and the outcomes were mainly respiratory effects (symptoms and diseases) and birth related outcomes.

■ **Study design.** Most of the studies were descriptive (32.5%), 16.3% were cross-sectional, followed by narrative review (14.8%), case-control and cohort studies (9.6% and 8.4%, respectively), HBM (6.9%) and the reminder by temporal changes study, case-report, and randomized controlled trials. Only 2 systematic reviews were included as they focused on a specific Country. Analytical study design was adopted mostly in Europe, North America, and Asia, less in Australia, New Zealand, and Central and South America, while no study was from Africa; descriptive studies were reported from all continents. Among the 58 studies with HBM, 39.6% were conducted in Asia and, among them, 48% concerned the e-waste contamination. The biomonitoring approach was applied within a cross-sectional epidemiological study design in 12.1% of the papers, thus providing also information about the health effects on residents. Figure 4 shows the temporal trend in the number of studies by specific study design, by decades. In all decades, descriptive studies account for the greatest part of evidence, while systematic reviews, cohort, case-control, and temporal changes studies have grown over time. Narrative reviews are more represented in the decade 1997-2006 than in the most recent period (figures 5 and 6).

■ **Outcomes.** Over the 655 studies, the most frequently studied outcome was cancer (33.7%), followed by respiratory diseases (11.4%) and reproductive health outcomes (e.g., congenital anomalies, birth outcomes, fertility problems) (11.4%). Cardiovascular outcomes were rarely specifically mentioned in the abstracts (15 studies). The outcome of the studies differs according to the study design, with more objective outcomes adopted in cohort studies.

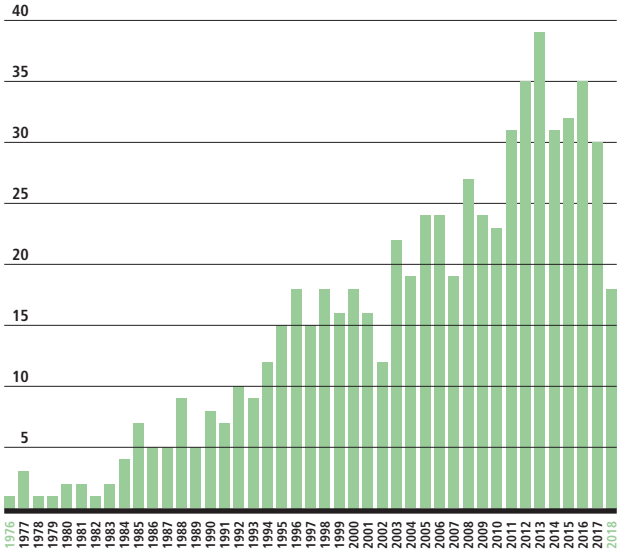

Figure 4. Temporal trend in publication years of the ICS studies identified from the Medline search (No. 655).

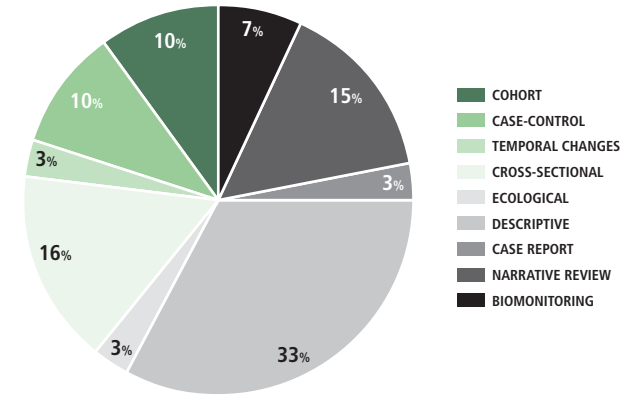

Figure 5. Distribution of study design of the ICS studies identified from the MedLine search (No. 655).
* Trials and systematic reviews are not included due to their very low numbers.

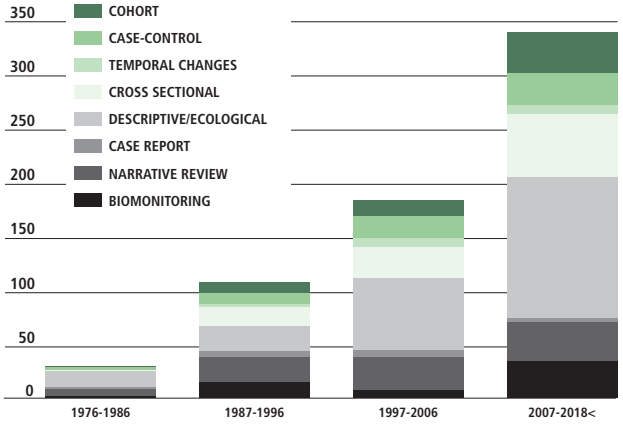

Figure 6. Temporal changes in epidemiological study design by decades of the ICS studies identified from the MEDLINE search (No. 655).*
* Trials and systematic reviews are not included due to their very low numbers.

Figure 7. Geographic distribution of the ICSs in Italy (No. 58).

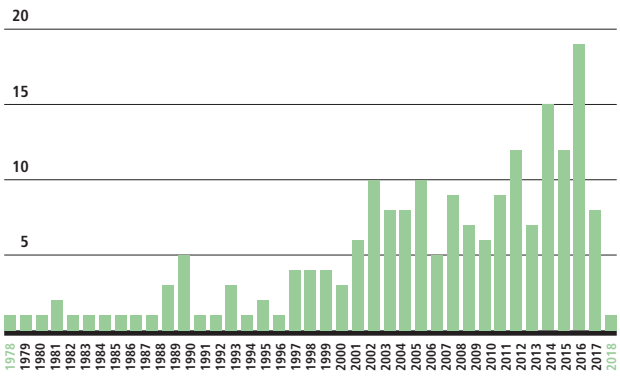

Figure 8. Temporal trend in publication years of the studies identified from total Italian ICSs (No. 195).

STUDY DESIGN (No. OF STUDIES)	OUTCOME
TRIAL (No. 0)	
SYSTEMATIC REVIEW (No. 0)	
Cohort (No. 37) • 26 studies on industrial accidents (Seveso, Lombardia region) • no birth cohort • 4 studies include children	• cancer (pituitary, breast, lung, mesothelioma) • cardiovascular diseases • respiratory diseases • diabetes • neurological problems • reproductive health • skin disease
Case-control (No. 20) • 1 study on industrial accident (Seveso, Lombardia region) • 3 studies include children	• cancer (lung, bladder, mesothelioma, sarcoma) • reproductive health • skin disease
Temporal changes (No. 8) • 2 studies on industrial accident (Seveso, Lombardia region) • 2 studies included children • No panel study	• cardiovascular diseases • respiratory diseases • reproductive health
Descriptive (No. 67) • 2 studies on industrial accident (Seveso, Lombardia region) • 11 studies include children	• cancer (lymphohaematopoietic, gastric, bladder, lung, mesothelioma, sarcomas) • cardiovascular diseases • respiratory diseases • reproductive health • congenital malformations • Parkinsonian disturbances
Ecological (No. 3) • No study on children	• cancer (mesothelioma, lymphohaematopoietic) • respiratory diseases
Cross-sectional (No. 14) • 10 studies on industrial accident (Seveso, Lombardia region) • 5 studies include children • 8 studies used biomonitoring for individual exposure assessment	• cancer (pituitary tumours) • respiratory diseases • genetic/epigenetic changes • reproductive health • liver and metabolic alteration • dental problems
Case-report (No. 6) • 3 studies on industrial accident (Seveso, Lombardia region) • 2 studies on children	• cancer (mesothelioma) • genetic/epigenetic changes • skin disease
Narrative review (No. 23) • 7 studies on industrial accident (Seveso, Lombardia region) • 4 studies include children	• cancer (bladder, lymphohaematopoietic, mesothelioma) • cardiovascular diseases • respiratory diseases • diabetes • reproductive health • skin diseases • neurological problems • genetic/epigenetic changes
Biomonitoring (No. 17) • 8 studies on industrial accident (Seveso, Lombardia region) • 1 study include children	• genetic/epigenetic changes • immune alterations

Table 2. Description of the studies identified from the Italian ICSs (No. 195), by study design and outcome.

■ **Industrial contamination.** Regarding the types of ICS, the most represented were mining industry (15.1%) and nuclear power plants (14.8%); 185 studies (28.2%) were conducted on a waste-related activity (incinerator, urban waste landfill, hazardous waste site, waste management plant, e-waste site), 83 studies (12.7%) were on petrochemical plants, 73 studies (11.1%) involved metallurgic plants, and 45 studies (6.9%) were on population living close to chemical plants. The detailed description of study design, outcome, and continent by type of ICS is reported in Appendix 3 (see on-line supplementary material).

The Italian ICS studies

The main search identified 88 Italian ICS studies (table 2). The literature search for additional ICS studies identified 624 studies, which were not identified with our main systematic search. Of these, 107 studies met the inclusion criteria. (Appendix 4, see on-line supplementary material). Figure 7 shows the map of all Italian ICSs identified from the 195 retrieved abstracts (88+107). The geographical location of these studies reflects the location of the national priority contaminated sites (NPCSs)[14,15] and covers most Italian regions. Figure 8 shows that the number of

studies increases over time similarly to what was observed for the studies identified through Medline. Most studies are descriptive (56% in the Medline search and 20% in the ad-hoc search) (figure 9). Compared to the Medline search, cohorts (27%), cross-sectional (10%), and case-control (11%) studies are more frequent in the ad-hoc search. Thirty percent of the studies dealt with the Seveso accident; 32 studies included children (16.0%).
The full list of included studies is reported in Appendix 5 (see on-line supplementary material).

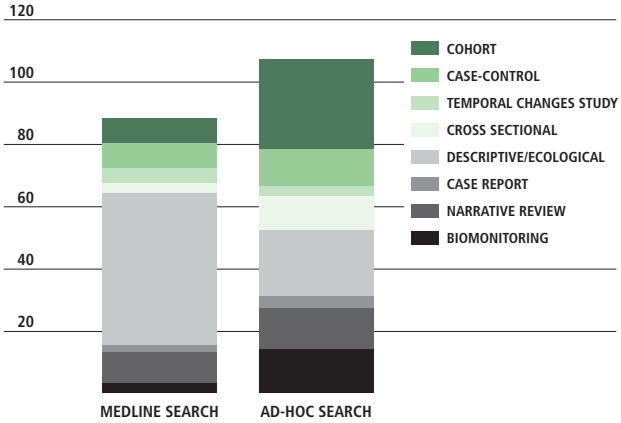

Figure 9. Distribution of study design of the studies identified from the Medline search and from additional searches for Italian ICSs.

DISCUSSION

This scoping review provides an overview of the epidemiological study design adopted on resident population close to ICSs without any restriction of time or Country. A large body of evidence on the potential relationship between exposure and health outcome in ICSs is based on descriptive studies. There is also a positive signal of a growing evidence from analytical studies (cohort, case-control) and biomonitoring investigations. This study underlines a lack of sensitivity when the Medline search is the single strategy used, and the consequent need for a site-by-site ad-hoc search considering grey literature and local experts involvement to improve the collection of potentially informative studies carried out in a given ICS. It is interesting to note that exposure assessment is improving with time even in descriptive studies as they shifted from distance from the source, as a proxy of exposure[16,17] to more advanced GIS techniques with exposure attributed at small area levels[18,19] or at individual level.[20,21] The use of HBM approach is more recent and increasingly used,[22-25] with almost half of the HBM studies included in the review which provided not only the individual exposure level, but also a measure of the effect of contamination.[26-29] However, this review did not address the quality of information on exposure assessment in the single papers.
The most tangible output of this review is an extensive literature database with an inventory of 762 epidemiological studies on the effects of ICSs, including the 107 papers from the Italian case study. This inventory can be updated and will hopefully provide the basis for carrying out systematic reviews on health effects related to a specific contamination, on a specific area, and on a specific outcome or population. The same database can be explored to analyse the contribution of different study designs in pursuing different aims in a specific ICS, also exploring the best approaches for combining different study designs in progressively providing evidence for remediation activities and public health interventions.
Authors' expertise allowed us to carry out a special focus on Italy. It is worth noting that after additional search using the name of the ICSs, that is the references from SENTIERI and EPIAMBNET collaborations, the number of Italian studies grew from 88 to 195 (+122%). This increase was mainly due to cohort and biomonitoring studies. The Italian case study has proved the lack of sensitivity of our main search strategy based on index and free terms. A standard definition of the term 'contaminated site' is not available and, as a result, a variety of definitions are currently used in the different Countries (Superfund in USA; definition based on documented contamination of soil in Europe)[30] and this has greatly limited our search strategy. One of the reasons seems to be linked to the choice of the keywords adopted by the authors of these studies, which did not favour the inclusion of their works in the main search strategy. In the Italian case study, the use of a targeted sensitive local search strategy was essential and increased the body of evidence.
Scoping reviews are preliminary assessment of potential size and scope of available research literature[31] and are likely to be incomplete. In this review, a critical aspect was the decision to retrieve information only from the abstracts. This choice was mainly driven by the number of papers to screen and may have limited the ability to properly categorize the study design, especially in the broad and heterogeneous descriptive group. Information on study area, ICS type, and outcomes could be incomplete for the same reason. However, because of the good agreement among reviewers on a sample of studies, we are still confident this review is a good overview of the epidemiological study design carried out in ICSs.

CONCLUSIONS

Some conclusions may be derived from the present work. One is the recommendation for search coordinators of future systematic reviews to improve the present inventory with a more focused search by contacting local experts on

ICSs. Another recommendation is for researchers to be more specific in describing an ICS (location, type of contamination) and, above all, the study design and any other information, including keywords, that could allow the inclusion of their work in future literature reviews. Future research should adopt the most valid and suitable study design, according to the area-specific social and environmental context, also in less-studied areas of the world, but with very high environmental worries of the resident population suffering the industrial contamination. In Countries where health information systems are available, the surveillance of population residing nearby ICSs might be a valuable and less costly approach to increase knowledge about the impact of ICS exposures on local populations, especially when health monitoring covers a wide range of health outcomes and address population subgroups (children, pregnant women, elderly people, ethnic minorities).[32] Moreover, many contaminants usually found in ICSs (heavy metals, dioxins, PCB, aromatic hydrocarbons, PM, and gaseous pollutants), especially in ICSs of less research-intensive Countries, are already well known in term of toxicological effects, and information on associated human health risks and impacts are available from scientific literature or from assessments carried out by Agencies like the International Agency for Research on Cancer (IARC), the Environmental Protection Agency (EPA), the World Health Organization (WHO). Analytical epidemiologic studies are therefore expected for emerging environmental hazards or when findings of the new studies are able to implement public health actions without postponing remediation of ICSs.

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