SENTIERI PROJECT: EPIDEMIOLOGICAL STUDY OF RESIDENTS IN NATIONAL PRIORITY CONTAMINATED SITES IN ITALY

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Introduction

Human health is intimately connected to the surrounding environment. This is particularly the case of the health of people living in a Contaminated Site (CS), which is affected by the legacy of past industrialization and current industrial activities, often in absence of environmental remediation. The total number of CSs that have been identified and require remediation worldwide has been estimated to be in the order of hundreds of thousands. In Europe out of around three million potentially contaminated sites, about 250,000 are in need of remediation. In the United States, around 1,300 sites are currently on the 'National Priorities List', around 30,000 contaminated sites have been identified in Canada. Estimates of potentially contaminated sites in Australia range from 60,000 to 200,000. In most South-Eastern European, Caucasus and Central Asian countries inventories have only been made for specific sites – such as mining or landfill sites – or are present only for some regions. In Latin America, individual countries are beginning to undertake inventories of potentially contaminated sites. Brazil, Chile and Mexico are in the process of establishing, or have already established, national inventories (1). The term CS can have different meanings. A general definition, following the public health perspective, is "areas hosting or having hosted human activities which have produced or might produce environmental contamination of soil, surface or ground water, air, food chain, resulting or being able to result in human health impacts" (2). There are several approaches and methods for assessing the health impact of CSs. A first descriptive level is based on epidemiological tools that do not require an ad hoc collection of data, and aims at describing the health profile of populations documenting ascertained or suspected associations with local environmental risks. More detailed analyses can be carried out, at a higher level of approximation, by collecting individual level data on health outcomes and/or on exposure (2).

SENTIERI project (epidemiological study of residents in Italian contaminated sites) (3-5) is an example of first level descriptive approach adopting an ecological study design, looking at the aggregate population level rather than at individual level. The project describes the health profile of residents in National Priority Contaminated Sites (NPCSs), labelled as such because of their substantial contamination, documented in qualitative and/or quantitative terms, and the consequent potential impact on the health of residents. The methods proposed under the approach exemplified by SENTIERI can be generalized and applied to other NPCSs. SENTIERI approach was among those sanctioned by the World Health Organization to conduct an initial description of the health status of residents of contaminated sites (2).

This chapter presents the rationale and methods underlying SENTIERI project, and to describe data and resources required to apply a similar approach in other countries.

When studying how the environment adversely affects human health, it is usually very difficult to identify clear cause-effect relationships because they are characterized by multi-causality with different strengths of association. In addition, these relationships are influenced by individual factors (e.g. genetic, diet, life-style, occupation and socioeconomic status) that can also have a role on both disease development and exposure characteristics. SENTIERI project was developed to deal with this complex scenario. It describes the health profile of residents in contaminated sites through small area analysis by applying the multi-step procedure described in the following sections.

Study of the health profile of residents in NPCSs: what to do and why

Site selection

As a first step, NPCSs to be studied should be chosen, and the criteria adopted to define NPCS/NPCSs clearly indicated. The NPCS selection will depend on the aims of the study to be undertaken, on the availability of the NPCSs related information and on any other consideration researchers would make and consider appropriate. In many instances, NPCSs to be studied are chosen by third parties, such as an environmental authority, by public concern, media pressure and so on. It is advisable that criteria used throughout this phase are clearly stated.

Environmental data

Numerous and different environmental sources of contamination possibly leading to human exposures are usually present in NPCSs. All the available NPCS data should be collected and described in a standardized, homogeneous way. Geographical characteristics, extension of the contaminated area and demographic information about residents potentially affected should be listed. Detailed description of contamination characteristics should be included, as well as the presence of industries and all other human activities that have contributed to the environmental deterioration of the NPCS. Researchers will specify the sources used for this task: scientific reports, acts, and so on.

Study population

Criteria to define populations affected by contamination may vary. Populations at risk are generally identified as people living in the neighbourhood or in areas defined as contaminated. Tipically, the residence in the area and the distance from the areas affected by contamination are used but also dispersion modelling results are applied. There are several models used to evaluate the areas affected by contaminants, their implementation and improvement depend on the information available on several parameters. When defining contaminated areas in case of complex industrial contamination, it should be considered that populations can experience several routes of exposure, mainly through inhalation of pollutants emitted into the atmosphere, and through ingestion when contaminants are accumulated in soil, water and in the food chain.

Reference population

For the reference population the same data of the area units under study are needed: cases and populations stratified by gender and age categories. The reference population should be selected balancing two different needs: 1) be comparable to the studied populations for factors that can affect the health profile with the exception of the contamination at study – the differences in the health profile between the compared populations should be ideally due only to the differences in environmental exposures, namely to the contamination; 2) be sufficiently numerous to obtain stable reference rates also for rare diseases. The reference populations should be selected balancing these two needs. Usually one or two populations among the following are selected as reference population: national, regional, local (i.e. a population composed of populations residing in the neighbourhood of the contaminated area).

Outcome selection

The aims of the study will imply a sound outcomes selection to include the ones for which environmental exposure/s is/are suspected or ascertained to play an etiologic role. The possible health impact from environmental exposures is measured in terms of mortality, morbidity, incidence of neoplastic diseases, etc. General considerations about the quality of available information and data, as well as intrinsic limitations of the selected outcome should be described and discussed. Health indicator characteristics should be carefully examined and multiple aspects considered taking into account the inherent uncertainty. Sources of national or local routinely collected data, spatial and temporal coverage, quality aspects are all of extreme importance for the validity of study results and their usefulness in terms of general knowledge and public health relevance. An appropriate length of the period under study will make research results and conclusions more informative for diseases with long latency times, precision of the epidemiological parameters will also improve with a longer study period.

Small area studies

Small area studies investigate the role of environmental exposure at neighbourhood level (6). The specific value of small-area analysis is that it permits the examination of data for population which tend to be more homogeneous in character and in their environmental circumstances than are larger and more widely spread populations (7). The smallest territorial unit that can be used in small area studies depends on data availability that may vary in different countries.

Socioeconomic confounding

In geographical studies of environment and health, confounding from social and economic factors may occur. To control such confounding effect, standardization techniques have been extensively used since the mid 1990s. To account for possible confounding from socioeconomic factors in SENTIERI project an *ad hoc* Deprivation Index was built and applied to the SMR estimates (8).

A priori evaluation of the epidemiological evidence

When performing epidemiologic studies, there is a risk for researchers to become data-driven. This can be the case when commenting results for causes showing an increase, possibly

on the sole basis of statistical significance. To control at least partially this problem, SENTIERI, for each NPCS focused on those causes identified *a priori*, from the strength of their association with selected environmental exposures. This is the basic, key aspect of the SENTIERI approach. In SENTIERI possible relevant exposures were abstracted from Legislative Decrees, i.e. administrative sources defining NPCSs boundaries and coded on a productive sectors basis (i.e. petrochemicals and/or refineries, harbours areas, etc.). The choice was made because NPCSs had different level of environmental characterization (for some NPCSs information on specific chemical contaminants were available, for others only productive plants were listed). This is to point out that researchers should be able to adapt this approach to their specific situation. Once identified the environmental exposures of interest, researchers should examine the updated scientific literature to evaluate the associated health effects. This apparently easy task is in fact quite demanding, because by browsing the literature different kind of publications are collected: handbooks, meta-analyses, reviews, multi-centric studies, original articles, letters to scientific journals, editorials, and so on. Therefore, the first decision to be taken is about the "relevance" to give to the collected material.

SENTIERI study group defined a hierarchy in the literature sources. Sources expressing the epidemiological community consensus, evaluating scientific evidence by means of standardized criteria, weighting the study design and the occurrence of biased results (i.e. IARC monographs, WHO publications, European Environment Agency publications, handbooks of environmental and occupational medicine) were considered most important. They were followed in the hierarchy by quantitative meta-analyses. Multi-centric studies, systematic reviews and single investigations were also considered. Consistency among sources was a criterion used to classify the strength of the causal association. Literature sources were presented in the final report in a tabular form to let the reader follow the entire process of evaluation for each cause combined with different exposures. On the basis of explicit criteria shown in Table 1 the strength of the causal association for each cause-exposure combination was classified as Sufficient (S), Limited (L), and Inadequate (I) (3).

Table 1. Evaluation of the epidemiological evidence of the association between cause of death and environmental exposures

Level	Description
SUFFICIENT (S) Sufficient to infer the presence of a causal association	one or more primary sources provide S evaluation
	some meta-analyses provide data for S evaluation
LIMITED (L) Limited but not sufficient to infer the presence of a causal association	one or more primary sources/quantitative meta-analyses/reviews/ multicentric studies/two or more single studies report the existence of a causal association but they do not express an S evaluation, or they do not provide data for L evaluation
INADEQUATE (I) Inadequate to infer the presence or the absence of a causal association	some primary sources study the causal association, but they disagree about the evaluation (conflicting evidence)
	some quantitative meta-analyses / reviews/multicentric studies/ two or more single studies analyze the association but they disagree about the evaluation
	some primary sources/quantitative meta-analyses/reviews/multicentric studies/two or more single studies analyze the causal association but none of them reports its existence
	the available studies are not consistent and there is a conflicting evidence
	only one single study analyzing the causal association is available

Table 2 presents an example of the *a priori* evidence evaluation for environmental exposures in NPCSs and some selected causes of death (3). Details on how all the above steps were to put into practice in SENTIERI project can be found in Pirastu *et al*. 2013.

Table 2. SENTIERI Project: matrix of epidemiological *a priori* evidence evaluation for environmental exposures in National Priority Contaminated Sites (NPCSs) and some selected causes

Environmental exposures in NPCSs	Cause of death				
	All ages				*Up to 14 yrs old*
	Malignant neoplasms of trachea, bronchus and lung	Malignant neoplasms of pleura	Diseases of the respiratory system	Asthma	Asthma
Chemical plant	I		L	L	L
Petro chemical plant & refinery	L	I	L	L	L
Steel plant	I	I	L	L	L
Electric power plant	L	I	L	L	L
Mine and/or quarry	I	S	I		
Harbour area	I	L	L	L	
Asbestos or other mineral fibers	L	S			
Landfill	I		I	I	I
Incinerator	L		I	I	I

I: Inadequate; **L**: Limited; **S**: Sufficient

Results for a single NPCS and for all NPCSs combined

SENTIERI project presented results both for single NPCS and for all sites combined.

For single sites a homogeneous way of presenting and discussing results were adopted to make the study results clearer and more readable. Specific causes with a Sufficient or Limited strength of causal association with the environmental exposures present in each NPCS, were reported and discussed in detail; to have a general description of the residents' health profile, main broad groups of causes of death were also considered. The assessment and appropriate consideration of previous studies performed on the same NPCS, if any, ameliorates the level of knowledge, reducing scientific uncertainties about the heath impact of contamination, and facilitating the process of identification and implementation of remediation interventions. An example of how results for one NPCS are presented and commented is found in Pirastu *et al*. in 2013 (9).

SENTIERI project also assessed the overall mortality profile in all the NPCSs combined. The number of excess deaths over the period 1995-2002 was 9,969 for all causes (SMR 102.5, about 1,200 excess deaths/year), for all neoplasms 4,309 (about 538 excess deaths/year), 1887 for circulatory system diseases, and 600 for respiratory system diseases (4). In 2014 a third

report of SENTIERI project (5) was published presenting an updated mortality analysis (2003-2010), hospital discharges (2005-2010) and cancer incidence (1996-2005) analyses. The study of cancer incidence in 17 NPCSs combined (10) showed in both genders an excess for overall cancer (9% in men and 7% in women) as well as for specific cancer sites (colon and rectum, liver, gallbladder, pancreas, lung, skin melanoma, bladder and Non Hodgkin lymphoma).

Discussion

The ecological approach used in SENTIERI does not allow to draw definite conclusions on the causal relationships between environmental exposures and health status in residents in a contamined site. The causal inference might be complicated for causes with multifactorial etiology in areas with multiple sources of different pollutants and concurrent presence of air pollution from urban areas. Notwithstanding these difficulties, in a number of instances, the *a priori* evaluation of the epidemiological evidence as carried out in SENTIERI reinforced the findings and strengthened the case of an etiological role to some environmental exposures. These have varying degrees of persuasiveness, for example an increased lung cancer and respiratory disease risk was observed in sites hosting refineries and petrochemical plants, suggesting the need for further studies; the ascertained exposure-disease association between pleural neoplasm mortality and asbestos was confirmed in sites with documented presence of asbestos and asbestos-like fibres (4). Other aspects which could increase the persuasiveness of environmental related health effects is the identification of increased health risks only in women or in children living in contaminated sites. The value of an ecological study like SENTIERI should be measured, as recently suggested (11), against the baseline level of knowledge, in this context SENTIERI contribution can be considered high given the absence of systematic and standardized epidemiological investigations of the health impact of residents in NPCSs.

Exposure ascertainment is a key phase in ecological environmental investigations; the exposures affecting the study population should ideally be described in detail, while in practice a number of limitations affect this crucial aspect in most studies. In some investigations the exposure/s is a time-bound event in a limited geographical area, leading to a point source emission of a limited number of contaminants whose nature has been identified and whose toxicological properties can be partially known. More frequently the environment has been progressively contaminated by a heterogeneous mixture of pollutants originating from industry (often a variety of industrial activities) or waste treatment/disposal activities so that several environmental matrices are contaminated over a period of years, leading to multiple sources of exposure to a variety of exogenous agents, possibly changing qualitatively or quantitavely overtime. Often, the available exposure information is indirect and qualitative. In addition, for most NPCSs no information is available on sources of exposure that can have a health impact, such as concurrent air pollution from road traffic and exposures in the occupational setting. Another limitation in exposure ascertainment lies in the implicit assumption that all residents in the area under investigation experience the same exposures, while exposure variability is likely to be substantial. The possible consequences of exposure misclassification are complex and direction of the resulting bias is not predictable (12). An additional limitation derives from the territorial size and the population dimension of the areas at study for which vital statistics are available. Whatever the administrative boundaries are, they hardly correspond to the distribution of environmental pollutants, so that the misclassification of exposure (and loss of statistical power) is common.

As far as outcome measures are concerned, many studies in polluted areas consider mortality, based on death records. However, the analysis of hospital discharge records, ad hoc

Registry data of specific pathologies (e.g. cancer, congenital malformations) can give a better picture of the health profile of residents in NPCSs (5). Each vital statistics is able to provide information only about the events that it is designed to record, and databases need to be validated for use in epidemiological studies. In the majority of countries death rates from all causes are unlikely to be biased because reporting the event of death is exhaustive. Therefore the overall mortality, which is an important indicator of conditions of life, can be analyzed with confidence (13). In most European countries Hospital Discharge Records (HDRs) are indicators of hospital activity and their main use is for administrative purposes (14): validity when employed in ecologic studies has not been systematically evaluated. Some Italian Reports (15, 16) comment on some critical aspects of this novel utilization of HDRs.

The analysis of cancer incidence and congenital malformations data in environmental epidemiology investigations can be considered, subject to validity evaluation. In Italian NPCSs cancer incidence has been investigated (10) and congenital anomalies have been used in a descriptive study (17).

In environmental health studies factors as socioeconomic status, occupational exposures and individual lifestyles can have an etiologic role on the health effects under study thus possibly confounding the exposure-disease relationships. Socioeconomic status is a determinant of health and disease. Since the mid 1990s ecologic studies of environment and health in UK adjusted for deprivation using Census data; for a review refer to Pasetto 2010 (18).

Occupational exposures are potential confounders in ecological studies of environment and health; individual based studies may be needed to disentangle environmental and occupational risk.

The links between environmental exposures and health effects depend on the environmental pollutants and diseases being considered, but are also influenced by factors such as genetic constitution, age, nutrition and lifestyles and the above mentioned occupational and socioeconomic factors. Identifying these relationships is therefore challenging, however, the effort is often worthwhile as it may help to redefine priorities and unlock resources.

The main strengths of the SENTIERI approach are the standardization of the mortality analysis and NPCSs classification in terms of environmental exposure which allow the study of all NPCSs in one country; the a priori evidence evaluation to comment and interpret study results is a key characterizing element of the project. Additional assets are that the mortality analysis can be updated and other vital statistics data can be analysed, also the a priori evidence evaluation can be brought up to date following the established criteria and procedures.

Concluding remarks

The SENTIERI approach is, in its essence, a tool to describe the health profile of residents in NPCSs to document ascertained or suspected associations with local environmental risks; it does not require an ad hoc data collection (2). The approach can also be of value for health surveillance activities in NPCSs (possibly analysing different outcomes); in addition it can contribute to etiological evaluation of cause-effect associations if additional data from biomonitoring investigations, risk assessment studies and individual based epidemiological studies are available.

Notwithstanding the remarkably laborious activities required to set up a national project such as SENTIERI, major benefits in terms of quality and quantity of findings, and a favourable cost/gain balance can be expected in-as-much as this becomes a permanent system of epidemiological observation on health of residents in NPCSs.

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