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Industrially Contaminated Sites and Health

Guest Editors: Marco Martuzzi, Roberto Pasetto, and Piedad Martin-Olmedo

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Editorial

Industrially Contaminated Sites and Health

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According to data collected by the European Environment Agency, Europe has hundreds of thousands of contaminated sites [1], many of them resulting from earlier industrialization and poor environmental management. Past and present activities can cause dispersion and accumulation of countless contaminants, mainly chemicals, to an extent that might affect human health by compromising air quality, altering soil functions, entering the food chain, and polluting groundwater and surface water. Typically, but not always, these stressors occur in localized areas near the point sources and affect local communities.

The assessment of possible health impacts related to sites hosting or having hosted large or intensive production and processing plants (such as chemicals, petrochemicals, manufacturing, waste disposal and treatment, cement, power generation, mining, and metals) is the main focus of this special issue. Such assessments entail considerable challenges, but the scientific literature repeatedly documented these impacts, often substantial. A variety of methods and tools have been developed for the analysis of these studies: the review included in this special issue by M. Pascal et al., for example, describes the available methodologies for assessing the impacts of airborne contaminants around major industrial areas. These and other resources are available and have been applied in numerous investigations, examples of which are also presented in this special issue: L. Pascal et al. report on hospital admissions near a large industrial area in France; O. Breugelmans et al. studied cancer incidence around a steel plant in The Netherlands, using hierarchical Bayesian models; and R. Pirastu et al. applied different epidemiological approaches to study the health profile of residents in the Italian National Priority Contaminated Site in Taranto. All three studies indicate elevated risks for some of the health outcomes considered, in some cases with large excesses.

A number of agents and contaminants examined in these studies are well-established risk factors (e.g., asbestos) and in many cases the evidence provided was instrumental to undertake effective remediation.

Available assessments indicate that industrially contaminated sites represent an important public health issue for several reasons: the large extent of contamination and ensuing health impacts, documented in many contaminated sites; the coexistence of multiple environmental stressors; the concurrence of several residential and/or occupational exposure pathways; the largely unknown interaction with risk factors from the social environment, such as lifestyle (nutrition, tobacco consumption, alcohol, physical activity, and housing quality); and the markedly uneven distribution of the risks that raises issues of health inequality and environmental justice.

However, while the scientific literature on the subject is rich, it is not yet possible to draw a reliable comprehensive picture of the health impacts of contaminated sites, as

some questions remain open. Some of these questions are addressed in this special issue.

For a start, the heterogeneity of these sites makes a classification difficult; a common legal definition of contaminated site is not available, nor are common criteria to set up inventories. However, commonalities between certain kinds of areas with respect to the possible health effects exist, and an operational definition of contaminated sites has been proposed as follows: 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 [2].

The most relevant health outcomes to be considered *a priori* for different types of industrial activities are identified in this special issue, in a paper by R. Pirastu et al. that also presents an approach to describe the health profile of populations living in industrially contaminated sites using routinely collected data.

Epidemiological studies in contaminated sites, especially those focusing on residents (rather than workers), are beset by problems of exposure assessments. Exposure misclassification may in fact compromise the ability of these studies to detect health effects and also, though more rarely, generate false positives. Progress has been made, however, notably through biomonitoring [3] and modelling of dispersion and uptake, as described in this special issue in connection to waste incineration.

To pursue better quantification of the overall health impact of contaminated sites, more systematic data are needed to improve the assessment of human exposure. In this respect, many initiatives at the European level have been developed, especially with soil as an entry point. In this special issue, P. Panagos et al. describe the work undertaken in the framework of the European Union (EU) Thematic Strategy for Soil Protection, where the European Commission has identified soil contamination as a priority for the collection of policy-relevant data at continental scale.

In addition to raising problems with exposure assessment, industrially contaminated sites are often located close to urban areas and/or socially deprived neighbourhoods; this increases the possible extent of the impacts, makes exposure patterns more complex, and is involved in interactions with other health determinants.

Because often the rationale behind these studies is to inform policy decisions, such as remediation, reconversion, or industrial development, there is a need, ideally, to consider all the health stressors occurring in a contaminated site in their entirety, rather than breaking down the question to independent analyses focussing on single contaminants. Such an aspiration to holistic assessments makes the above challenges particularly demanding and should be considered in order to set a research agenda in this domain.

Current efforts include WHO-led expert consultations [2]. Taking stock from important national initiatives and current research in epidemiology, exposure assessment, toxicology, environmental monitoring and modelling, human biomonitoring, risk perception, and other disciplines, consensus has emerged on the urgency of the problem and on possible ways forward and goals for international collaborative work, which include

(i) producing guidelines on (a) strategies for studying environment and health in contaminated sites and (b) communication strategies;

(ii) developing resources, materials, and training modules on (a) approaches and methods to be applied in different sites and contexts and (b) communication strategies;

(iii) strengthening the methodology on exposure assessment, in particular, on biomonitoring and through the food-chain;

(iv) implementing health assessments that include detailed analyses of population subgroups, in particular, children;

(v) planning a system to collect data and produce comparative analyses of the health impact of different sources of contamination within and among different countries, allowing for the inclusion of socioeconomic factors.

In conclusion, on the basis of the accumulating evidence on the relevant health impacts (including the contributions contained in this special issue), the need for consistent policies on remediation, and the compelling dimension of the underlying health inequalities, the issue of contaminated sites and health can be considered of priority in the environment and health domain. Existing resources should be further developed and deployed to tackle this important question.

Marco Martuzzi
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Review Article

Environment and Health in Contaminated Sites: The Case of Taranto, Italy

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The National Environmental Remediation programme in Italy includes sites with documented contamination and associated potential health impacts (National Priority Contaminated Sites—NPCSs). SENTIERI Project, an extensive investigation of mortality in 44 NPCSs, considered the area of Taranto, a NPCS where a number of polluting sources are present. Health indicators available at municipality level were analyzed, that is, mortality (2003–2009), mortality time trend (1980–2008), and cancer incidence (2006-2007). In addition, the cohort of individuals living in the area was followed up to evaluate mortality (1998–2008) and morbidity (1998–2010) by district of residence. The results of the study consistently showed excess risks for a number of causes of death in both genders, among them: all causes, all cancers, lung cancer, and cardiovascular and respiratory diseases, both acute and chronic. An increased infant mortality was also observed from the time trends analysis. Mortality/morbidity excesses were detected in residents living in districts near the industrial area, for several disorders including cancer, cardiovascular, and respiratory diseases. These coherent findings from different epidemiological approaches corroborate the need to promptly proceed with environmental cleanup interventions. Most diseases showing an increase in Taranto NPCS have a multifactorial etiology, and preventive measures of proven efficacy (e.g., smoking cessation and cardiovascular risk reduction programs, breast cancer screening) should be planned. The study results and public health actions are to be communicated objectively and transparently so that a climate of confidence and trust between citizens and public institutions is maintained.

1. Introduction

Contaminated sites are extensively present in Europe where approximately 250,000 sites require cleanup interventions, as listed by the European Environment Agency [1]. Several thousands of these sites are located in Italy, and a total of 57 sites, defined in 2009 as National Priority Contaminated Sites (NPCSs), qualify for remediation because of contamination documented in qualitative and/or quantitative terms, and because of a potential health impact.

The site of Taranto, located in Apulia region (southern Italy), includes two municipalities and 216,618 inhabitants at 2001 Census. This site is of interest because of several polluting sources, such as a large steel plant, a refinery, the harbor, and both controlled and illegal waste dumps.

Previous environmental and epidemiological investigations in the area have provided evidence of environmental contamination [2–9]. These studies have documented severe air pollution originating mainly from the steel industry, that is, particulate matter, heavy metals, polycyclic aromatic hydrocarbons, and organ-halogenated compounds.

Epidemiological studies showed an increased mortality/morbidity from respiratory, cardiovascular diseases and several cancer sites [10–13].

SENTIERI Project (epidemiological study of residents in National Priority Contaminated Sites—NPCSs) funded by the Italian Ministry of Health studied mortality for 63 causes among residents of 44 NPCSs included in the "National Environmental Remediation Programme" [14].

The distinguishing feature of SENTIERI Project is that the epidemiological evidence evaluation has been carried out before the study to minimize the risk for researchers to be data-driven when performing and interpreting the specific epidemiologic investigation. SENTIERI dealt with the complexity of the relation between area contamination and health effects by examining, for each combination of causes of death/*environmental exposures*, the epidemiological evidence (1998–2009) and then building a matrix of the *a priori* evaluation of the strength of the causal association. The *environmental exposures* were classified as chemicals, petrochemicals and refineries, steel plants, power plants, mines and/or quarries, harbour areas, asbestos or other mineral fibers, landfills, and incinerators—labelled on the basis of the legislative decrees defining the sites' boundaries. A standardized procedure was set up to collect the available epidemiological literature, which was reviewed on the basis of explicit criteria and led to classify each cause of death/*environmental exposures* combination in terms of strength of causal association. The evaluation was categorized as sufficient to infer the presence of a causal association (S), limited to infer the presence of a causal association (L), and inadequate to infer the presence or the absence of a causal association (I). The rationale, scope, methods, and details of the *a priori* evidence evaluation can be found in [15], and the procedures and results of the evidence evaluation have been published in Italian [16].

With specific reference to the *environmental exposures* in Taranto NPCS, this procedure led to classify the presence of a steel industry, a refinery, a harbour area, and a number of landfills and waste dump sites as associated, with limited evidence, with an increased risk of lung cancer, pleural mesothelioma, nonmalignant respiratory diseases, congenital malformations, and perinatal conditions. In this context, residence near steel industry was evaluated as specifically associated with the occurrence of both acute and chronic respiratory diseases in adults and children, based on studies by [17–23]. It should be underlined, however, that air pollution from particulate matter has been causally linked by WHO with several health effects, including all-cause mortality and cardiovascular and respiratory morbidity [24].

SENTIERI analyzed mortality at municipality level in the period 1995–2002, computing standardized mortality ratios (SMR) both crude and adjusted for a deprivation index [25]. While SENTIERI strengths are the *a priori* epidemiological evidence evaluation and the mortality analysis of all NPCSs adopting the same analytical approach and adjusting for deprivation, there are several limitations that should be noted, such as its ecological design and the use of mortality data at municipal level for a short period of time.

With the aim of overcoming the above limitations, this paper presents an epidemiological profile of Taranto NPCS residents analyzing different health indicators available at municipality level, that is, cause-specific mortality (2003–2009), mortality time trend (1980–2008), and cancer incidence (2006-2007). A cohort study of the resident population examined mortality (1998–2008) and morbidity (1998–2010) in the districts close to the steel plant.

2. Material and Methods

2.1. Data Source. Details on the codes used during the study period for the 9th and 10th revisions of the International Classification of Diseases (ICD-9 and ICD-10) and on the demographic data of the two municipalities included in Taranto NPCS are presented in Appendix A.

2.2. Mortality 2003–2009. Mortality in Taranto NPCS residents was initially studied for the period 1995–2002 [12] and then updated for the years 2003–2009 (note that the period 2004-2005 was not available from ISTAT). The analysis considered 63 single or grouped causes (all ages, both genders); 0-1 and 0–14 age classes were also analyzed for a selection of causes (both genders combined). Standardized mortality ratios both crude (SMRs) and adjusted for deprivation together with 90% confidence intervals (90% CIs) were computed using regional rates for comparison [14]. In SENTIERI Project the deprivation index (DI) was constructed using the 2001 national census variables representing the following socioeconomic domains: education, unemployment, dwelling ownership, and overcrowding. The strengths and weaknesses of SENTIERI ID, its correlation with 2001 national deprivation index, its efficacy in representing deprivation in different categories of demographic dimensions, together with suggestions about the use of socioeconomic indices in small area studies of environment and health are discussed in Pasetto et al. 2011 [26].

2.3. Mortality Time Trend 1980–2008. Mortality was analyzed for a twenty-seven-year period: 1980–2008. The analysis was performed for the population 0–99 years separately for men and women; directly standardized death rates (SDRs) per 100,000 were calculated (standard: Italian population at 2001 Census) together with their 90% CI. The population size of Taranto NPCS is relatively small; therefore the study period was divided into three-year periods to obtain stable values of the indicators. The overall mortality was analyzed together with specific diseases, selected on the basis of the *a priori* evidence evaluation of their link with *environmental exposures* in Taranto NPCS. The selected diseases were all cancers (in particular lung cancer), circulatory diseases (in particular ischemic heart disease), and respiratory diseases (in particular, the acute, and chronic ones).

We also analyzed the overall infant mortality (i.e. mortality from all causes during the first year of life) without gender distinction, as not informative in this age group.

2.4. Cancer Incidence 2006-2007. For cancer incidence (2006-2007), standardized incidence ratio (SIR) and 90% CI were calculated for both genders; the incidence rates of Italian South and Islands Cancer Registries macroarea (2005–2007) and of Taranto Province, excluding NPCSs municipalities (2006-2007), were used for comparison.

2.5. Mortality (1998–2008) and Morbidity (1998–2010) of the Residential Cohort. A cohort study design was applied to evaluate cause-specific mortality and hospitalization in relation to residence in specific districts close to the industrial sites. A cohort of residents (all subjects living in Taranto, Massafra, and Statte as January 1, 1998, and subsequently entered in these municipalities up to 2010) was enrolled from the municipal register. Individual follow-up for vital status assessment at 31.01.2010 was performed using municipality data. This cohort population is different from the base population analyzed for mortality in 2003–2009 (see previous paragraph for details). The socioeconomic position level (SEP) of the census block of residence and the district of residence were assigned to each participant (five categories from low to high SEP), on the basis of the addresses geocoded at the beginning of the follow-up. Occupational history for all cohort members was traced through the national insurance company (INPS) database (people employed in 1974 and subsequently), and the subcohort of individuals employed in industries located in the area was identified. Mortality/morbidity information was retrieved from Regional Health Databases (1998–2008 for mortality, 1998–2010 for hospital admissions). The associations of district of residence with mortality/morbidity were estimated by calculating mortality and morbidity hazard ratios (HR, CI 95%) using the proportional Cox models. All models considered age (temporal axis), calendar period, and area-based socioeconomic status [25], and they were calculated separately for men and women [13].

3. Results

3.1. Mortality 2003–2009-SENTIERI. Tables 1–3 show mortality results in the periods 1995–2002 and 2003–2009.

In Table 1, mortality, from the main causes of death, is displayed for descriptive purposes; Tables 2 and 3 present the results for the causes selected on the basis of the *a priori* evidence evaluation, the distinguishing feature of SENTIERI Project [15].

Table 1 shows that in both periods, for both genders, for all causes and all neoplasms, there was an excess of mortality ranging between 7% and 15%; adjustment for deprivation did not substantially change SMRs values. In both periods, among males and females, the observed mortality was above expected for circulatory, respiratory, and digestive systems diseases; also in these cases, accounting for socioeconomic factors did not essentially change the study results. For diseases of the genitourinary system, the observed mortality was similar to the expected one.

Table 2 presents the results for the causes of death for which SENTIERI classified the epidemiological evidence of causal association with the *environmental exposures* in Taranto NPCS as "Limited". From now on, reference will only be made to results adjusted for deprivation. Among males, lung cancer showed a 20% excess in the first period, confirmed in the second one; among females the excesses were, respectively, about 30% (1995–2002) and 20%. Correspondingly, in the two periods excesses for pleural tumors were 193% and 167% among males, 90% and 103% among females. Excesses for acute respiratory diseases among males were 49% (1995–2002) and 37% (2003–2009), and for females 38% and 14%, respectively. The observed mortality for chronic respiratory diseases in 1995–2002 was as expected in both genders, while in 2003–2009 a 10% excess was present for males. Asthma mortality was not increased, but the observed number of death is small.

Table 3 displays the results combined for males and females, again for causes with limited epidemiological evidence of causal association with the *environmental exposures* in Taranto NPCS. The mortality from congenital anomalies showed a 17% excess in 1995–2002, while in 2003–2009 it was below expectation. For mortality from perinatal conditions, an heterogeneous group of diseases affecting fetus or newborn spanning from pregnancy and delivery complications to digestive or hematological disorders, the excess was 21% and 47%, in the first and second periods, respectively. In the age class 0–14 less than 3 deaths from acute respiratory diseases and asthma were observed.

Some noteworthy results should be considered (results not shown in Tables). Among males, the observed deaths were above expected in 1995–2002 and 2003–2009 for dementia (resp., 105 and 102 deaths), hypertensive diseases (resp., 307 and 287 deaths), ischemic heart diseases (resp., 1032 and 679 deaths), and cirrhosis (resp., 266 and 156 deaths). In 2003–2009 excesses were reported for melanoma (50%, 26 deaths), non-Hodgkin lymphoma (34%, 45 deaths), and myeloid leukemia (35%, 37 deaths).

3.2. Mortality Time Trend Analysis 1980–2008. Time trends for mortality from all causes and selected causes among adults and overall infant mortality are presented in Figures 1–17 and in Appendix B (see Tables S2, S3, and S4 in Supplementary Material available online at http://dx.doi.org/10.1155/2013/753719).

3.2.1. Men. Since many decades, overall mortality in Italy and in Apulia has been declining (resp., 44% and 45%). This favorable trend was also observed in Taranto NPCS, where the regular fall showed a slackening in the last three-year period. Since the early 90s, the SDRs observed in Taranto NPCS were higher than those observed in Apulia, which in turn were lower than the Italian ones; in the most recent three-year period the SDR observed in Taranto site was higher than that in Apulia and Italy (Figure 1).

Table 1: SENTIERI—Taranto NPCS. Mortality for the main causes of death. Number of observed cases (Obs), standardized mortality ratio crude (SMR), and adjusted for deprivation (SMR ID); 90% IC: 90% confidence interval; regional references: 1995–2002 and 2003–2009. Males and females.

Causes of death (ICD IX)	1995–2002						2003–2009*					
	Males			Females			Males			Females		
	OBS	SMR (90% CI)	SMR ID (90% CI)	OBS	SMR (90% CI)	SMR ID (90% CI)	OBS	SMR (90% CI)	SMR ID (90% CI)	OBS	SMR (90% CI)	SMR ID (90% CI)
All causes (1–999.9)	7585	109 (107–111)	107 (105–109)	7104	107 (105–109)	107 (105–109)	4936	114 (111–117)	111 (108–113)	4847	108 (105–110)	107 (104–109)
All neoplasms (140.0–239.9)	2529	115 (112–119)	113 (109–116)	1716	113 (108–117)	112 (108–117)	1650	114 (110–119)	111 (106–115)	1208	113 (108–118)	111 (106–116)
Diseases of the circulatory system (401.0–405.9)	2654	105 (102–108)	103 (99–106)	3118	101 (98–104)	100 (97–103)	1645	114 (109–119)	109 (105–114)	1968	104 (100–108)	103 (99–107)
Diseases of the respiratory system (460.0–519.9)	666	107 (100–114)	107 (100–114)	406	113 (104–123)	111 (102–120)	447	117 (108–126)	112 (103–121)	268	104 (94–115)	105 (95–116)
Diseases of the digestive system (520.0–579.9)	442	114 (105–123)	114 (106–124)	472	142 (132–153)	141 (131–153)	283	147 (133–162)	136 (123–150)	233	119 (106–132)	117 (104–130)
Diseases of the genitourinary system (580.0–629.9)	101	92 (78–109)	97 (82–115)	107	89 (75–104)	91 (77–108)	71	94 (77–115)	101 (82–123)	85	89 (74–107)	87 (72–104)

*2004-2005 not available from ISTAT.

Table 2: SENTIERI—Taranto NPCS. Mortality for causes of death with limited evidence of association with *environmental exposures* in Taranto NPCS. Number of observed cases (Obs), standardized mortality ratio crude (SMR), and adjusted for deprivation (SMR ID); 90% IC: 90% confidence interval; regional references: 1995–2002 and 2003–2009. Males and females.

Causes of death (ICD IX)	1995–2002						2003–2009*					
	Males			Females			Males			Females		
	OBS	SMR (90% CI)	SMR ID (90% CI)	OBS	SMR (90% CI)	SMR ID (90% CI)	OBS	SMR (90% CI)	SMR ID (90% CI)	OBS	SMR (90% CI)	SMR ID (90% CI)
Malignant neoplasm of trachea bronchus and lung (162.0–162.9)	840	130 (122–137)	119 (112–126)	121	135 (115–157)	130 (111–151)	516	133 (124–143)	123 (114–132)	97	130 (109–153)	121 (101–143)
Malignant pleural neoplasm (163.0–163.9)	83	521 (430–625)	293 (242–352)	14	242 (147–379)	190 (115–297)	44	519 (397–667)	272 (208–350)	12	311 (180–505)	210 (121–340)
Diseases of the respiratory system (460.0–519.9)	666	107 (100–114)	107 (100–114)	406	113 (104–123)	111 (102–120)	447	117 (108–126)	112 (103–121)	268	104 (94–115)	105 (95–116)
Acute diseases of the respiratory system (460.0–466.9, 480.0–487.9)	125	156 (134–181)	149 (127–173)	135	145 (125–167)	138 (119–159)	50	136 (106–172)	137 (107–174)	58	112 (89–140)	115 (91–143)
Chronic diseases of the respiratory system (491.0–492.9, 494.0–496.9)	388	96 (88–105)	97 (89–105)	151	92 (80–105)	92 (80–105)	322	116 (106–127)	110 (100–121)	149	104 (90–119)	100 (87–114)
Asthma (493.0–493.9)	9	41 (22–72)	42 (22–73)	11	73 (41–121)	68 (38–113)	0			1	25 (1–118)	29 (1–137)

*2004-2005 not available from ISTAT.

Table 3: SENTIERI—Taranto NPCS. Mortality for causes of death with limited evidence of association with *environmental exposures* in Taranto NPCS. Number of observed cases (Obs), standardized mortality ratio crude (SMR), and adjusted for deprivation (SMR ID); 90% IC: 90% confidence interval; regional references: 1995–2002 and 2003–2009. Males and females combined.

Causes of death (age classes) (ICD IX)	1995–2002 Total			2003–2009* Total		
	OBS	SMR (90% CI)	SMR ID (90% CI)	OBS	SMR (90% CI)	SMR ID (90% CI)
Congenital anomalies (all ages) (740.0–759.9)	59	115 (91–142)	117 (93–145)	20	82 (54–119)	93 (62–135)
Certain conditions originating in the perinatal period (0-1) (760.0–779.9)	79	135 (111–162)	121 (100–146)	37	165 (123–218)	147 (110–193)
Acute diseases of the respiratory system (0–14) (460.0–466.9, 480.0–487.9)	4	96 (33–219)	95 (33–219)	<3	—	—
Asthma (0–14) (493.0–493.9)	<3	—	—	<3	—	—

*2004-2005 not available from ISTAT.

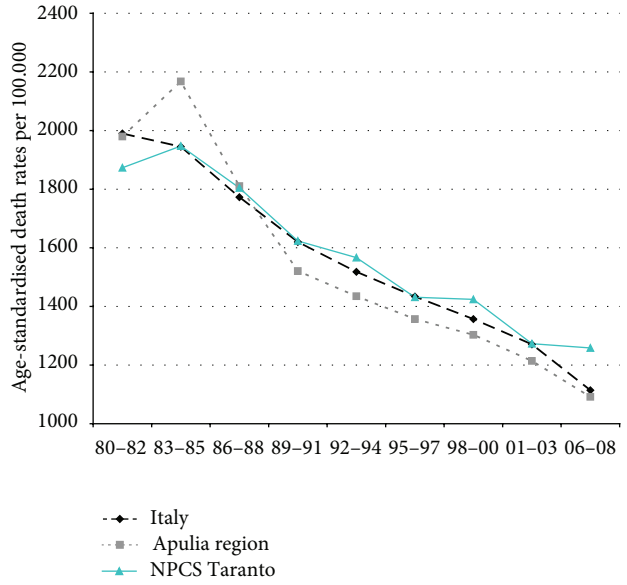

Figure 1: Overall mortality. Trends in age-standardised (Italian Census 2001) death rates per 100.000 (1980–2008) (2004-2005 data were not available). All ages. Men.

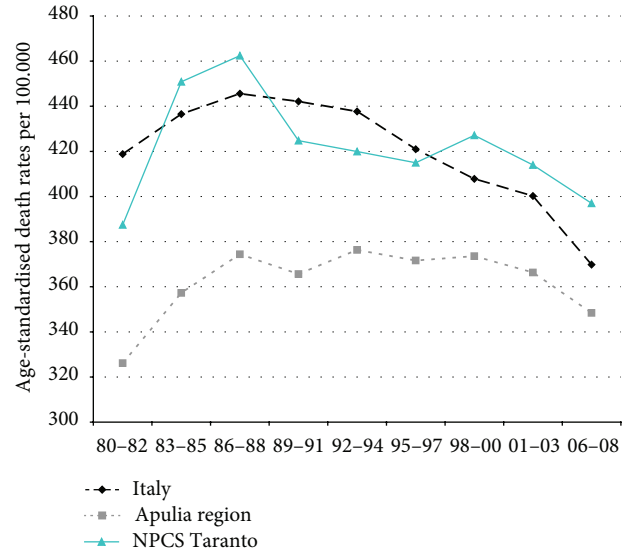

Figure 2: All cancers. Trends in age-standardised (Italian Census 2001) death rates per 100.000, from selected causes of death (1980–2008) (2004-2005 data were not available). All ages. Men.

In Italy, mortality from all neoplasms has been falling throughout the study period, while in Taranto NPCS and in Apulia, the trend has been moderately increasing for the same study period. In Taranto NPCS SDRs tend to be higher than in Apulia, which in turn are lower than in Italy (Figure 2).

Mortality from lung cancer has been declining in Italy, Apulia, and Taranto NPCS throughout the years 1980–2008; SDRs in the study site are higher than in Italy and Apulia, since 1995–1997, this differential shows a reduction (Figure 3).

Mortality from circulatory diseases in Italy, Apulia, and Taranto site decreased, and the mortality rates almost halved during the study period; yet, in the most recent time, Taranto's mortality rates are higher than in Italy (Figure 4).

Mortality trends from ischemic heart disease have been declining in Italy, Apulia, and Taranto site; yet, since the end of the 1980s, Taranto's SDRs are higher than in Apulia (Figure 5).

Mortality trends from respiratory diseases (overall, acute, and chronic) showed a decrease in Italy, Apulia, and Taranto. The rates in Taranto site are higher than those in the Italian ones over the whole study period, the exception being the last decade, when only mortality due to acute respiratory was higher in Taranto (Figures 6, 7, and 8).

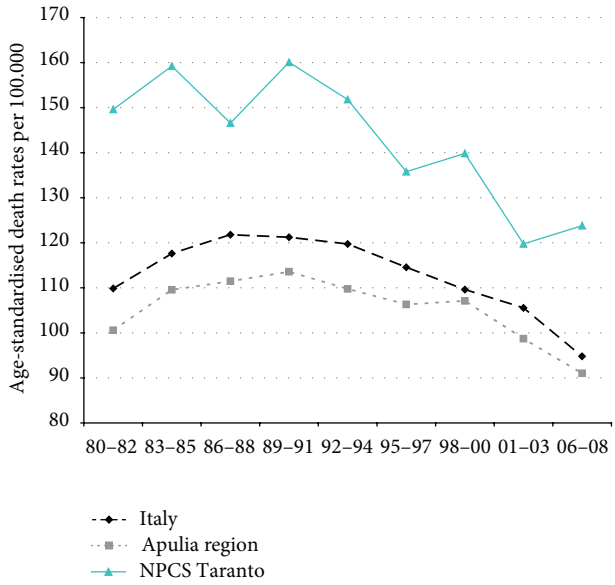

Figure 3: Lung cancer. Trends in age-standardised (Italian Census 2001) death rates per 100.000, from selected causes of death (1980–2008) (2004-2005 data were not available). All ages. Men.

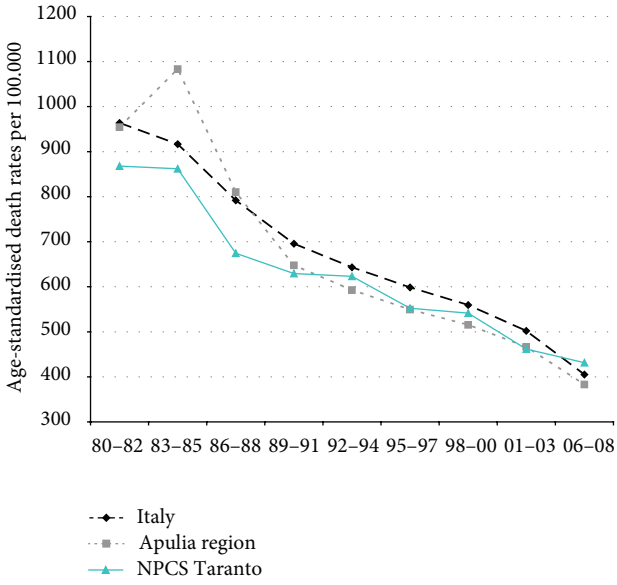

Figure 4: Circulatory diseases. Trends in age-standardised (Italian Census 2001) death rates per 100.000, from selected causes of death (1980–2008) (2004-2005 data were not available). All ages. Men.

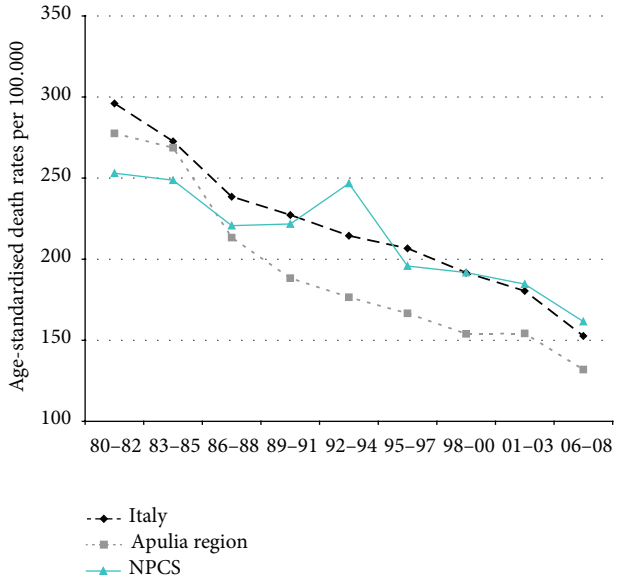

Figure 5: Ischaemic heart diseases. Trends in age-standardised (Italian Census 2001) death rates per 100.000, from selected causes of death (1980–2008) (2004-2005 data were not available). All ages. Men.

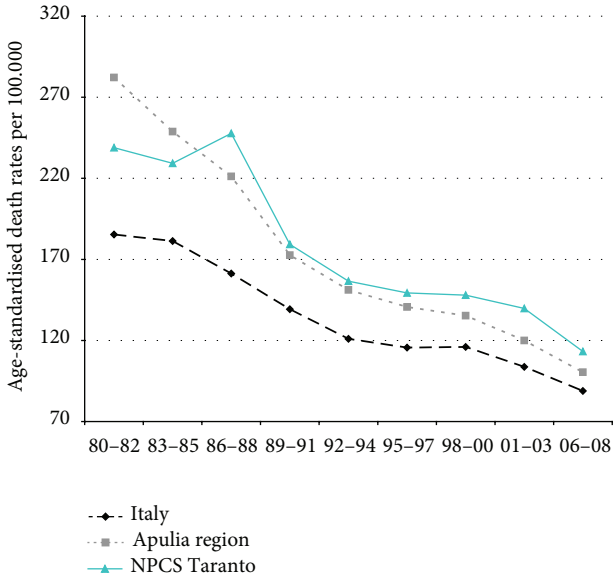

Figure 6: Respiratory diseases. Trends in age-standardised (Italian Census 2001) death rates per 100.000, from selected causes of death (1980–2008) (2004-2005 data were not available). All ages. Men.

3.2.2. Women. Overall mortality among women in Italy, Apulia, and Taranto site showed a long-term decreasing trend: from 1980 to 2008 the decrease was respectively 45%, 46%, and 38%; yet, since the beginning of the 2000s, mortality rates in Taranto are higher compared to those in Apulia and Italy (Figure 9).

Mortality from cancer (all sites) has been decreasing in Italy, remaining stable in Apulia, and increasing in Taranto site (Figure 10).

In contrast with the overall cancer mortality, lung cancer mortality has been rising steadily; in the study period the increase was 59% in Italy, 44% in Apulia, and 78% in Taranto NPCS, where SDRs were higher than in Apulia (Figure 11).

Mortality from circulatory diseases showed a declining trend in Italy, Apulia, and Taranto site (Figure 12). Mortality from ischemic heart disease declined as well, but the rates observed in Taranto NPCS were higher than in Apulia and Italy throughout the study period (Figure 13).

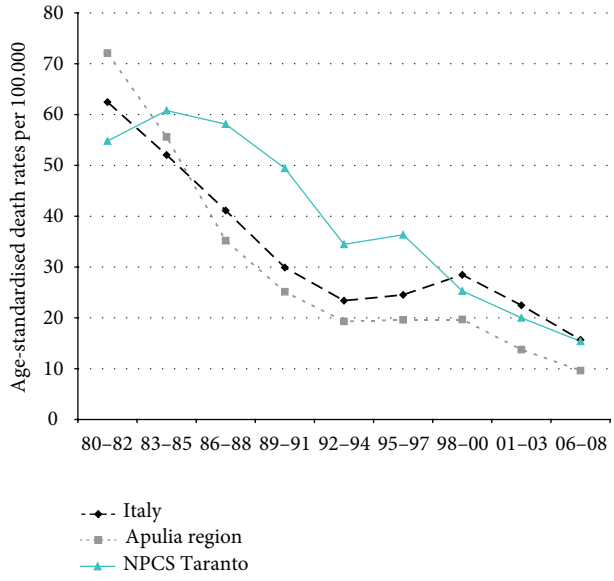

Figure 7: Acute respiratory diseases. Trends in age-standardised (Italian Census 2001) death rates per 100.000, from selected causes of death (1980–2008) (2004-2005 data were not available). All ages. Men.

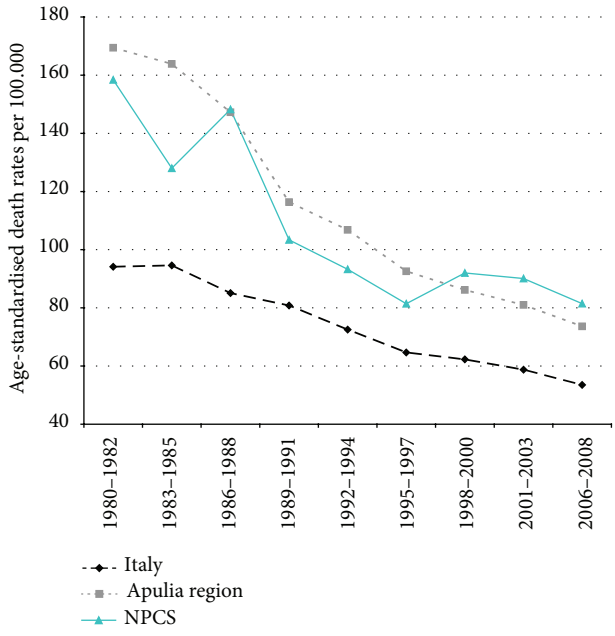

Figure 8: Chronic respiratory diseases. Trends in age-standardised (Italian Census 2001) death rates per 100.000, from selected causes of death (1980–2008) (2004-2005 data were not available). All ages. Men.

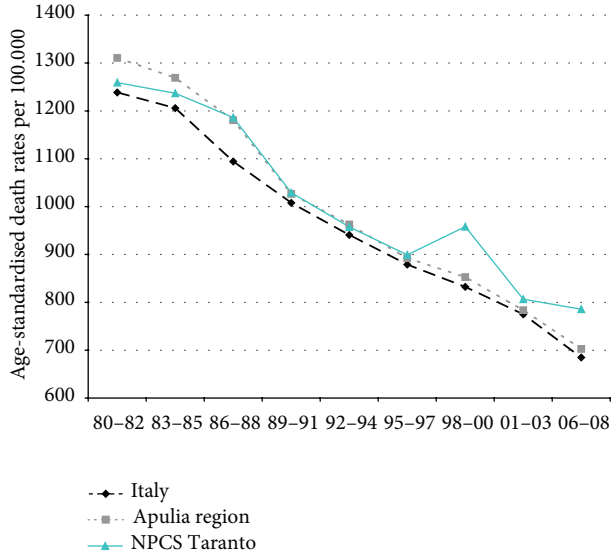

Figure 9: Overall mortality. Trends in age-standardised (Italian Census 2001) death rates per 100.000 (1980–2008) (2004-2005 data were not available). All ages. Women.

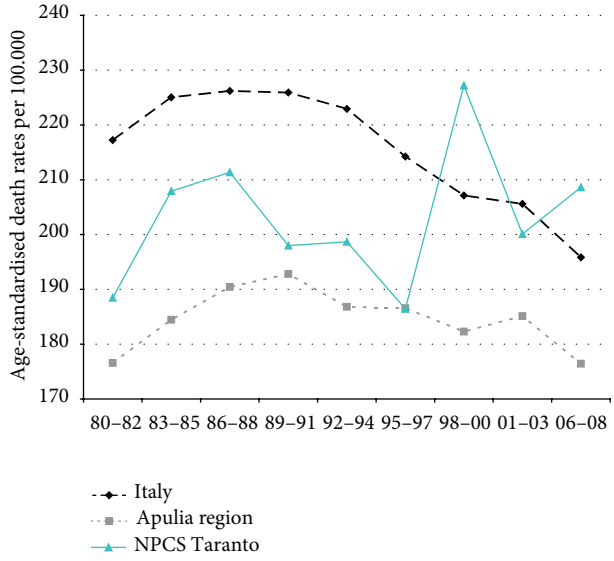

Figure 10: All cancer. Trends in age-standardised (Italian Census 2001) death rates per 100.000, from selected causes of death (1980–2008) (2004-2005 data were not available). All ages. Women.

Finally, mortality from respiratory diseases (overall, acute, and chronic) showed a decline in Italy, Apulia, and Taranto site, but the rates in Taranto are higher than in Italy (Figures 14, 15, and 16).

The results indicate that some differential between Taranto and other areas are emerging in recent years; it may be attributed to the presence for many years of pollutants in the environment, given that no remediation has been performed in the Taranto area.

3.2.3. Infant Mortality. Infant mortality showed a steady decline both in Italy and Apulia; SDRs in Taranto were decreasing, but they stayed higher in Taranto than in Apulia and Italy (Table S4 and Figure 17).

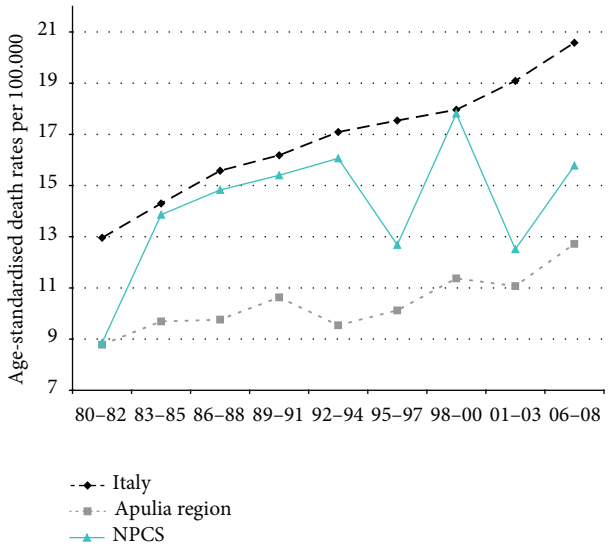

Figure 11: Lung cancers. Trends in age-standardised (Italian Census 2001) death rates per 100.000, from selected causes of death (1980–2008) (2004-2005 data were not available). All ages. Women.

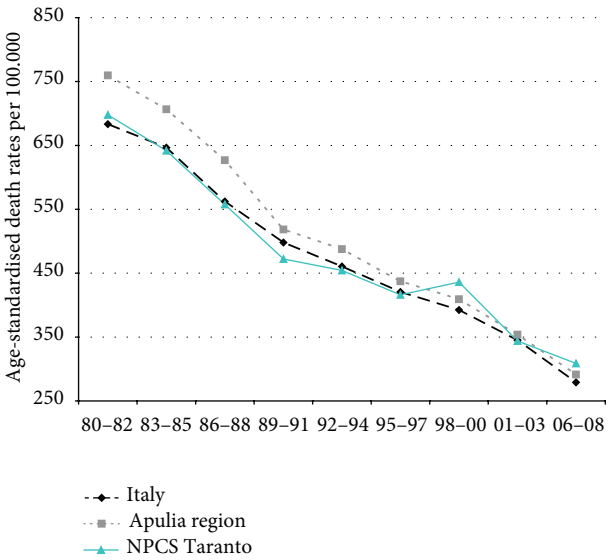

Figure 12: Circulatory diseases. Trends in age-standardised (Italian Census 2001) death rates per 100.000, from selected causes of death (1980–2008) (2004-2005 data were not available). All ages. Women.

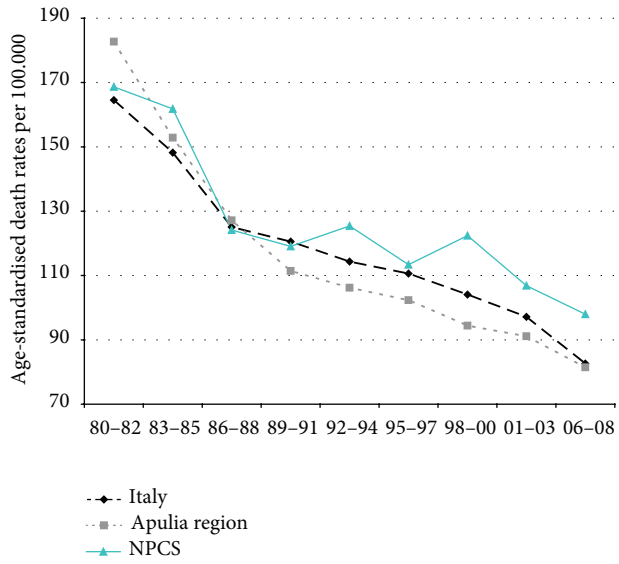

Figure 13: Ischaemic heart diseases. Trends in age-standardised (Italian Census 2001) death rates per 100.000, from selected causes of death (1980–2008) (2004-2005 data were not available). All ages. Women.

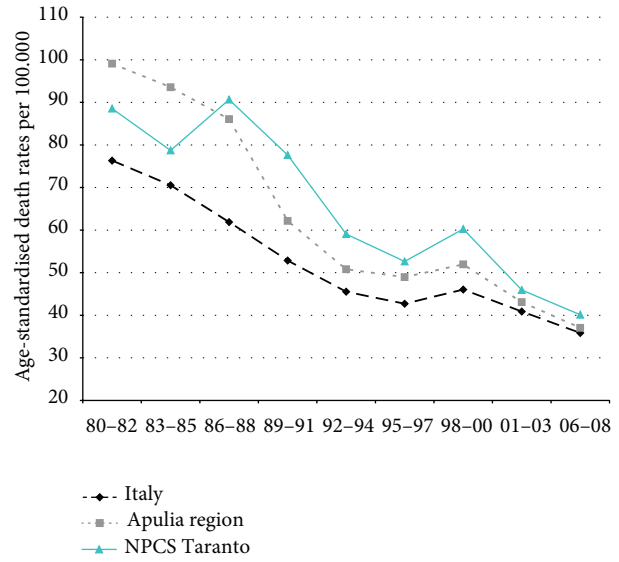

Figure 14: Respiratory diseases. Trends in age-standardised (Italian Census 2001) death rates per 100.000, from selected causes of death (1980–2008) (2004-2005 data were not available). All ages. Women.

3.3. Cancer Incidence 2006-2007. In Taranto NPCS (Table 4) excesses were observed among both males and females when using for comparison both the rates of South and Islands macroarea and of the province (Taranto and Statte excluded) for all tumors and a number of tumor sites (stomach, colon-rectum, liver, pancreas, lung, mesothelioma, skin melanoma, kidney and other unspecified genitourinary organs, and leukemia). Among males an increase was present for prostate cancer and among females for breast cancer. For most sites, the excesses were confirmed when province rates (Taranto and Statte excluded) were used for reference, thus supporting a major health impact among residents in Taranto NPCS.

3.4. Mortality 1998–2008 and Morbidity 1998–2010 of the Residential Cohort. The study area was divided into 9 districts in Taranto city and 2 municipalities (Massafra and Statte). Figure 18 shows the districts investigated and the location of the industrial area. We considered that the districts located close to the industrial zone were the most areas affected by environmental pollution, especially considering

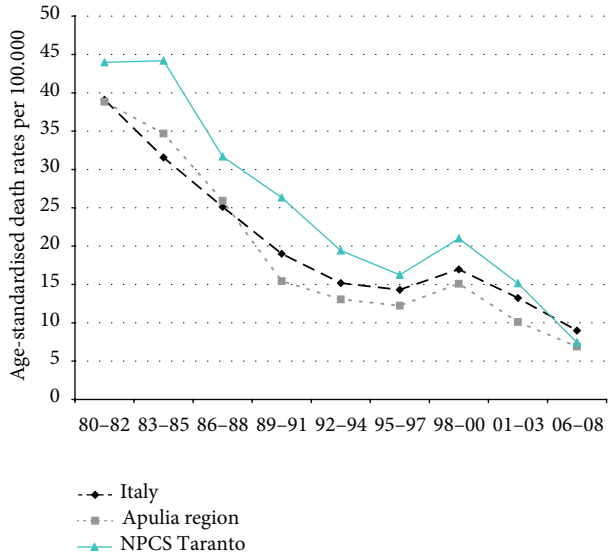

Figure 15: Acute respiratory diseases. Trends in age-standardised (Italian Census 2001) death rates per 100.000, from selected causes of death (1980–2008) (2004-2005 data were not available). All ages. Women.

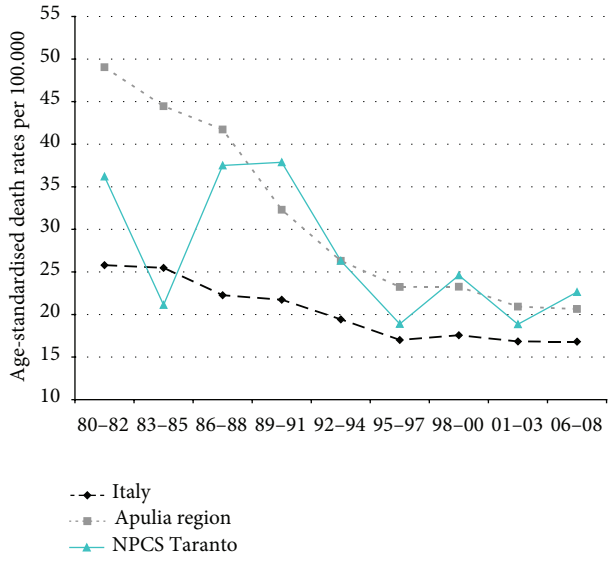

Figure 16: Chronic respiratory diseases. Trends in age-standardised (Italian Census 2001) death rates per 100.000, from selected causes of death (1980–2008) (2004-2005 data were not available). All ages. Women.

the prevailing winds from northwest. The *exposed* districts were (1) Tamburi (we also included in this category the small districts of Isola, Porta Napoli, and Lido Azzurro), (2) Borgo, (3) Paolo VI, and (4) Statte. All the other districts were considered the reference zone (Italia-Montegragnano, San Vito-Lama-Carelli, Salinella, Solito, Corvisea, Talsano, Tre Carrare-Battisti, and Massafra).

A total of 321,356 people (157,031 males and 164,325 females) were enrolled in the cohort. At the time of the

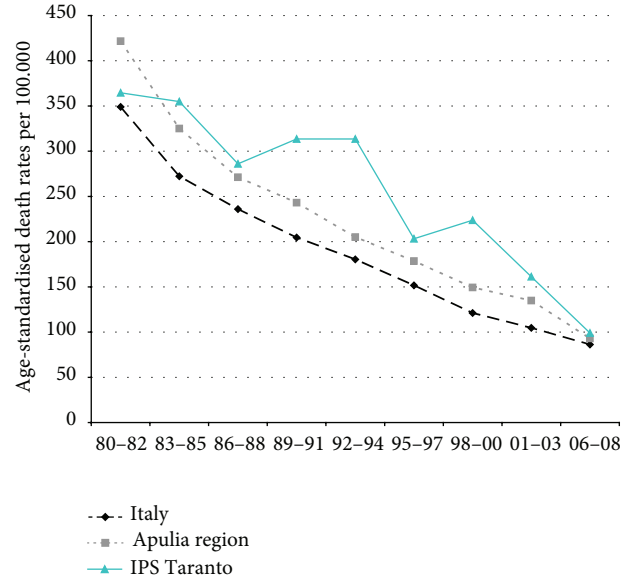

Figure 17: Overall mortality. Trends in age-standardised (Italian Census 2001) death rates per 100.000 (1980–2008) (2004-2005 data were not available). Infant Mortality (0 yrs).

enrolment (January 1, 1998), 84.9% of the subjects were already resident in the study area, and 39.1% of them had been residing at the same address for more than 20 years. As far as socioeconomic status is concerned, 35% of the cohort members were in the low SEP category and 21.4% in the high SEP category. The social distribution in the different districts was heterogeneous, with elevated proportion of high social level (62.2%) in some districts in the reference area (San Vito, Lama, Carelli) and low social level in Tamburi (69.4%) and Paolo VI (64.3%). In the Tamburi and Paolo VI districts there was a higher proportion of subjects with previous employment at the steel industry than in other areas.

A total of 3,384,302 person years were accumulated for the cohort. At the end of follow-up (December 31, 2010), 76.6% of the cohort members were alive and resident in the study area, 14.6% had moved, and 28,171 individuals (8.8%) had died. The cause of death was known only for 23,004 individuals deceased by 2008. Only 2.3% of the study subjects were born abroad, and most of the cohort members were born in Taranto (81.6%) and in southern Italy (93.5%).

An analysis of the mortality differences by socioeconomic status (low *versus* high category) shows (data not in Tables) in both genders a higher mortality for all causes (Hazard ratio—HR 1.25, 95% CI 1.19–1.31 among males and HR 1.18, 95% CI 1.13–1.24 among females), cardiovascular diseases (HR 1.14, 95% CI 1.04–1.25 among males and HR 1.21, 95% CI 1.11–1.32 among females), respiratory diseases (HR 1.89, 95% CI 1.55–2.29 among males and HR 1.38, 95% CI 1.11–1.72 among females), and digestive diseases (HR 1.46, 95% CI 1.19–1.79 among males and HR 1.56, 95% CI 1.24–1.95 among females). Socioeconomic differences in mortality were observed among males for all neoplasms (HR 1.26, 95% CI 1.15–1.37) and cancer of the stomach (HR 1.69, 95% CI 1.10–2.59), larynx (HR 3.32, 95% CI 1.55–7.09), lung (HR 1.40, 95%

Table 4: Cancer incidence Taranto NPCS. Number of observed cases (Obs), standardized incidence ratio crude (SIR); 90% IC: 90% confidence interval; Reference SIR: macroarea South and Islands 2005–2007; Reference SIR: Taranto province excluding NPCS municipalities (TA-NPCS) 2006-2007.

Cancer site	Males			Females		
	OBS	SIR-macroarea South and Islands (90% CI)	SIR (TA-NPCS) (90% CI)	OBS	SIR-macro-area South and Islands (90% CI)	SIR (TA-NPCS) (90% CI)
Head and neck	52	98 (77–123)	131 (103–165)	13	96 (57–153)	134 (79–213)
Stomach	51	130 (102–164)	117 (91–148)	43	167 (127–215)	224 (171–289)
Colon and rectum	145	112 (97–129)	122 (106–140)	131	115 (99–133)	121 (104–140)
Liver	64	110 (88–135)	140 (113–172)	36	110 (82–145)	175 (130–231)
Pancreas	28	100 (71–137)	135 (96–185)	31	113 (82–153)	129 (93–174)
Lung	245	144 (129–160)	150 (135–167)	47	117 (90–149)	148 (114–189)
Skin melanoma	35	214 (158–284)	193 (143–256)	23	143 (98–203)	120 (82–170)
Mesothelioma	21	429 (287–618)	256 (172–369)	3	197 (53–509)	81 (22–209)
Breast	—	—	—	317	130 (118–143)	124 (113–136)
Prostate	204	129 (112–148)	121 (105–139)	—	—	—
Testis	12	109 (63–177)	79 (46–128)	—	—	—
Uterus, cervix	—	—	—	14	93 (56–145)	88 (53–138)
Uterus, body	—	—	—	69	134 (109–164)	188 (152–230)
Ovary	—	—	—	35	119 (88–158)	81 (60–107)
Kidney and other unspecified urinary organs	51	164 (128–207)	201 (157–254)	18	119 (77–176)	114 (74–169)
Bladder	188	141 (125–159)	136 (120–153)	23	62 (42–88)	92 (63–130)
Brain and CNS (malignant)	16	86 (54–131)	88 (55–134)	12	78 (45–126)	65 (37–105)
Thyroid	23	169 (115–239)	126 (86–179)	71	152 (124–185)	94 (76–115)
Hodgkin lymphoma	6	88 (38–174)	63 (27–124)	8	131 (65–236)	70 (35–126)
Non-Hodgkin lymphoma	42	119 (90–154)	160 (122–207)	28	88 (63–121)	143 (102–196)
Myeloma	18	140 (90–208)	135 (87–200)	15	107 (66–165)	97 (60–149)
Leukemia	30	108 (78–146)	82 (59–111)	37	164 (122–216)	103 (77–136)
All tumors excluding skin, nonmalignant brain, and CNS	1338	131 (125–137)	130 (124–136)	1084	126 (120–132)	121 (115–127)

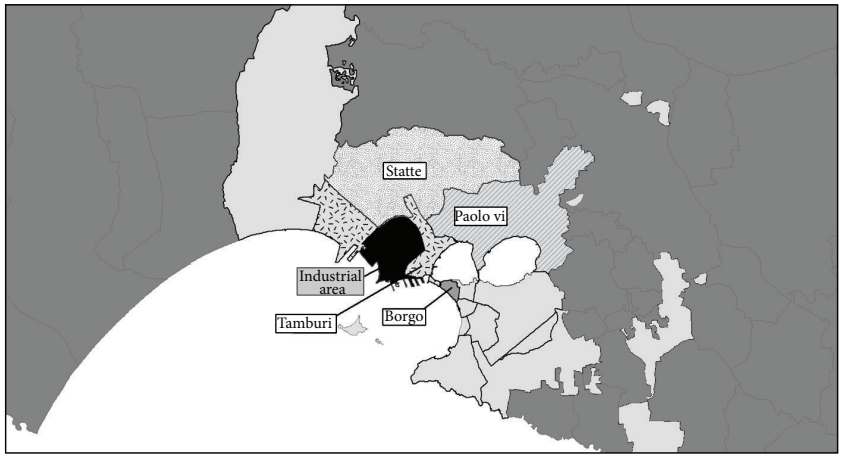

Figure 18: Taranto study area, districts.

Table 5: Association between district and cause-specific mortality (HR, 90% CI) (males, 1998–2008). Hazard Ratio (HR) from the Cox model stratified by calendar period and adjusted for age (underlying time) and socioeconomic position.

Cause of Death (ICD-9-CM)	Reference districts		Tamburi			Borgo				Paolo VI				Statte			
	n = 107,909		n = 14,067			n = 16,312				n = 10,097				n = 8,283			
	n	n	HR	90% CI		n	HR	90% CI		n	HR	90% CI		n	HR	90% CI	
All causes (001–999)*	9.378	1.470	1,12	1,07	1,18	1.973	1,07	1,03	1,12	684	1,27	1,19	1,36	654	1,08	1,01	1,15
Malignant cancers (140–208)	2.650	400	1,11	1,01	1,21	505	1,00	0,93	1,09	223	1,42	1,26	1,59	178	1,05	0,93	1,20
Stomach (151)	126	22	1,24	0,83	1,84	28	1,20	0,85	1,71	12	1,62	0,97	2,69	7	0,85	0,45	1,61
Colorectal (153-154)	220	19	0,62	0,41	0,92	48	1,13	0,87	1,48	12	1,07	0,65	1,75	11	0,79	0,48	1,32
Trachea, bronchus, and lung (162)	829	127	1,09	0,93	1,28	150	0,97	0,84	1,13	94	1,76	1,46	2,11	61	1,12	0,90	1,39
Pleura (163)	80	12	1,09	0,64	1,85	16	1,08	0,68	1,71	6	1,19	0,59	2,42	2	0,39	0,12	1,27
Prostate (185)	244	45	1,42	1,07	1,89	53	0,98	0,76	1,26	8	0,84	0,46	1,52	12	0,85	0,52	1,39
Bladder (188)	189	34	1,20	0,87	1,66	29	0,73	0,53	1,02	13	1,45	0,90	2,35	13	1,17	0,73	1,87
Kidney (189)	21	5	2,23	0,93	5,33	5	1,30	0,56	2,98	2	1,85	0,53	6,39	5	3,69	1,62	8,45
Brain and other parts of CNS (191-192; 225)	83	15	1,37	0,85	2,23	18	1,23	0,80	1,90	10	1,64	0,93	2,88	6	1,07	0,53	2,14
Lymphatic and hematopoietic tissue (200–208)	212	27	1,05	0,74	1,49	41	1,07	0,81	1,43	14	1,01	0,64	1,60	9	0,69	0,39	1,20
Neurological diseases (330–349)	190	28	1,09	0,77	1,54	30	0,76	0,54	1,05	7	0,72	0,38	1,36	15	1,32	0,85	2,06
Cardiovascular diseases (390–459)	2.442	378	1,10	1,00	1,21	551	1,02	0,94	1,10	147	1,28	1,11	1,47	137	0,93	0,81	1,08
Cardiac diseases (390–429)	1.688	260	1,09	0,98	1,23	387	1,03	0,94	1,13	106	1,27	1,08	1,51	84	0,82	0,68	0,99
Ischemic heart diseases (410–414)	733	116	1,20	1,01	1,42	152	1,04	0,89	1,20	56	1,37	1,09	1,73	30	0,66	0,49	0,90
Cerebrovascular diseases (430–438)	551	86	1,06	0,87	1,29	109	0,87	0,73	1,04	25	1,07	0,76	1,50	43	1,34	1,04	1,75
Respiratory diseases (460–519)	697	122	1,08	0,91	1,27	177	1,05	0,91	1,20	48	1,64	1,28	2,11	59	1,46	1,17	1,82
COPD (490–492, 494, 496)	469	93	1,17	0,96	1,41	110	0,94	0,79	1,12	32	1,70	1,25	2,32	39	1,44	1,10	1,90
Diseases of the digestive system (520–579)	527	81	1,06	0,86	1,30	111	1,07	0,90	1,27	47	1,47	1,14	1,90	27	0,79	0,57	1,09
Renal diseases (580–599)	146	27	1,36	0,94	1,95	37	1,13	0,83	1,54	3	0,50	0,19	1,30	9	1,00	0,57	1,76

*Referring to the period 1998–2010.

Table 6: Association between district and cause-specific mortality (HR, 90% CI) (females, 1998–2008). Hazard Ratio (HR) from the Cox model stratified by calendar period and adjusted for age (underlying time) and socioeconomic position.

Cause of death (ICD-9-CM)	Reference districts	Tamburi				Borgo				Paolo VI				Statte			
	n = 112,897	n = 14,625				n = 18,528				n = 9,714				n = 8,271			
	n	n	HR	90% CI		n	HR	90% CI		n	HR	90% CI		n	HR	90% CI	
All causes (001–999)*	9.015	1.479	1,09	1,04	1,15	2.482	1,01	0,97	1,05	489	1,28	1,18	1,38	547	1,06	0,98	1,14
Malignant cancers (140–208)	1.900	230	0,84	0,75	0,95	434	0,95	0,87	1,04	126	1,23	1,06	1,44	102	0,92	0,78	1,08
Stomach (151)	96	20	1,52	0,99	2,34	24	1,01	0,69	1,48	7	1,47	0,76	2,83	7	1,31	0,69	2,51
Colorectal (153-154)	226	23	0,62	0,43	0,90	45	0,78	0,59	1,02	16	1,35	0,87	2,08	7	0,54	0,29	1,02
Trachea, bronchus and lung (162)	144	15	0,76	0,48	1,20	34	1,06	0,77	1,46	13	1,71	1,05	2,79	6	0,68	0,34	1,34
Pleura (163)	20	2	0,66	0,19	2,31	6	1,16	0,53	2,52	3	2,95	1,03	8,46	0			
Breast (174)	349	41	0,92	0,69	1,22	89	1,18	0,96	1,44	28	1,29	0,93	1,79	22	1,04	0,72	1,49
Bladder (188)	33	7	1,23	0,61	2,50	12	1,13	0,64	1,97	2	1,29	0,39	4,34	1	0,58	0,11	3,06
Kidney (189)	17	0				3	0,87	0,30	2,49	0	0,00	0,00	0,00	1	1,06	0,19	5,79
Brain and other parts of CNS (191-192; 225)	90	6	0,48	0,24	0,97	17	0,85	0,55	1,33	4	0,67	0,29	1,57	7	1,30	0,68	2,48
Lymphatic and hematopoietic tissue (200–208)	202	22	0,74	0,50	1,08	33	0,65	0,47	0,88	11	0,98	0,59	1,65	11	0,99	0,60	1,66
Neurological diseases (330–349)	216	35	1,08	0,79	1,47	50	0,83	0,64	1,08	13	1,68	1,04	2,71	11	0,87	0,52	1,45
Cardiovascular diseases (390–459)	2.945	529	1,15	1,06	1,24	876	0,93	0,88	1,00	125	1,18	1,01	1,37	166	0,98	0,86	1,12
Cardiac diseases (390–429)	1.910	371	1,24	1,12	1,37	623	1,04	0,96	1,12	84	1,22	1,01	1,47	90	0,81	0,68	0,97
Ischemic heart diseases (410–414)	565	124	1,46	1,23	1,73	171	1,02	0,88	1,18	24	1,15	0,81	1,63	27	0,86	0,62	1,19
Cerebrovascular diseases (430–438)	820	122	0,93	0,79	1,10	207	0,77	0,68	0,88	35	1,19	0,90	1,59	62	1,38	1,11	1,71
Respiratory diseases (460–519)	476	82	1,09	0,89	1,34	169	1,09	0,94	1,26	22	1,26	0,88	1,82	34	1,28	0,95	1,71
COPD (490–492, 494, 496)	220	49	1,39	1,06	1,83	70	0,97	0,77	1,21	16	2,14	1,38	3,29	14	1,16	0,74	1,83
Diseases of the digestive system (520–579)	484	77	0,95	0,77	1,16	119	0,88	0,74	1,04	29	1,43	1,04	1,97	30	1,13	0,83	1,54
Renal diseases (580–599)	166	38	1,57	1,15	2,14	49	1,01	0,77	1,33	10	1,68	0,98	2,90	11	1,12	0,67	1,87

*Referring to the period 1998–2010.

Table 7: Association between district and cause-specific hospitalization (HR, 90% CI) (males, 1998–2010). Hazard Ratio (HR) from the Cox model stratified by calendar period and adjusted for age (underlying time) and socioeconomic position.

Diagnosis (ICD-9-CM)	Reference districts $n = 108,272$	Tamburi $n = 14,067$				Borgo $n = 16,312$				Paolo VI $n = 10,097$				Statte $n = 8,283$			
	n	n	HR	90% CI		n	HR	90% CI		n	HR	90% CI		n	HR	90% CI	
Malignant cancers (140–208)	4.818	685	1,12	1,05	1,21	861	1,06	0,99	1,12	444	1,31	1,21	1,43	354	1,06	0,97	1,16
Stomach (151)	166	27	1,21	0,85	1,73	30	1,05	0,75	1,46	19	1,63	1,09	2,46	15	1,29	0,83	2,02
Colorectal (153-154)	520	52	0,86	0,67	1,10	73	0,87	0,70	1,07	28	0,82	0,59	1,13	39	1,08	0,82	1,41
Trachea, bronchus, and lung (162)	866	149	1,29	1,10	1,50	156	1,06	0,92	1,22	101	1,61	1,34	1,92	60	0,98	0,78	1,22
Pleura (163)	75	18	1,80	1,14	2,84	18	1,38	0,89	2,15	7	1,44	0,74	2,79	4	0,77	0,33	1,79
Connective and other soft tissue (171)	32	4	0,91	0,37	2,24	10	1,80	0,98	3,31	5	1,66	0,74	3,72	3	1,30	0,48	3,52
Prostate (185)	639	80	1,10	0,90	1,35	113	1,04	0,88	1,24	40	0,98	0,75	1,29	51	1,22	0,96	1,56
Testis (186)	49	3	0,42	0,15	1,13	9	1,23	0,67	2,25	2	0,40	0,12	1,34	5	1,31	0,60	2,84
Bladder (188)	787	106	1,12	0,94	1,34	121	0,90	0,77	1,06	84	1,62	1,34	1,97	50	0,95	0,74	1,20
Kidney (189)	149	23	1,26	0,85	1,85	37	1,47	1,08	1,99	15	1,41	0,89	2,22	14	1,37	0,86	2,17
Brain and other parts of CNS (191-192; 225)	187	23	0,98	0,67	1,43	30	1,01	0,73	1,41	14	0,89	0,56	1,41	16	1,19	0,77	1,83
Lymphatic and hematopoietic tissue (200–208)	400	58	1,20	0,94	1,53	80	1,26	1,03	1,55	35	1,13	0,84	1,52	24	0,84	0,60	1,19
Neurological diseases (330–349)	1.850	329	1,26	1,14	1,40	337	1,11	1,00	1,22	226	1,43	1,27	1,61	140	1,04	0,90	1,20
Cardiovascular diseases (390–459)	14.504	2.078	1,18	1,13	1,23	2.457	1,03	1,00	1,07	1.388	1,32	1,26	1,39	1.076	1,06	1,01	1,12
Cardiac diseases (390–429)	9.866	1.411	1,20	1,15	1,27	1.699	1,04	0,99	1,09	957	1,41	1,33	1,49	752	1,10	1,04	1,17
Acute coronary events (410-411)	2.328	310	1,13	1,02	1,26	396	1,09	0,99	1,19	241	1,39	1,24	1,56	167	1,00	0,87	1,14
Heart failure (428)	1.878	317	1,21	1,09	1,34	375	1,03	0,94	1,14	180	1,54	1,35	1,76	119	0,97	0,83	1,13
Cerebrovascular diseases (430–438)	3.124	525	1,30	1,19	1,41	581	1,04	0,96	1,12	211	1,01	0,89	1,13	226	1,09	0,97	1,22
Respiratory diseases (460–519)	8.906	1.836	1,36	1,30	1,43	1.493	1,01	0,96	1,06	1.255	1,52	1,44	1,60	752	1,12	1,05	1,19
Acute respiratory infections (460–466, 480–487)	3.769	961	1,51	1,42	1,61	746	1,19	1,11	1,27	625	1,54	1,44	1,66	315	1,05	0,95	1,15
COPD (490–492, 494, 496)	2.350	450	1,31	1,20	1,43	379	0,85	0,78	0,93	252	1,60	1,43	1,79	203	1,29	1,14	1,46
Diseases of the digestive system (520–579)	15.628	2.465	1,20	1,15	1,24	2.301	0,94	0,91	0,98	1.682	1,23	1,18	1,29	1.229	1,06	1,01	1,12
Renal diseases (580–599)	3.252	562	1,35	1,25	1,46	521	0,98	0,90	1,06	331	1,35	1,22	1,49	282	1,22	1,10	1,36

Table 8: Association between district and cause-specific hospitalization (HR, 90% CI) (females, 1998–2010). Hazard Ratio (HR) from the Cox model stratified by calendar period and adjusted for age (underlying time) and socioeconomic position.

Diagnosis (ICD-9-CM)	Reference districts $n = 113{,}187$	Tamburi $n = 14{,}625$				Borgo $n = 18{,}528$				Paolo VI $n = 9{,}714$				Statte $n = 8{,}271$			
	n	n	HR	90% CI		n	HR	90% CI		n	HR	90% CI		n	HR	90% CI	
Malignant cancers (140–208)	3.878	530	1,03	0,95	1,12	713	0,91	0,85	0,97	295	1,17	1,06	1,29	225	0,91	0,81	1,02
Stomach (151)	129	23	1,26	0,85	1,85	24	0,89	0,61	1,28	7	1,06	0,55	2,02	9	1,10	0,62	1,94
Colorectal (153-154)	483	60	0,93	0,74	1,18	62	0,62	0,50	0,78	35	1,21	0,90	1,62	17	0,58	0,39	0,88
Trachea, bronchus, and lung (162)	149	17	0,89	0,57	1,37	30	0,94	0,67	1,33	10	1,04	0,60	1,80	5	0,53	0,25	1,12
Pleura (163)	23	3	0,87	0,31	2,44	2	0,44	0,13	1,48	4	3,35	1,31	8,54	2	1,25	0,37	4,22
Breast (174)	990	127	1,03	0,87	1,21	179	0,98	0,86	1,12	94	1,33	1,11	1,59	59	0,89	0,72	1,11
Vescica (188)	146	22	1,12	0,76	1,66	37	1,16	0,85	1,58	5	0,61	0,29	1,29	5	0,56	0,27	1,19
Kidney (189)	78	10	0,95	0,53	1,68	13	0,84	0,51	1,39	5	1,06	0,49	2,28	10	2,10	1,21	3,66
Brain and other parts of CNS (191-192; 225)	204	25	0,94	0,65	1,35	30	0,77	0,55	1,06	17	1,18	0,77	1,80	17	1,27	0,84	1,93
Lymphatic and hematopoietic tissue (200–208)	398	55	1,03	0,80	1,31	58	0,72	0,57	0,91	26	1,00	0,71	1,40	24	0,95	0,67	1,35
Neurological diseases (330–349)	2.151	351	1,11	1,01	1,23	378	0,89	0,81	0,98	168	1,06	0,93	1,21	141	0,98	0,85	1,14
Cardiovascular diseases (390–459)	13.500	2.072	1,15	1,11	1,20	2.611	0,90	0,87	0,93	1.059	1,31	1,25	1,39	888	1,05	0,99	1,11
Cardiac diseases (390–429)	9.366	1.478	1,17	1,12	1,23	1.897	0,93	0,89	0,97	752	1,40	1,31	1,49	632	1,09	1,02	1,17
Acute coronary events (410-411)	1.060	197	1,32	1,16	1,51	254	1,08	0,96	1,22	88	1,42	1,18	1,72	64	1,02	0,82	1,26
Heart failure (428)	2.449	368	0,95	0,87	1,05	628	1,02	0,94	1,09	154	1,32	1,15	1,52	106	0,77	0,65	0,90
Cerebrovascular diseases (430–438)	3.595	600	1,15	1,06	1,24	728	0,84	0,79	0,90	220	1,21	1,07	1,35	212	1,01	0,90	1,13
Respiratory diseases (460–519)	6.673	1.336	1,28	1,21	1,34	1.273	1,00	0,95	1,05	813	1,39	1,31	1,49	514	1,07	0,99	1,16
Acute respiratory infections (460–466, 480–487)	3.020	705	1,39	1,29	1,49	599	1,08	1,00	1,17	422	1,37	1,25	1,49	228	0,98	0,88	1,10
COPD (490–492, 494, 496)	1.433	262	1,19	1,06	1,33	325	0,94	0,85	1,04	126	1,62	1,39	1,89	91	1,09	0,91	1,30
Diseases of the digestive system (520–579)	12.952	2.067	1,18	1,13	1,22	2.038	0,89	0,85	0,92	1.288	1,25	1,19	1,31	905	1,00	0,95	1,06
Renal diseases (580–599)	3.187	662	1,47	1,37	1,59	609	0,99	0,92	1,07	320	1,35	1,22	1,49	248	1,17	1,05	1,31

CI 1.20–1.64), and bladder (HR 1.55, 95% CI 1.08–2.23). The results for hospitalizations confirm the increased risks among subjects in the low socioeconomic category when compared with those in the highest socioeconomic group.

Tables 5 and 6 show, respectively, for males and females, cause-specific mortality in the *exposed* subareas, that is, Tamburi, Borgo, Paolo VI, and Statte, compared with mortality observed in the reference ones. After adjusting for socioeconomic status, the *exposed* subareas (Tamburi, Borgo, Paolo VI, and Statte) have a higher mortality for all causes in comparison with the reference in males (in particular, Paolo VI and Tamburi). The most notable increases in mortality among males were in Paolo VI, with 42% excess for all malignant neoplasms (especially lung cancer, +76%), diseases of the cardiovascular (+28%), respiratory (+64%) and digestive (+47%) systems. In Tamburi, an excess was observed among males for all malignant neoplasms (+11%) and cardiovascular diseases (+10%), specifically ischemic heart diseases (+20%). Among females, in Paolo VI, excesses are present for all cancers (+23%), in particular lung, pleural and liver cancer, cardiovascular diseases (+18%), chronic obstructive pulmonary disease (COPD), and digestive system diseases. In Tamburi, excesses were present among females for cardiovascular diseases (+15%), in particular ischemic heart diseases, COPD (+39%), and renal diseases (+57%).

Tables 7 and 8 display the results for hospital admissions. The hospitalization analysis confirms the mortality results, documenting the major health impact on residents in Tamburi and Paolo VI areas, where excesses were observed among males for a number of causes such as lung cancer (29% and 61% in Tamburi and Paolo VI, resp.), neurological (26% and 43% in Tamburi and Paolo VI, resp.), cardiovascular (18% and 32% in Tamburi and Paolo VI, resp.), respiratory (36% and 52% in Tamburi and Paolo VI, resp.), and renal diseases (35% both in Tamburi and Paolo VI). Among females, similar excesses were observed for cardiovascular diseases (15 and 31% in Tamburi and Paolo VI, resp.), respiratory diseases (28% and 39% in Tamburi and Paolo VI, resp.), digestive diseases (18% and 25% in Tamburi and Paolo VI, resp.), and renal diseases (47% and 35% among males in Tamburi and Paolo VI, resp.). In Paolo VI, pleural (235%) and breast cancer (33%) were also in excess among females.

4. Discussion

The health impact of residence in Taranto NPCS was investigated using different epidemiological approaches: geographical (mortality and cancer incidence at municipality level), historical (mortality time trends at municipality level), and residential cohort studies (mortality and hospital discharge records at individual level). We adopted an analysis at small-area scale which includes a mix of small area and individual based data. The design issues relevant to this type of investigation have been thoroughly examined by Elliott and Savitz [27], some of them are briefly examined in the following paragraphs.

In environmental epidemiology, exposure ascertainment is a key phase because the exposure/s affecting the study population should ideally be described in detail, while in most instances the available exposure information is indirect and qualitative. In ecological investigations, the exposure/s can be a single event from a point emission source of some contaminants; more often the contaminants are heterogeneous mixture progressively polluting different matrices in the area. For example, in SENTIERI Project the sources of *environmental exposures* were abstracted from the legislative decrees defining sites' boundaries and fixed on the basis of the possible sources of contamination (e.g., chemical industry, steel plants, and landfills). A further limitation 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, due to many factors (e.g., concentration of contaminants and their diffusion to soil and water, distance of residence from polluting sources). The possible consequences of such nondifferential exposure misclassification are complex, and the direction of the resulting bias is not predictable [28]. In addition, information exposure source/s with possible health impact, such as concurrent air pollution from road traffic and exposures in the occupational setting, are often not available. Finally, vital statistics are accessible for a given administrative area whose boundaries hardly correspond to the distribution of environmental pollutants, so that the misclassification of exposure (and loss of statistical power) is common. A more detailed description of these limitations of ecological study design is available [15, 28, 29].

Exposure ascertainment is a critical issue in ecological investigations as well as in studies based on individuals, as cohort of residents are. In this case residential history, overtime information on exposure/s in different residences and different environmental matrices, daily variability, and seasonal variability should be available to classify subjects in different exposure categories. Obtaining individual-based measures of exposure as described above is clearly infeasible, and modeling of exposures, ranging from simple measures such as distance from a point source or distance to nearest road to more complex estimation, for example, dispersion modeling around a point source, is used. The possible exposure misclassification in such approaches has been discussed in [27].

As far as outcome measures are concerned, many studies of environmental healthin 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. The key issue is that, whatever the outcome under investigation, databases need to be validated for use in epidemiological studies.

Reporting the event of death is usually exhaustive; therefore the overall mortality can be analyzed with confidence [30]. In Italy, validity of cause of death certification has been documented for specific diseases [31–34]. The validity of hospital discharge records (HDRs), indicators of hospital activity, has not been systematically evaluated, although in Italy some critical aspects of this novel utilization of HDRs have been examined [35].

Another crucial aspect in environmental health studies is that factors such as socioeconomic status, occupational exposures/s, and individual lifestyles can have an etiologic role on the health effects under study thus possibly confounding the exposure-disease relationships.

For a review of adjustment for socioeconomic status using census data in ecological studies of environment and health refer to Pasetto et al, 2010 [36]. To account for deprivation in SENTIERI Project, mortality data both crude and adjusted were analyzed using an *ad hoc* built deprivation index [25]. Also in individual-based studies, the analyses can be adjusted for socioeconomic factors, usually with an aggregate indicator based on residence address. In the present cohort of residents in Taranto NPCS SEP was assigned to each participant on the basis of the geocoded addresses at the beginning of the follow-up.

Occupational exposure/s are also potential confounders in environmental health studies. The ecological components of the present investigation are affected by this limitation, while for the cohort study individual occupational history was traced through the national insurance company (INPS) database, and the subcohort of individuals employed in industries located in the area was identified indicating a high proportion of past employment at the steel plant among residents in Tamburi and Paolo VI.

Again on this topic, with specific reference to pleural mesothelioma, it should be noted that the Italian National Mesothelioma Registry analysis of residential asbestos exposure showed that steel mills and iron foundries were the second most frequent sources of asbestos in the neighborhood (after asbestos-cement factories), ranking equal to asbestos textiles production [37]. Furthermore a case-control study in the area of Taranto (HDR, 1998–2002) adjusted for occupational exposures [11], showed an increase in malignant pleural neoplasms among residents close to the steel mill (or 1.62, 95% CI 0.37–7.10, 11 cases) and the coke plant (or 2.18, 95% CI 0.31–15.31, 9 cases).

Another aspect to consider in environmental epidemiology is that large populations are needed to study many of the health concerns of greatest interest. In ecological investigations, the reference populations should be selected balancing the need for comparability of study and reference populations for factors other than the environmental exposure/s with possible health impact (socioeconomic status and lifestyle factors as diet and tobacco use) and the requirement of sufficiently numerous populations to have stable reference rates also for rare diseases. These needs are satisfied in the present investigation where national, macroregional, and regional populations were used for comparison in the mortality, time trend, and cancer incidence analysis. In the cohort study an internal comparison was carried out, and the reference population was composed of residents in districts distant from the industrial area.

For chronic diseases including most cancers, latency effects are important, such that exposures experienced many years previously, or accumulated exposures, may be crucial. In Taranto NPCS, the mortality (1995–2009) and the time trends analyses (1980–2008) show consistent results and cover a time span which should encompass latency effects. Analogously in the cohort of residents, most subjects were present at enrolment in 1998 (85%), and half of them had a residence duration of 10 or more years.

A brief comment on the use of 90% CI in our analyses is needed. In this respect we refer to Sterne and Smith [38], who affirm that confidence intervals for the main results should always be included, but 90% rather than 95% levels should be used. CI should not be used as a surrogate means of examining significance at the conventional 5% level. Interpretation of CI should focus on the implications (clinical importance) of the range of values in the interval.

5. Conclusions

In Taranto NPCS, mortality data at municipality level analyzed, in the context of SENTIERI Project, time trend analysis and cancer incidence results coherently showed, in both genders, excess risks for a number of causes of death, among them: all causes, all cancers, lung cancer, cardiovascular, and respiratory diseases, both acute and chronic. For these causes, an etiologic role of environmental exposure present in Taranto NPCS can be supported on the basis of *a priori* evaluation of the epidemiological evidence completed in SENTIERI. In the cohort study among residents in the districts nearer to the industrial area, excess mortality/morbidity risks were shown for natural cause, cancers, cardiovascular, and respiratory diseases. These excesses were also observed in low socioeconomic position groups compared to high ones, some of them could be explained on the basis of previous employment of residents in industries active in the study area.

As discussed above the present results for Taranto NPCS are based on sound study design and valid data, which make a low potential for bias and help to strengthen etiologic inference. The present findings further corroborate the need to promptly proceed with environmental cleanup interventions.

It should not be disregarded the fact that most diseases showing an increased risk have multifactorial etiology, therefore interventions of proven efficacy, such as smoking cessation, food education, measures for cardiovascular risk reduction, and breast cancer screening programs, should be planned. To build a climate of confidence and trust between citizens and public institutions, study results and public health actions are to be communicated objectively and transparently.

Appendices

A. International Classification of Diseases to Code Mortality: From ICD-9 to ICD-10

Mortality data are coded according to the International Classification of Disease (ICD) which has been revised approximately every 10 years; the purpose of the revision is to stay abreast of medical advances in terms of disease nomenclature and etiology. In Italy, deaths have been coded according to the Ninth Revision (ICD-9) until 2002 [39]; since 2003, the Tenth Revision (ICD-10) has been adopted [40].

ICD-10 differs from ICD-9 in several respects: ICD-10 is far more detailed than ICD-9, with about 12,000 categories versus about 5,000 categories; ICD-10 uses alphanumeric codes compared with numeric codes in ICD-9; some additions and modifications were made to the chapters in the ICD; and some of the coding rules and rules for selecting the underlying cause of death have been changed.

Because of these modifications, comparability studies, also called bridge-coding studies, were carried out to measure the effects of a new revision of the ICD on the comparability with the previous revision of mortality statistics by cause of death. These studies involve the dual classification of a single-year mortality data, that is, classifying the underlying cause of death on mortality records by both the new revision and the previous revision. The key element of a comparability study is the "comparability ratio", which is derived from the dual classification.

Operationally, the comparability ratio for the cause of death i (Ci) is calculated as follows:

$$Ci = \frac{D_{i,\text{ICD-10}}}{D_{i,\text{ICD-9}}}, \quad \text{(A.1)}$$

where $D_{i,\text{ICD-10}}$ is the number of deaths due to cause i classified by ICD-10. $D_{i,\text{ICD-9}}$, is the number of deaths due to cause i classified by ICD-9.

A comparability ratio of 1.00 indicates that the same number of deaths was assigned to cause i under both ICD-9 and ICD-10.

Comparability studies between ICD-9 and ICD-10 have been conducted in the USA, in Europe (by Eurostat), and also in Italy (by the Italian Census Bureau, ISTAT) [41–44]. The Italian study [44] documented that comparability ratios of the main causes of death are close to the value of one.

Table S1 presents the comparability study results that referred to some causes investigated in the time trend analysis.

In Italy the definition of municipalities has varied over time: some municipalities have been suppressed, others have been modified, and others have been created.

Generally, these modifications are not implemented at the same time by the office that registers deaths (Civil Status Office) and by the office that registers the population (General Registry office).

Therefore, it may occur that a "new" municipality (created by the subdivision of another municipality) creates first the General Registry, beginning to register its own populations, while the deaths continue to be registered by the Civil Status Office of the "old" municipality [45, 46].

In the context of SENTIERI Project the situation of all of the municipalities constituting the NPCSs has been studied [47].

As far as Taranto and Statte municipalities, that constitute Taranto NPCS, the description is as follows: until 1993, Statte was a district of Taranto; in 1994 it became a new municipality and created immediately its own General Registry Office; on the other hand, its own Civil Status office was set up some years later (1998).

To "synchronize" data regarding deaths and populations of both Statte and Taranto, we decided to attribute the population and the deaths of Statte to Taranto until 1997; since 1998, they have been attributed to Statte itself.

B. Mortality Trends from Selected Causes in Taranto NPCS, 1980–2008

See Supplementary Tables S2, S3, and S4.

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Research Article

Lung Cancer Risk and Past Exposure to Emissions from a Large Steel Plant

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We studied the spatial distribution of cancer incidence rates around a large steel plant and its association with historical exposure. The study population was close to 600,000. The incidence data was collected for 1995–2006. From historical emission data the air pollution concentrations for polycyclic aromatic hydrocarbons (PAH) and metals were modelled. Data were analyzed using Bayesian hierarchical Poisson regression models. The standardized incidence ratio (SIR) for lung cancer was up to 40% higher than average in postcodes located in two municipalities adjacent to the industrial area. Increased incidence rates could partly be explained by differences in socioeconomic status (SES). In the highest exposure category (approximately 45,000 inhabitants) a statistically significant increased relative risk (RR) of 1.21 (1.01–1.43) was found after adjustment for SES. The elevated RRs were similar for men and women. Additional analyses in a subsample of the population with personal smoking data from a recent survey suggested that the observed association between lung cancer and plant emission, after adjustment for SES, could still be caused by residual confounding. Therefore, we cannot indisputably conclude that past emissions from the steel plant have contributed to the increased risk of lung cancer.

1. Background

Residents living in the surrounding area of a large steel plant located near the Dutch town of IJmuiden have been concerned about health effects from plant emissions for some time. This led to studies into the acute effects of air pollution in the vicinity of the plant [1, 2]. But concerns were augmented by a television documentary broadcast in May 2008, which presented results from a study of metal concentrations in hair from children living in the area [3]. Earlier, in 2007, the Community Health Service reported an increased lung cancer incidence for the region as a whole and for the nearby municipality of Beverwijk in particular [4].

In a large number of studies the health of the residents in the vicinity of steel plants has been investigated. The health effects of long-term exposure include, among, others lung cancer and mortality [5–21]. We present the results from a study, which aims to investigate the spatial distribution of lung cancer incidence rates in a large area around the industrial site at a lower aggregation level than was previously available for studies into the health effects of the steel plant [4]. The study furthermore addresses the influence of smoking habits on lung cancer incidence and aims to assess the association between air pollution from the steel mill and observed lung cancer incidence rates.

2. Method

2.1. Study Area and Population. The steel plant is located at the west coast of The Netherlands in the IJmond region, covering a terrain of 750 hectares. The plant was developed from 1920 onwards, first producing iron, later steel, and in addition

aluminium. The plant consists of 16 factories, including blast furnaces and coke ovens, and has its own harbour. The selected study area surrounds the plant location to the south, east, and north (Figure 1). The study area was selected based on the service area of the Community Health Service that originally investigated the public concern. It is an area in which south-westerly winds prevail, which makes it plausible that plant emissions tend to distribute in a north-eastern direction. The study area was expanded with the inclusion of additional postcodes in this direction. The final study area consists of 17 municipalities and comprises 106 4-digit postcode areas with a total population just below 600,000. Population data at the postcode level were available from Statistics Netherlands (CBS) stratified by age and sex.

2.2. Air Pollution Data. Plant emissions have been recorded since 1985. Historic emission data for the period 1950–1984 were obtained by combining the emission registration data from 1985 with historic production data. Polycyclic aromatic hydrocarbons (PAH), lead, and cadmium were the relevant and available air pollution indicators for the health effect under study. The concentrations of these components were modelled for seven (PAH) or eight (metals) consecutive periods from 1950 to 2007 for a 15 × 15 km model area at a 100 × 100 m resolution [22]. The period lengths varied from 3 to 23 years according to assumed invariance of emissions. From the geographical distributions of the concentrations, we calculated population density weighted average concentrations for each postcode situated (for the greater part) within the air pollution modelling area. Subsequently, the postcode areas were divided into four exposure categories based on quartiles. Figure 3 shows that the air pollution modelling area covers only part of the total study area; the remaining 63 postcodes outside the modelling area constituted the fifth (reference) category. Effects of air pollution concentrations due to steel plant emissions were assumed to be negligible for these areas.

2.3. Lung Cancer Data. Yearly lung cancer incidences (ICD10 C34) were obtained for a consecutive period of 12 years (1995–2006) from the Comprehensive Cancer Centre Amsterdam (IKNL). Since 1989, IKNL maintains the only Dutch oncology registry with a coverage of at least 95% of all cancer patients. The study period was started in 1995 as age and gender specific population data at postcode level have become available since then. Due to privacy regulations, the observed number of lung cancer cases cannot be reported below the postcode aggregation level, making this the aggregation level of choice for the analysis.

2.4. Data on Potential Confounders. Cancer risk is determined to a large extent by individual lifestyle factors such as smoking, diet, alcohol use, and obesity. For lung cancer risk, smoking behaviour is the dominant factor that might influence the results of this study. As no historical data on lifestyle factors were available at postcode level for the study area as a whole, we used socioeconomic status (SES) as a proxy to adjust for potential confounding. SES categories constructed from level of income, education, and professional status are

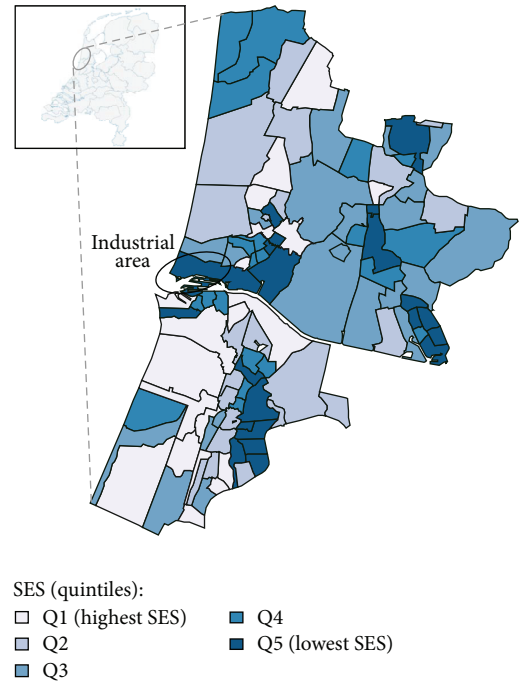

Figure 1: Study area and socioeconomic status. Location of the industrial area within the study area and socioeconomic status (SES—quintiles) of the postcode areas.

available for every 4 years since 1994 from The Netherlands Institute for Social Research [23]. We used percentile values for postcode areas based on the ranking order for SES of all postcode areas in The Netherlands. In addition, we obtained data from recent health surveys among 6,044 adults (19–65 years) and 5,691 elderly (over 65 years) for 2007 and 2008 on current and past smoking habits that was conducted for part of the study area (67 postcode areas) by one of the Community Health Services [24, 25]. With this survey data, the prevalence of current and past smoking was calculated per postcode area. Comparison of smoking prevalence and SES in a smaller part of the study area served as a check on the ability of the SES indicator to serve as a proxy for the differences in smoking behaviour between postcodes.

2.5. Data Analysis. The expected number of lung cancer cases per postcode area was calculated through indirect standardization, based on the age and gender distribution of the population in a postcode and using the age and gender distribution of the lung cancer cases for the whole study region as the reference population. As second step, a Poisson regression model with indicator variables for each year was applied. This model was subsequently extended to a Bayesian hierarchical Poisson regression model with a conditional autoregressive spatial correlation structure to determine spatially smoothed expected incidences [26–28]. As a fourth step, the regression model was adjusted for SES. Maps of spatially smoothed standardized incidence ratios of observed and expected rates (SIR) for the postcode areas were produced to assess the spatial pattern of lung cancer incidence for the population as

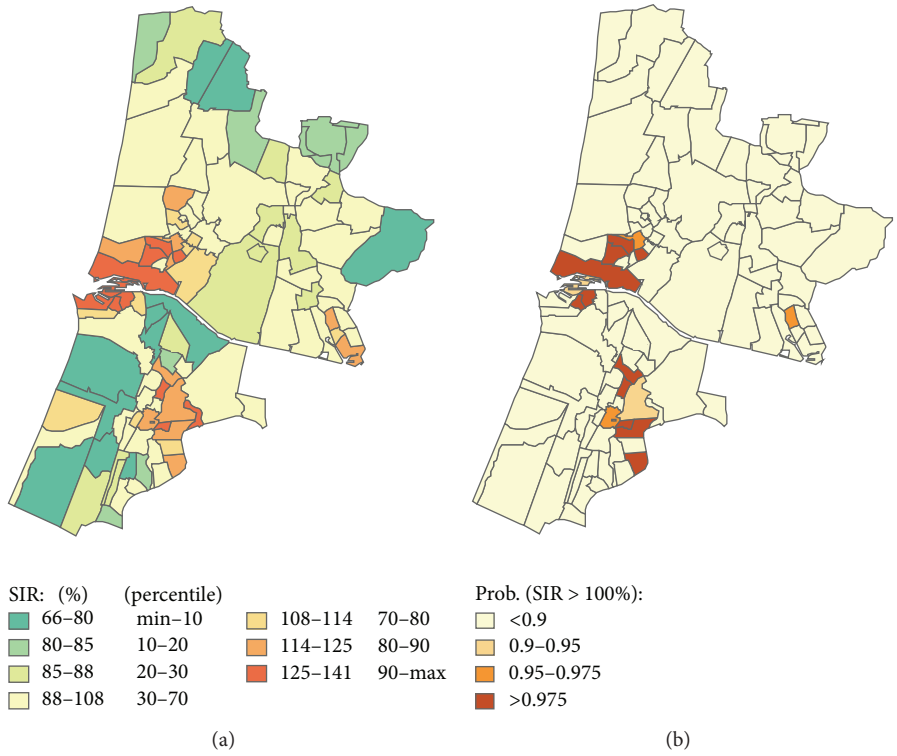

Figure 2: Lung cancer incidence. Standardized incidence ratios (SIR) for lung cancer within each postcode area (left) and the statistical probability that the SIR of a postcode area is higher than expected.

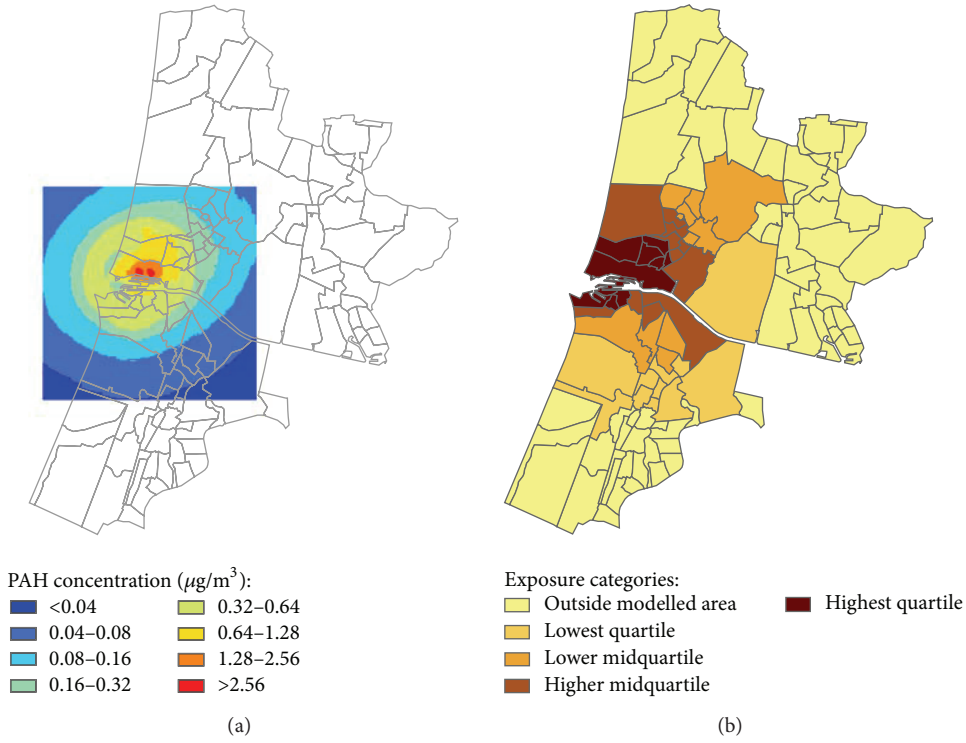

Figure 3: Average PAH concentrations. Modelled concentrations of polycyclic aromatic hydrocarbon (1972–1994) and allocation of postcode area to exposure categories based on the average PAH concentration within the postcode areas.

Table 1: Standardized incidence ratios for lung cancer.

SIR	Age standardization	Age + spatial smoothing	Age + spatial smoothing + SES
Mean	1.01	1.00	0.97
Median	0.97	0.97	0.97
Standard deviation	0.43	0.17	0.08
Minimum	0.00	0.66	0.81
Maximum	3.55	1.41	1.20
Interquartile range	0.79–1.21	0.86–1.12	0.90–1.04

Distribution of SIRs for lung cancer within the study area after indirect standardization for age and sex, spatial smoothing, and correcting for the influence of SES.

a whole as well as for men and women separately. To assess the association between air pollution indicators from the steel mill and observed lung cancer incidence rates, the 5 exposure categories for PAH and cadmium were added to separate regression models. We evaluated the effect of exposure on lung cancer incidence as relative risk (RR). To evaluate potential residual confounding by smoking after adjustment for SES, we determined whether a relation between exposure and smoking was present in part of the study area and whether this relationship still existed after adjusting for SES.

3. Results

The average yearly population for the area consisted of 290,160 men and 303,860 women, while the average population within the postcodes amounted to 5,600 ranging from approximately 100 inhabitants up to almost 16,000 inhabitants. The total number of lung cancer cases during the 12-year period was 3,029 for men and 1,388 for women (4,417 cases in total). The yearly lung cancer incidence for the population in the study area was on average 5% lower than for the total population in The Netherlands.

The distribution of the standardized incidence ratios (SIR) and the effect of spatial smoothing are shown in Table 1. After spatial smoothing, lung cancer showed significant increases in the SIR of up to 40% in postcode areas in 2 municipalities located within 5 km from the industrial area. Similar increases were seen in parts of an urban area in the southern part of the study area further away from the industrial complex (Figure 2).

There was very little or no discernible difference in ranking of postcode areas over time for both PAH and metal concentrations. Similarly, there was little or no discernible difference in ranking of postcode areas between lead and cadmium concentrations. Therefore, analyses were performed using average data from a single time period (1972–1994) for PAH and cadmium only. The exposure categories for PAH and cadmium did not exactly coincide due to different locations of the emission sources of PAH and cadmium at the plant site. On the left side, Figure 3 shows the geographical distribution of the modeled average PAH concentrations for the period 1972–1994 and the location of the modelling area within the total study area. The right side of Figure 3 shows how the postcodes that are located completely or partly within the modelling window were assigned to the four exposure categories based on the average PAH concentrations of the postcodes. The remaining 63 postcodes outside the modelling window were assigned to the reference category.

The distribution of the SES categories (quintiles) across the study area is shown in Figure 1. On average, the SES scores in the study area were 8% lower than within The Netherlands as a whole. However, the SES scores covered almost the full scale ranging from the 5th to the 99th percentile. SES scores for a single point in time could be used in the analysis because SES ranking of the postcodes hardly varied over the years during the study period (1995–2006). The relative risks (RR) for lung cancer in postcodes within the lowest SES quintile compared to postcodes within the highest SES quintile were 1.59 (95%CI: 1.36–1.85) for men and 1.83 (95%CI: 1.44–2.29) for women. Over the twelve-year study period (1995–2006), SES ranking for postcode areas varied little over the years.

The PAH exposure range, average population per year during the study period, and the total number of lung cancer cases are given in Table 2 for each exposure category. The table also shows the RR for lung cancer in each exposure category and the effect of smoothing and correction for SES on the RR. The RR to develop lung cancer for those living in postcode areas in the highest PAH exposure category compared to those living outside the exposure modelling area is 1.35 (95%CI: 1.23–1.48). The effect size diminishes slightly after applying spatial smoothing and adjustment for SES resulting in a RR of 1.21 (95%CI: 1.01–1.40) for men and women combined. The RR in the highest exposure category is 1.22 (95%CI: 1.02–1.50) for men and 1.16 (95%CI: 0.87–1.50) for women in the model taking into account spatial smoothing and adjustment for SES. The RR was significantly increased for men living in the highest exposure category only. The SIR for lung cancer at postcode level after correction for SES is presented in Figure 4. Compared to Figure 2, the number of postcodes with a SIR that is higher than expected is reduced.

Similar results were found for cadmium (Table 3). The RR in the highest exposure category decreased from 1.34 (95%CI: 1.21–1.48) to 1.23 (95%CI: 1.03–1.50) after adjustment for SES and applying spatial smoothing for men and women combined. Again the results for men and women separately were comparable: 1.22 (95%CI: 1.01–1.50) for men only and 1.26 (95%CI: 0.94–1.70) for women only. Statistically significant elevated RRs due to exposure to air pollution from the industrial area were only found in the highest exposure category.

Table 2: Relative risks for lung cancer in relation to PAH exposure.

	Range PAH conc. period 1972–1994 (μg/m3)	Average population per year	No. of cases in 12 years	RR without smoothing [95% CI]	RR after smoothing without SES [95% CI]	RR after smoothing and SES correction [95% CI]
Outside modelled area	n.a.	370,259	2,646	1	1	1
First quartile	0.032–0.052	72,962	533	1.07 [0.97–1.17]	1.02 [0.85–1.23]	1.05 [0.91–1.20]
Second quartile	0.055–0.159	63,508	380	0.91 [0.82–1.01]	0.91 [0.73–1.12]	0.93 [0.80–1.10]
Third quartile	0169–0.390	45,911	364	1.09 [0.98–1.22]	0.98 [0.76–1.25]	1.03 [0.86–1.20]
Fourth quartile	0.426–0.636	46,931	494	1.35 [1.23–1.48]	1.27 [0.97–1.66]	1.21 [1.01–1.40]

RR for lung cancer in relation to PAH exposure from the lowest (first) to the highest (fourth) exposure quartiles with and without smoothing and correction for SES.

Table 3: Relative risks for lung cancer in relation to cadmium exposure.

	Range cadmium conc. period 1973–1984 (ng/m3)	Average population per year	No. of cases in 12 years	RR without smoothing [95% CI]	RR after smoothing without SES [95% CI]	RR after smoothing and SES correction [95% CI]
Outside modelled area	n.a.	370,259	2,646	1	1	1
First quartile	0.30–0.42	60,837	443	0.97 [0.88–1.07]	0.90 [0.74–1.09]	0.99 [0.85–1.10]
Second quartile	0.42–0.72	69,253	381	0.93 [0.84–1.04]	0.95 [0.79–1.15]	0.95 [0.83–1.10]
Third quartile	0.73–0.87	57,464	501	1.19 [1.08–1.31]	1.26 [1.01–1.61]	1.11 [0.94–1.30]
Fourth quartile	0.89–1.65	41,758	446	1.34 [1.21–1.48]	1.38 [1.06–1.83]	1.23 [1.03–1.50]

RR for lung cancer in relation to cadmium exposure from the lowest (first) to the highest (fourth) exposure quartile with and without smoothing and correction for SES.

As SES can only serve as a proxy for smoking behaviour, potential residual confounding was further analyzed using an external data source on smoking habits, which covers only part of the study area and which was collected by one of the Community Health Services after the time window of our study. In the highest air pollution exposure category, among women younger than 65 years of age, the odds ratio (OR) for "current smoking" after adjusting for SES is 1.34 (95%CI: 1.09–1.64), indicating that the prevalence of female smokers in this air pollution exposure category is higher than in the reference area and even higher than could be expected on the basis of lower SES. In addition, in the highest air pollution exposure category among men of 65+ years of age an increased OR after adjusting for SES of 1.82 (95%CI: 1.20–2.75) was observed for "ever smoking."

4. Discussion

In this study, we found that the SIR for lung cancer was up to 40% higher than average in postcode areas in two municipalities in the proximity of the industrial terrain of a steel plant. With a total number of over 4,000 lung cancer cases over a period of twelve years, this study was relatively large in comparison to similar research from other scientific publications. We found two studies of similar size [11, 17]. The first concerned the mortality risk of residents living near 22 coke plants in England, Scotland, and Wales over the period 1981–1992 and reported a small but significant excess mortality risk of 3% for residents living within 2 kilometres of the coke plants, after correction for SES. This is considerably less than the 21% excess risk found in this study. The second describes lung cancer risks due to a coke oven plant near Genoa, Northern Italy. Only a marginal excess risk was found in the exposed area compared to the two reference areas. Published ecological studies with a smaller number of cases tend to report higher relative risks than we found, albeit with much larger confidence intervals. Extensive research has been carried out around the steel foundries in Armadale, Bathgate, and Kirkintilloch in Scotland using both ecological and case-control study designs [15, 16, 20, 21, 29]. The researchers attributed the increased cancer mortality risk that was found to a change in production process of the plants in the sixties. Due to the small number of cancer cases this was difficult to confirm using the available statistical methods at the time. Later research [14] did indeed find a lung cancer cluster using more advanced statistical methods. Ecological research around the large complex of steel and petrochemical plants near Teesside indicated increased lung cancer mortality over the period 1981–1991 in areas with increased exposure to air pollution [9, 18]. This was confirmed by a subsequent case-control study that found, after correction for confounding factors, a RR of 1.83 (95%CI: 0.82–4.08) for women living more than 25 years near heavy industry and 1.10 (95%CI: 0.96–1.26) for women living there more than 10 years. Similar

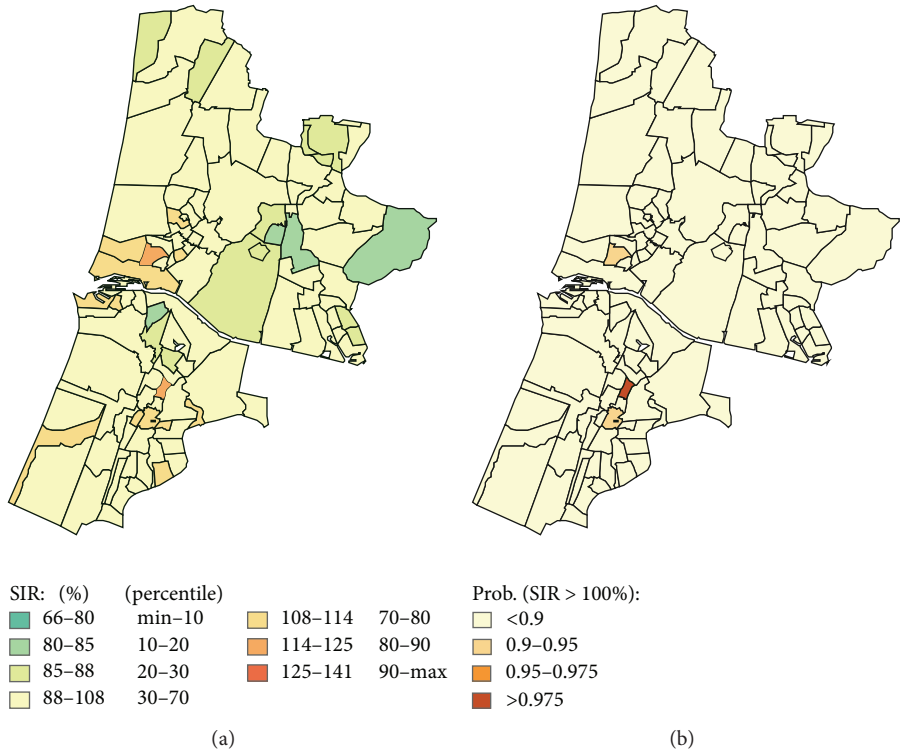

Figure 4: Lung cancer incidence—correction for socioeconomic status. SIR for lung cancer within each postcode area after correction for the influence of differences in SES (left) and the statistical probability that the SIR of a postcode area is higher than expected.

ecological research near a coke plant in South Tyneside over the period 1981–1989 did not show elevated lung cancer risks [8]. The finding that length of residence influences the cancer risk is an important one. However, this factor is difficult to take into account using an ecological study design. It was not possible to assess and account for the migration patterns of the population in our study.

Results from studies in North America show inconsistent findings. Archer studied lung cancer mortality risks in 3 communities in Utah and estimated an increase of 30–40% due to air pollution from a steel factory over the period 1950–1987 [5]. However, a similar study carried out in the same area did not find increased mortality risks after standardizing for smoking behaviour [10]. Both studies have been found sensitive for the way confounding factors were taken into account and the construction of control areas [19]. Several studies have been carried out in Sydney (Nova Scotia, Canada) around a coke plant and steel foundry [6, 7, 13]. Over a period of 45 years, mortality in Sydney was higher for breast and intestinal cancer compared to Canadian reference figures. In three highly exposed areas near the plants, an increased lung cancer risk was found with a standard mortality ratio of 1.41 for men (95%CI: 1.11–1.77) and 1.76 for women (95%CI: 1.13–2.63). A subsequent case-control study could not confirm these findings due to the small number of cases that could be reached.

Older studies do not correct for SES. Those studies that do correct for SES or smoking habits like in our study find similar decreases in relative risks. A few case-control studies have been published [6, 12, 16]. The latter was the only study that produced information on relative risks for lung cancer in relation to living near an industrial area including a steel plant. For 204 female lung cancer cases and 339 controls they found a RR for lung cancer of 1.83 (95%CI: 0.82–4.08) at 25 years of residence and of 1.10 (95%CI: 0.96–1.26) at 10 years of residence.

The PAH and cadmium concentrations being modelled on the basis of emission data introduce uncertainty in the estimated absolute levels of historical environmental concentrations. As we were interested in the contrast in health effects between high and low exposed areas, the relative ranking of the postcode areas within the study area is of more importance than the absolute levels of the pollutant concentrations. This still leaves the possibility of exposure misclassification of postcodes due to uncertainties in the emission data and the modelling exercise, especially at larger distances from the industrial site where meteorological and model assumptions play a larger role on the outcome of the emission model. Since the observed effects only occur in the highest exposure category, the validity of the exposure contrast between the reference and the highest exposure category is most critical. As we expect the least misclassification in the highest exposure category, the misclassification in the reference category is the most relevant. However, as the reference category is very large consisting of 62% of the study population and 60% of the cancer cases, it is unlikely that misclassification of postcodes in this category will affect the baseline incidence rate in the reference category and thereby the RR.

The available data for the pollutants show a high degree of correlation in concentration across time and space [30]. Be-

cause of this correlation, it is not possible to distinguish between individual effects of each pollutant. The data for PAH and cadmium used must therefore be regarded as representative for historical exposure to the total air pollution from the steel plant. We did not investigate alternative sources of air pollution, such as other nearby industries or shipping. In a sensitivity analysis (not presented here), we investigated levels of air pollution from NO_2 and PM10, which can be attributed to various local sources [31–33]. We found no relation between these air pollution levels and the increased lung cancer incidences. As these concentrations of NO_2 and PM10 date from the start of this century, we cannot preclude that earlier air pollution from local sources may have contributed to the increased lung cancer risks found. If historical pollution from other sources was correlated with the PAH and cadmium concentrations from the steel plant which we used, it is possible they also contributed to the resulting increased risk.

At the postcode level, SES was the only available confounder that corresponded with the studied time window of the incidence of lung cancer. We are aware that the use of SES does not warrant a full adjustment for smoking habits. It is also possible that changes in smoking habits over time did not correspond to the SES strata in the studied time window [34]. Where this leads to misclassification relating in any way to exposure, residual confounding may occur. That residual confounding indeed may be present is suggested by results from an analysis of the only available additional smoking data, which covers only a part of the study area and which was collected after the time window of our study. The analysis shows that in some age categories higher smoking percentages were found in the highest exposed postcode areas than were expected based on SES for these areas.

Occupational exposure was not addressed in this study. As there is little difference between the relative risks found for both sexes, the increased lung cancer incidences are less likely to be explained by occupational exposure.

The ecological epidemiological design of the study allowed us to analyse the geographical distribution of lung cancer incidence for a large population in relation to certain risk factors. The lack of information at the individual level means that conclusions can only be interpreted at the group level. The increase in relative risk is an indication that possible past exposure to air pollution from the steel plant may have led to an increase in lung cancer incidence over the period 1995–2006. It is not certain whether SES provides a sufficient adjustment for past smoking habits. In addition, there is lack of information on past levels of PM10 and other components from other sources of air pollution. Contribution of these other factors to the increase in relative risk can therefore not be excluded.

5. Conclusion

We observed an increased lung cancer incidence in certain postcode areas near the steel plant, after adjustment for SES. In the areas in which the highest historical exposure to PAH and cadmium occurred, lung cancer incidence after adjustment for SES was increased by 21% over the average incidence for the study area. We were unable to ascertain that adjustment for SES fully compensates for the effect of smoking. Due to the possible residual confounding of smoking and the limited availability of and uncertainties in the historical exposure data, we cannot indisputably conclude that past emissions from the steel plant have contributed to an increased risk of lung cancer.

Conflict of Interests

The authors declare that they have no competing interests.

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Research Article

Comparative Assessment of Particulate Air Pollution Exposure from Municipal Solid Waste Incinerator Emissions

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Background. Research to date on health effects associated with incineration has found limited evidence of health risks, but many previous studies have been constrained by poor exposure assessment. This paper provides a comparative assessment of atmospheric dispersion modelling and distance from source (a commonly used proxy for exposure) as exposure assessment methods for pollutants released from incinerators. *Methods.* Distance from source and the atmospheric dispersion model ADMS-Urban were used to characterise ambient exposures to particulates from two municipal solid waste incinerators (MSWIs) in the UK. Additionally an exploration of the sensitivity of the dispersion model simulations to input parameters was performed. *Results.* The model output indicated extremely low ground level concentrations of PM_{10}, with maximum concentrations of $<0.01\,\mu g/m^3$. Proximity and modelled PM_{10} concentrations for both MSWIs at postcode level were highly correlated when using continuous measures (Spearman correlation coefficients ~ 0.7) but showed poor agreement for categorical measures (deciles or quintiles, Cohen's kappa coefficients ≤ 0.5). *Conclusion.* To provide the most appropriate estimate of ambient exposure from MSWIs, it is essential that incinerator characteristics, magnitude of emissions, and surrounding meteorological and topographical conditions are considered. Reducing exposure misclassification is particularly important in environmental epidemiology to aid detection of low-level risks.

1. Introduction

Incineration is being increasingly used as a waste management option in the United Kingdom (UK). This is in response to EU legislation restricting the amount of waste disposed of in landfills [1]. Up until the 1990s incineration in the UK was largely uncontrolled. Legislation pertaining to all incinerators in the UK, the EU Waste Incineration Directive (WID) (2000/76/EC), came into operation for new incinerators in 2002 and older ones in 2005. This has set strict limits on emissions into the air [2]; nonetheless, there remains public concern and scientific uncertainties about possible health risks from pollutants emitted from incinerators.

European waste legislation uses the Waste Hierarchy Framework to guide the use of different waste management options, prioritising the more environmental desirable and sustainable options. Incineration falls above disposal of waste in landfills within this framework but is not as desirable as recycling and composting, reuse, and prevention [3]. Municipal solid waste incinerators (MSWIs) burn waste assembled by collection authorities [4], at high temperatures, reducing the volume of waste, eliminating pathogens and are capable of recovering energy from the waste [5].

To date a number of epidemiological studies have investigated the relationship between incineration and health [4–12], with most focused on its association with risk of cancer

and more recently, the risk of adverse birth outcomes [8, 12–24]. The UK Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment released a statement about MSWIs and cancer in 2000 (updated in 2009), stating that, "*...any potential risk of cancer due to residency near to municipal solid waste incinerators was exceedingly low and probably not measureable by the most modern epidemiological techniques*" [6, 7]. This was supported by the UK Health Protection Agency's' statement in 2009 "*...While it is not possible to rule out adverse health effects from modern, well regulated municipal incinerators with complete certainty, any potential damage to the health of those living close-by is likely to be very small, if detectable*" [25]. However, the evidence base investigating this issue remains limited and most existing studies suffer from incomplete information on potential confounders, lack of statistical power, and poor exposure assessment.

Exposure assessment is often referred to as the "Achilles heel" of environmental epidemiology [26, 27]. Inaccurate and imprecise exposure estimates, leading to exposure misclassification, can create biases in health risk estimates. In many environmental epidemiology studies, exposure misclassification is unrelated to the health outcome, termed nondifferential exposure misclassification, which would be expected to bias observed effect estimates towards the null [28]. Accurate exposure assessment is particularly important for studies trying to detect/exclude small excesses in risk in relation to environmental exposures [29], such as due to incineration, in order to enable true risks, if present, to be detected.

The methods used to assess exposure to an environmental source, such as an incinerator, range in design and complexity, from simple proxy methods to detailed individual level measures of exposure. Simple proxy methods, such as distance to the incinerator, assume a linear decrease in exposure with distance from source but benefit from the ease of implementation and the limited data and resources required to undertake a study using this exposure assessment method. However, this approach is crude and does not account for the magnitude of emissions, incinerator characteristics, or the propagation of the emissions due to local meteorological and topographic conditions. Individual level direct measures of exposure, such as biomarkers in human tissue, provide an objective assessment of exposure to chemicals and are considered "gold standards" in exposure assessment [30]. Biomarkers are often not feasible in large studies due to the high cost of laboratory analysis, the difficulties in acquiring human tissue, and the burden and potential risks to participants involved [30]. Exposure modelling has largely bridged the gap between the need for more accurate exposure assessment and the practical and financial constraints of large epidemiological studies. Atmospheric dispersion models use monitored emission data along with information on local topographic and meteorological conditions, within a Gaussian framework, to estimate the concentration and dispersion pattern of pollutants around an identified source [31, 32]. New generation dispersion models have an updated understanding of atmospheric turbulence and boundary layer structure [33] and have been extensively evaluated [34–37].

Many studies investigating the relationship between incineration and adverse health outcomes have used distance as a proxy for exposure. Some studies have included additional information alongside proximity to strengthen this method, including wind patterns, soil concentrations [18], local topography, and complaints of nuisance caused by the plumes [24]. Only a limited number of more recent studies have used dispersion models [8, 12, 13, 17, 23] to assess exposures. As far as the authors are aware, no existing studies on incinerators have compared these two exposure assessment methods and quantified the extent of exposure misclassification between the two. Modelled exposure patterns are expected to be different when using the two comparative methods. The distance method will predict greatest exposure adjacent to the stack and will decrease linearly with distance from the stack. These exposures will also be fixed in time and will be homogenous in space at a given distance from the stack. In contrast, because stack height above ground is considered, the dispersion model will predict low concentrations of incinerator emissions near to the stack. Greatest concentrations will be at a distance from the stack (determined by the release conditions and meteorology) after which concentrations will decrease nonlinearly with distance. Temporal changes in release conditions and meteorology are taken into account to produce a concentration field that varies in time. Here, we provide a detailed comparison of atmospheric dispersion modelling and a distance based method to assess exposure to particulates from two MSWIs and explore issues of exposure misclassification.

2. Methods

2.1. Study Area and Study Population. Two UK MSWIs were included in this study, Crymlyn Burrows, located approximately 5 km east of Swansea, Wales and Marchwood, approximately 3 km west of Southampton, England. These two MSWIs are representative of operational MSWIs in Wales and England in terms of the operational standards they were built to (both have only ever operated to the most recent European Waste Incineration Directive [2]); their size (Crymlyn Burrows and Marchwood licensed throughput of 52,500 tonnes and 210,000 tonnes of MSW a year, respectively, where the typical median throughput of all operational UK MSWIs is 165,000 tonnes, ranging from 3,500 to 750,000 tonnes); and their rural locations (within 10 km surrounding Crymlyn Burrows 70% of the land is rural land and 69% for Marchwood, median for all operational MSWIs of 69%). The two selected incinerators additionally provided a number of contrasting features. Crymlyn Burrows has a single flue, is surrounded by hills, and lies 850 m from the coast, whereas Marchwood has two flues, is surrounded by flat land, and lies more inland. Incinerator characteristics and daily emissions data from their commissioning date (January 2003 for Crymlyn Burrows, January 2006 for Marchwood) until December 2010 were provided by the UK Environment Agency (EA).

The study area was defined as a 10 km radius around each MSWI. The 10 km distance was chosen for consistency with screening criteria used for implementing the Habitats

Table 1: Source characteristics of the two inclusive municipal solid waste incinerators.

Incinerator	County	Permitted throughput (tonnes/year)	Flue	Stack height (m)	Stack diameter (m)	Flue exit flow rate (m^3/s)	Flue exit velocity (m/s)	Temperature (°C)
Crymlyn Burrows	Neath Port Talbot (South Wales)	52,500	1	40	0.95	12.3	17.6	136
Marchwood	Hampshire (England)	210,000	1	65	1.25	30.3	24.7	150
			2	65	1.25	30.9	25.2	148

Flue exit flow rate, velocity, and temperature for Crymlyn Burrows provided are a mean of biannual measurements for most years of operation, whereas for Marchwood these measures are single measures derived from the permit application.

Regulations: incineration plants that are within 10 km of a European Site require an assessment of their impact for short range air emissions.

The study population was defined as all residents within the study area, calculated by extracting postcode headcount data from the 2001 census [38], where one UK postcode represents on average 12–15 properties and 40–45 people.

2.2. Emissions Dispersion Modelling. The Atmospheric Dispersion Modelling System Urban (ADMS-Urban) v2.3 modelling package was used [39] to model the dispersion pattern and ground level concentration of particles with a diameter <10 μm (PM_{10}) from both incinerators. ADMS-Urban is a new generation Gaussian plume air dispersion model that uses an updated understanding of turbulence and atmospheric boundary layer structure [33] and is capable of simulating the atmospheric dispersion patterns of pollutants from multiple sources and within complex terrain [40].

ADMS-Urban calculates atmospheric boundary layer parameters such as boundary layer height and Monin-Obukhov length from a variety of input parameters [40]: air temperature (°C), wind speed (m/s), wind direction (°), and cloud cover (oktas). The Monin-Obukhov length is an indicator of the atmospheric stability and is a key parameter in the dispersion of pollutant. It is defined by a quotient of heat flux at ground level by frictional velocity. It provides a height at which turbulent flows are created by buoyancy and not wind shear. In ADMS-Urban a minimum value for the Monin-Obkhov length is set, with the default value set to 30 m in order to account for the heat island effect of major cities and to prevent the model from stabilising [40, 41].

Another key model parameter that has impact on the dispersion of pollutants is the surface roughness length. Surface roughness length characterises the roughness of the terrain, providing an indicator of how much drag the wind experiences from the ground. Surface roughness is required to calculate convective turbulence.

2.2.1. Model Input Data. For each MSWI, information on the location of the stack, year commissioned, total annual waste licensed to incinerate and stack characteristics was extracted from their environmental permit application to the EA. The precise location of the stacks was verified by checking the incinerator address and postcode against six-figure grid references (georeferenced location of the stack in British National Grid projection), in addition to visually searching for stacks on satellite maps in Google maps. Stack data included number of lines, stack height (m), stack diameter (m), exit velocity (m/s), exit flow (m^3/s), and exit temperature (°C) (Table 1). For Marchwood only one measure of flue gas flow, velocity, and temperature was available from 2006 till 2010. For Crymlyn Burrows quarterly measures of these flue gas metrics were available for most years of operation. Annual averages of these quarterly measures were calculated and used. When quarterly measures were unavailable, the overall representative flue gas measures for Crymlyn Burrows were used. The concentration of total particulates at the flue exit for each MSWI was measured as daily means.

Sensitivity analysis of the dispersion conditions was conducted to select the most appropriate and representative surface roughness and Monin-Obukhov lengths. The fetch for roughness is defined by the US Environmental Protection Agency (US EPA) as 1 km surrounding the source [42]. Land cover data, extracted from the CORINE Land Cover Map 2000 [43] (Figure 1), was used to characterise the 1 km area around each MSWI. CORINE is an EU-wide dataset, generated by semiautomatic classification of satellite imagery [43] and comprises 44 land cover classes, of which 11 relate to urban land. Based on the land cover data around each MSWI, an array of relevant lengths was selected. As both MSWIs were partly surrounded by urban land cover (Marchwood 20% and Crymlyn Burrows 26%, resp., see Figure 1), a number of different surface roughness lengths and minimum Monin-Obukhov lengths were explored. Output concentrations were then compared when using the different values for both lengths.

The surface elevation in the area surrounding the MSWIs was extracted from Ordnance Survey PANORAMA digital terrain model (DTM), which has a horizontal resolution of 50 m [44]. As shown in Figure 1 the terrain surrounding Marchwood is low lying with a mean elevation of 23 m above sea level. However for Crymlyn Burrows there is a significant variation in elevation, with a range of 370 m. In order to account for this variation in terrain and therefore changes in the dispersion pattern of particulates, the hill option in ADMS-Urban was selected and a preprepared terrain file was extracted from the DTM and input into the model.

Meteorological conditions greatly influence the observed spatial pattern of emitted pollutants from a point source. Selecting an appropriate meteorological station, that best represents the area surrounding the MSWI, is therefore crucial. Hourly land surface meteorological observations from all Met Office stations in England and Wales between 2003 and 2010 were obtained from the British Atmospheric Data Centre

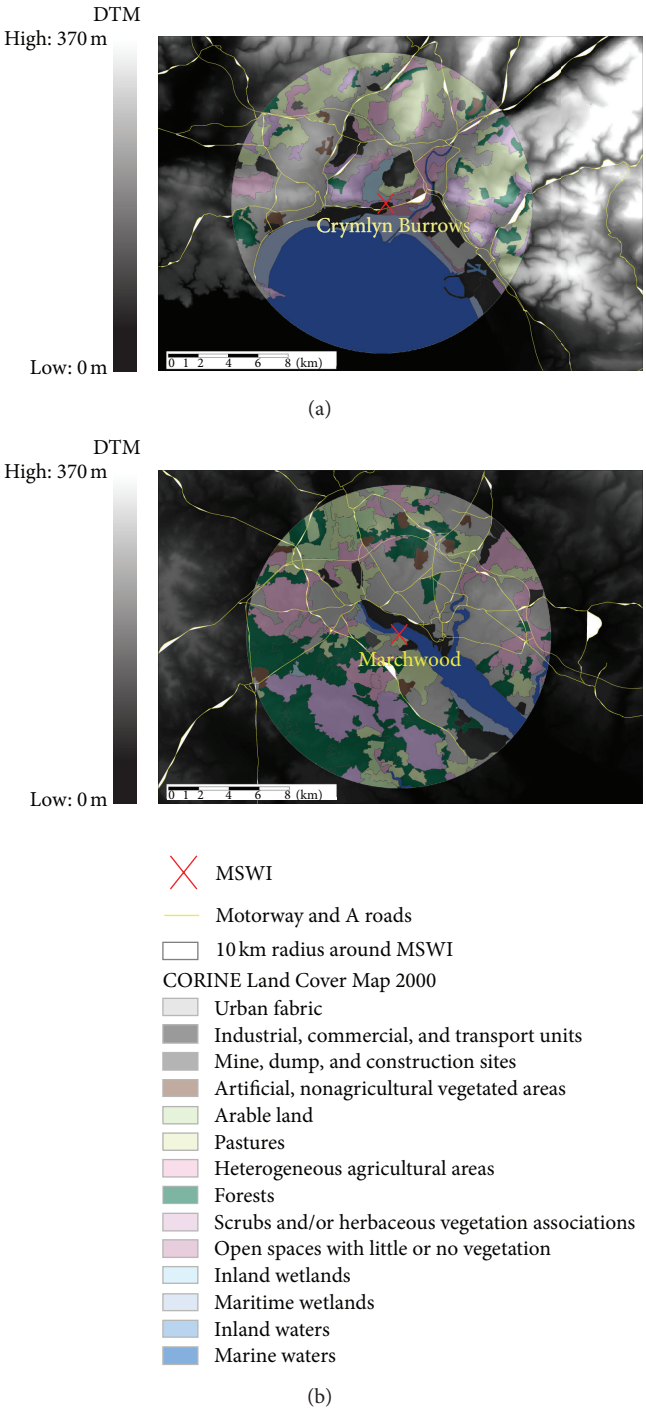


Figure 1: Land cover data from CORINE-Land 2001 and topography data from PANORMA 10 km around Crymlyn Burrows (a) and Marchwood (b) incinerators.

(BADC). Candidate meteorological stations located within approximately 30 km from the selected MSWIs were identified. Meteorological stations considered were those with 90% completeness for all weather variables (excluding cloud cover), for each year. The Air Quality Modelling Assessment Unit (AQMAU) at the EA advised that incorporating cloud cover from alternative nearby stations makes a very small contribution to overall modelling uncertainties. Therefore, cloud cover was obtained from the nearest station with 90% completeness where necessary [45]. Following the selection of candidate meteorological stations, wind roses were plotted for each station. These wind roses were used to spot anomalies in the data (e.g., apparent gaps in wind from a given sector) and comparisons were made between the sites. Following this, CORINE land cover and DTM data were extracted and compared for a 1 km radius around each meteorological station in order to select a meteorological station with similar surrounding topography and land use to the MSWI. The dispersion model was then run using these different meteorological stations and their outputs compared.

2.2.2. Model Output. Bag-filtered stack emissions from the MSWIs were not considered to contain a significant amount of particulates greater than 10 μm diameter. Emitted particulates were therefore modelled as PM_{10} and considered to disperse in the same manner as a gas.

Modelled ground level concentrations of PM_{10} for the sensitivity analysis were estimated for receptors in a 200 m × 200 m grid within the study areas. For Marchwood sensitivity analysis was performed for 2006 and Crymlyn Burrows for 2003.

For the exposure analysis, all residential postcode centroids within the study area were used as receptors and ground level concentrations of PM_{10} were modelled. For Marchwood models were run for 2006–2010 and Crymlyn Burrows 2003, 2005–2010.

For the exposure analysis, each modelled day required input of single daily mean particulate concentrations at the flue exit together with hourly meteorological data to produce a daily ground level PM_{10} concentration field. These daily modelled concentrations were aggregated to calculate annual means. Model outputs were mapped in ESRI ArcMap 10.0 [46].

2.3. Distance to Source. All residential postcode centroids within the study area were assigned a distance to their respective MSWI using the NEAR function in ArcGIS. The distance metric was chosen as distance from the edge of the study area rather than distance from the incinerator. This was termed proximity and had its greatest value at the incinerator and least value at the edge of the study area. The ordering of the magnitude of the proximity metric allowed a clearer comparison of the distance and dispersion approaches with the greatest proximity value and highest concentration found closest to the incinerator.

2.4. Comparison of Exposure Assessment Methods. All residential postcodes within the study areas were assigned both an average modelled PM_{10} concentration over the period in which the MSWI was in operation and a distance to the MSWI. Postcodes were classified into deciles, quintiles, and tertiles from high to low exposures (modelled PM_{10} concentrations sorted from high to low, distance to MSWI from low to high). A population was additionally assigned to each postcode using headcount data extracted from the 2001 census [38].

The comparison of exposure assessment by the dispersion model and by the distance method was undertaken in three ways.

(1) Calculation of Cohen's kappa coefficients of agreement between exposure deciles, quintiles, and tertiles as calculated by the distance method versus the dispersion model. Cohen's kappa coefficient provides a statistical measure of interobserver agreement taking into account chance, that is, a quantification of precision [47, 48]. Kappa coefficients range from 0 to 1, with 0 indicating no agreement and 1 perfect agreement between methods. As our exposure tertiles, quintiles, and deciles are ordinal categories, equal weighted kappa coefficients were calculated in addition to unweighted Cohen's kappa coefficients [49]. Weighted Cohen's kappa coefficients account for ordinal differences in categories; that is, a difference of two categories between the indices of exposure is a more severe misclassification error than a difference of one category.

(2) Calculation of weighted and unweighted Cohen's kappa coefficients of agreement between the distance method and the modelled particulate concentrations by population weighted exposure deciles, quintiles, and tertiles.

(3) Plotting of modelled long-term average PM_{10} concentrations against distance from the MSWI at each postcode centroid, with calculation of Spearman's correlation coefficients.

3. Results

3.1. Particulate Emissions from MSWI. Figures 2(a) and 2(b) display the daily concentrations of total particulates measured at the flue exit for Crymlyn Burrows and Marchwood, respectively. Figure 2(a) demonstrates the variability in concentrations for Crymlyn Burrows over the study period, 2003–2010, with the maximum concentration of 9.87 mg/m^3. The gap in the data shown for 2004 was due to a fire during the last quarter of 2003 causing Crymlyn Burrows to stop operation during 2004. Figure 2(b) shows the daily particulate concentrations for both flues for the Marchwood incinerator. Again, there was considerable variability in concentrations over time and also between the two flues. Both Flue 1 and 2 had a maximum concentration of 10 mg/m^3, the Waste Incineration Directive limit. Both MSWIs show a decreasing trend in particulate emissions from 2008 (Crymlyn Burrows) and 2009 (Marchwood) until 2010, from daily emissions of ~10 mg/m^3 to 1-2 mg/m^3. The maximum particulate emissions took place in 2008 for both MSWIs.

3.2. Dispersion Modelling. For Marchwood, three candidate meteorological stations were located within 30 km. The nearest meteorological station was Southhampton Oceanography Centre located 3.3 km east of Marchwood, followed by Solent (19.1 km south-east) and Middle Wallop (29.2 km north) (see Figure 3). For Crymlyn Burrows only one meteorological station was available located 9.4 km south-west from the incinerator.

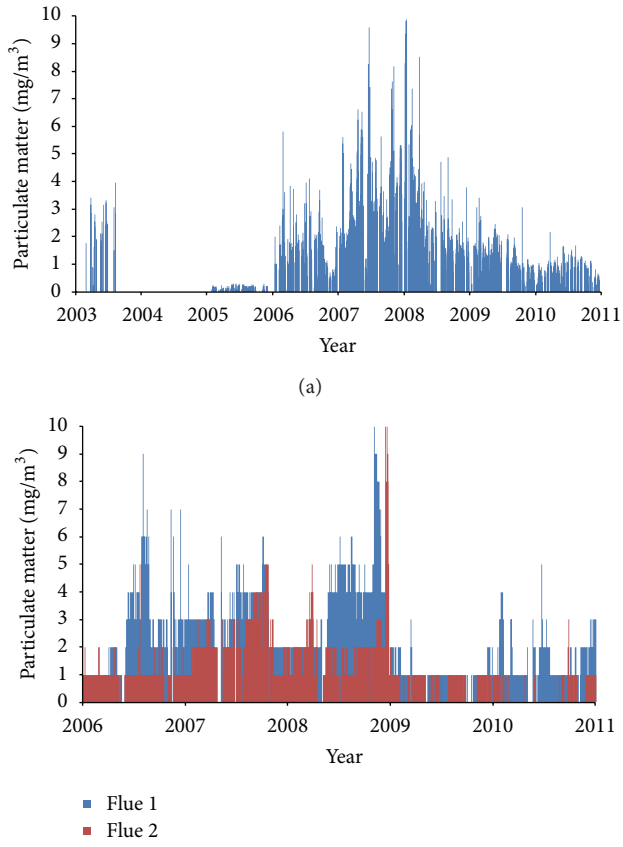
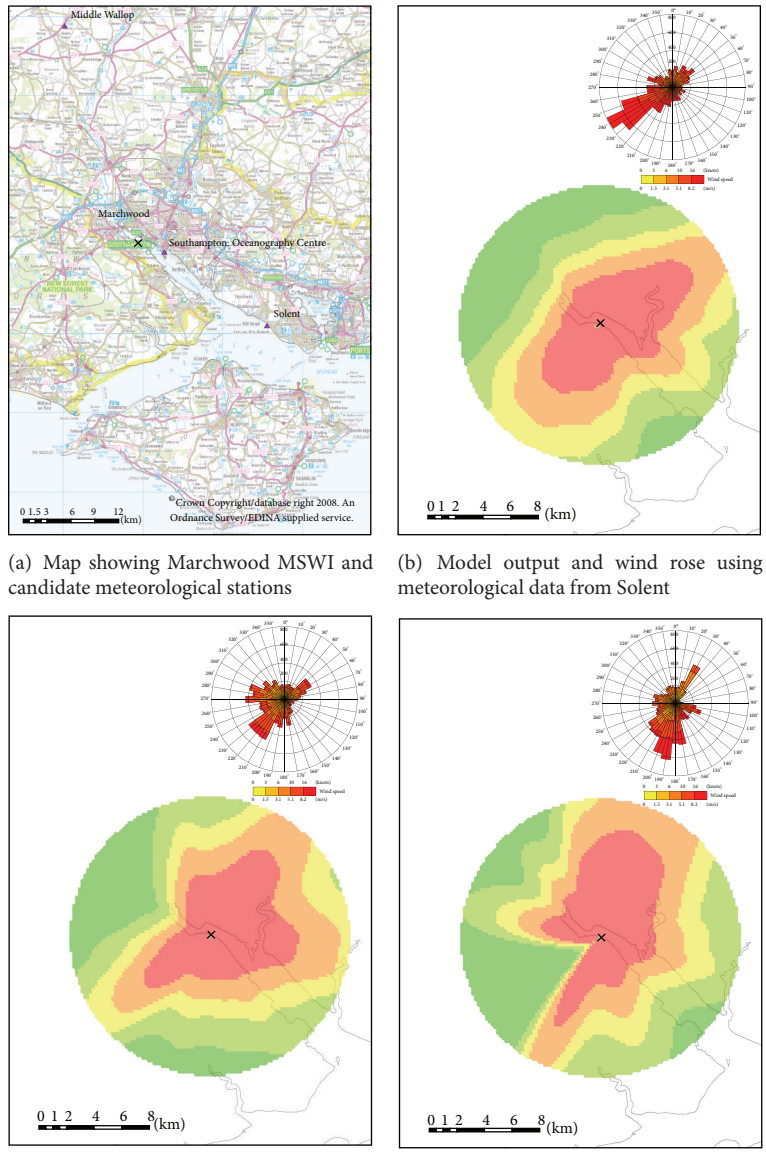


Figure 2: (a) Daily particulate concentrations measured at flue exit for Crymlyn Burrows from 2003 to 2010. (b) Daily particulate concentrations measured at flue exit for Marchwood from 2006 to 2010.

Comparisons were made between the three meteorological stations available for Marchwood. First, the wind roses for the three meteorological stations were compared. The wind rose for the Southhampton Oceanography Centre displayed very low frequency of wind from the north-east, between 50 and 80 degrees, for all years of operation (2006–2010) (Figure 3(d)). The other two meteorological stations, however, did not show this pattern (Figures 3(b) and 3(c)). The effect of this apparent gap in wind direction becomes particularly evident when using the data from these meteorological stations in our dispersion model simulations. Figure 3 shows the modelled annual mean particulate concentrations in 2006 using the three meteorological stations around Marchwood MSWI. The PM_{10} annual mean concentration using the Southampton Oceanographic Centre clearly shows a gap in the predicted concentrations south-west of the incinerator (Figure 3(d)), not seen when using the other two meteorological stations (Figures 3(b) and 3(c)). Based on this comparison the data from Southampton Oceanographic Centre meteorological station was deemed erroneous for unknown reasons and was therefore not used in subsequent



(a) Map showing Marchwood MSWI and candidate meteorological stations

(b) Model output and wind rose using meteorological data from Solent

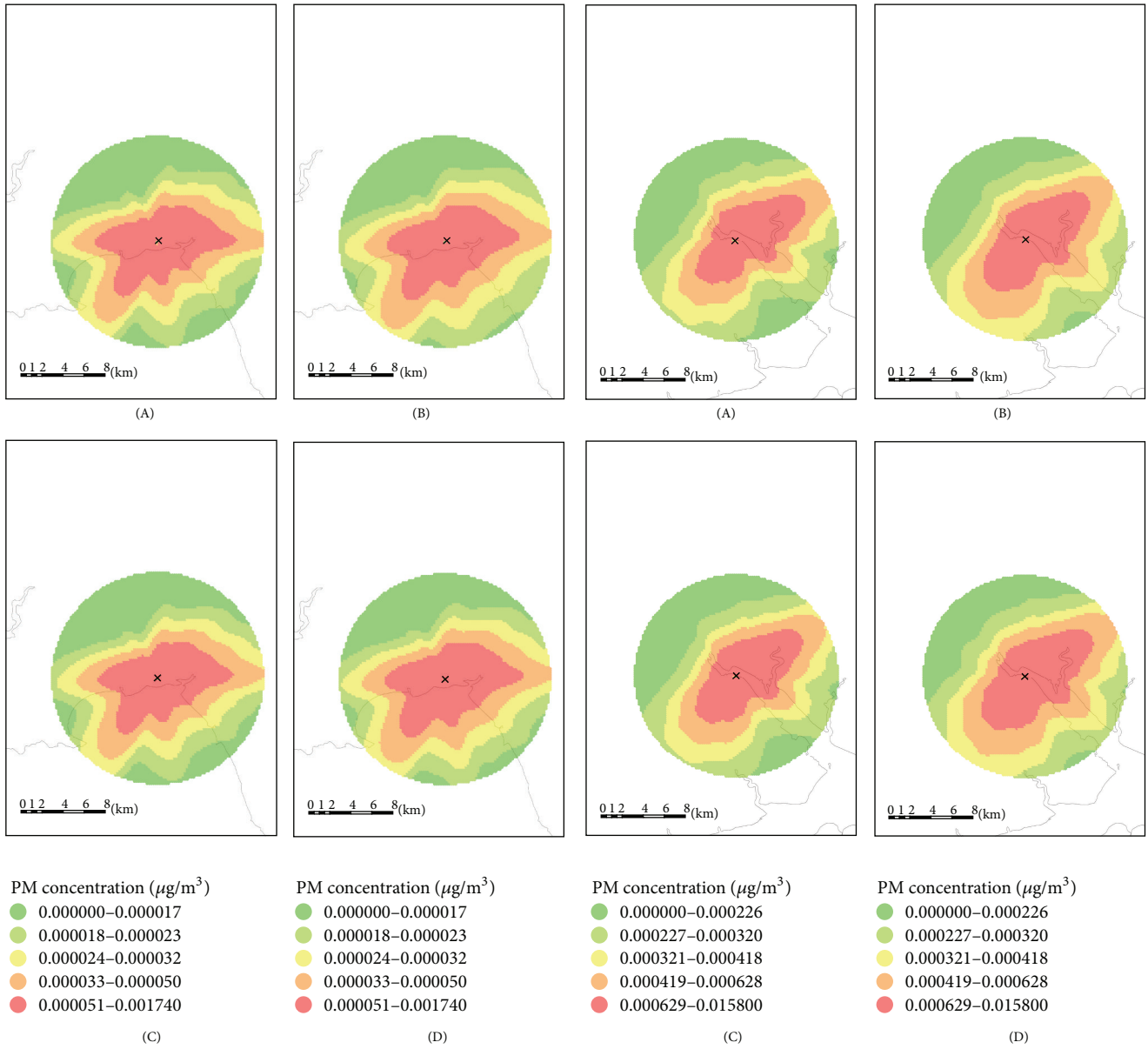
(c) Model output and wind rose using meteorological data from Middle Wallop

(d) Model output and wind rose using meteorological data from Southampton Oceanography Centre

FIGURE 3: Sensitivity of the model to the selected meteorological stations for Marchwood in 2006. Maps (b)–(d) use the same site surface roughness length and minimum Monin-Obukhov length.

analysis. The wind and dispersion patterns were similar for Solent and Middle Wallop, with higher PM_{10} concentrations in the SW-NE diagonal. Therefore the closest station, Solent, was selected for the exposure analysis. However when Solent cloud cover fell short of 90% capture annually, cloud cover data from Middle Wallop was used.

An exploration of surface roughness for both MSWIs showed little variation in the model output for surface roughness lengths varying from 0.2 m to 1 m (see Figures 4(a) and 4(b)). Only 7.7% of the model receptors had a difference in modelled particulate concentrations greater than 25% in Marchwood and 3.1% for Crymlyn Burrows



(a) (A) Model output using surface roughness length 0.2 m. (B) Model output using surface roughness length 1 m. (C) Model output using no set minimum Monin-Obukhov length. (D) Model output using 30 m set minimum Monin-Obukhov length

(b) (A) Model output using surface roughness length 0.2 m. (B) Model output using surface roughness length 1 m. (C) Model output using no set minimum Monin-Obukhov length. (D) Model output using 30 m set minimum Monin-Obukhov length

Figure 4: (a) Sensitivity of the model to site surface roughness length and minimum Monin-Obukhov length for Crymlyn Burrows. Maps (A)–(D) use the same meteorological station data for 2003. (b) Sensitivity of the model to site surface roughness length and minimum Monin-Obukhov length for Marchwood. Maps (A)–(D) use the same meteorological station data for 2006.

(Table 2). The difference in modelled particulate patterns and concentrations between no set minimum Monin-Obukhov length and 30m showed little variation, with a maximum percentage difference of 31% for Marchwood and 18% for Crymlyn Burrows (Table 2).

Table 3 demonstrates the extremely low concentrations of modelled annual PM_{10} concentrations within 10 km from the MSWI both for all days of the year (Table 3(a)) and also for only the days of operation (Table 3(b)). The modelled ground level concentrations of PM_{10} were extremely low for both MSWIs, with a mean concentration of 0.000117 μg/m^3 for Crymlyn Burrows for all days and 0.000334 μg/m^3 for operational days only; and 0.00129 μg/m^3 for Marchwood for all days and 0.00205 μg/m^3 for operational days only. Modelled long-term average PM_{10} concentrations were very small (maximum of 0.0022 μg/m^3 for Crymlyn Burrows and 0.0089 μg/m^3 for Marchwood). Figure 5 shows the modelled long-term average PM_{10} concentrations for both MSWIs

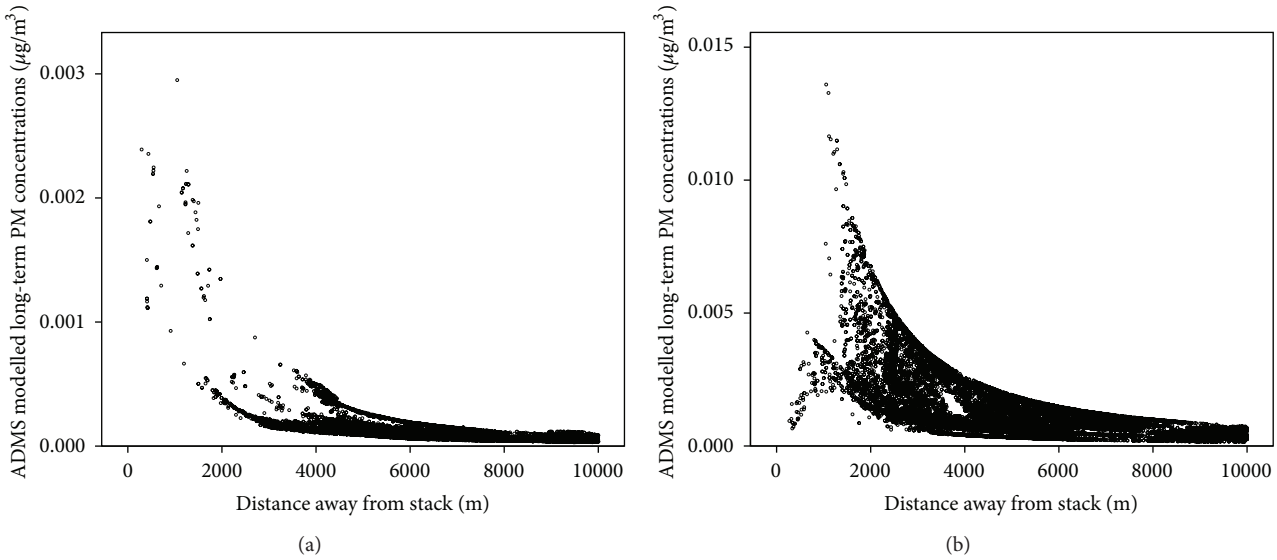


Figure 5: (a) Modelled long-term PM concentrations (μg/m^3) plotted against distance away from the MSWI (m) at postcode centroid for Crymlyn Burrows. (b) Modelled long-term PM concentrations (μg/m^3) plotted against distance away from the MSWI (m) at postcode centroid for Marchwood.

Table 2: Surface roughness sensitivity analysis. Percentage difference between extreme surface roughness values at all model receptors.

Percentage difference	Crymlyn Burrows	Marchwood
Surface roughness		
Mean (%)	8.7	12.3
Median (%)	6.9	11.2
Minimum (%)	0	0
Maximum (%)	116.6	117.5
Receptors > 25% difference (%)	3.1	7.7
Monin-Obukhov length		
Mean (%)	6.4	11.5
Median (%)	5.5	10.2
Minimum (%)	0	0
Maximum (%)	17.6	30.6
Receptors > 25% difference (%)	0	6.6

against distance from the MSWI at each postcode centroid. It is clear from Figure 5 that the concentrations at the 10 km edge of the modelled domain were <7% of the maximum concentration.

The pattern of the final dispersion model for Crymlyn Burrows showed irregular shapes, with symmetrical bands of increasing exposure from the source. This irregular dispersion pattern might be due to the hilly topography in the Swansea area that modifies the wind patterns and, therefore, the dispersion of emissions from the MSWI. Due to its coastal location a large proportion of the modelled area has no population. For Marchwood the final dispersion pattern was much more elliptical with the greatest PM_{10} concentration extending to the north-east of the MSWI following the main wind direction.

3.3. Distance to Source. Table 4 shows the number of postcodes and the population count in relation to distance from the two MSWIs. The area around the Marchwood MSWI is more densely populated (361,005 people within 10 km) than Crymlyn Burrows (248,937 people within 10 km). The population around Marchwood MSWI also resides closer to the MSWI than that at Crymlyn Burrows with the greatest population density between 3 km and 7 km.

3.4. Comparison of Exposure Assessment Methods. The agreement between exposure categories, as calculated by the dispersion modelling and distance methods, is shown in Table 5. Better agreement was achieved when using tertiles (Cohen's kappa coefficient of 0.424 unweighted and 0.553 weighted and 0.308 unweighted and 0.448 weighted from Crymlyn Burrows and Marchwood, resp.) compared with deciles and quintiles (Cohen's kappa coefficient ranging from 0.068 to 0.201 unweighted and 0.198 to 0.519 weighted).

Table 6 shows the population weighted agreement of the two exposure methods. Again, agreement improved with a reduction in the numbers of exposure categories. Best agreement between methods was displayed for Crymlyn Burrows exposure tertiles (but here the unweighted Cohen's kappa coefficient only reached 0.425, equally weighted Cohen's kappa coefficient only reached 0.548) and the poorest agreement for Marchwood exposure deciles (unweighted Cohen's kappa coefficient 0.0644, equally weighted Cohen's kappa coefficient 0.150).

Figure 5 shows the long-term mean PM_{10} concentration at each postcode centroid against distance from MSWI for Crymlyn Burrows (Figure 5(a)) and Marchwood (Figure 5(b)). Spearman correlations (R) for modelled long-term PM_{10} concentrations versus proximity from the edge of the modelling domain at postcode level were 0.765 and 0.688

Table 3: (a) Annual mean, median, and interquartile range of modelled PM_{10} concentration in the postcodes 10 km around Crymlyn Burrows (2003–2010) and Marchwood (2006–2010) weighted by postcode. (b) Annual mean, median, and interquartile range of modelled PM_{10} concentration in the postcodes 10 km around Crymlyn Burrows (2003–2010) and Marchwood (2006–2010) weighted by postcode for operational days only.

(a)

	Mean ($\times 10^{-5}$ $\mu g/m^3$)	Median ($\times 10^{-5}$ $\mu g/m^3$)	Interquartile range ($\times 10^{-5}$ $\mu g/m^3$)
Crymlyn Burrows			
2003	3.7	3.0	2.5
2005	0.8	0.6	0.5
2006	10.8	8.2	6.8
2007	29.4	24.2	17.1
2008	22.0	16.5	15.2
2009	10.3	7.7	7.1
2010	4.9	3.9	3.0
Marchwood			
2006	121.5	80.0	101.6
2007	186.3	127.7	149.9
2008	229.5	139.5	200.8
2009	59.6	44.5	50.3
2010	48.9	36.4	32.2

(b)

	Mean ($\times 10^{-5}$ $\mu g/m^3$)	Median ($\times 10^{-5}$ $\mu g/m^3$)	Interquartile range ($\times 10^{-5}$ $\mu g/m^3$)	Days of operation		
Crymlyn Burrows						
2003	51.5	4.25	31.7	33		
2005	2.61	2.10	1.59	150		
2006	29.1	23.6	17.1	204		
2007	61.2	51.1	33.6	264		
2008	52.7	42.6	32.6	227		
2009	23.1	18.8	13.8	225		
2010	13.3	10.6	7.77	188		
				Flue 1	Flue 2	Either one or both flues in operation
Marchwood						
2006	207.3	140.9	154.3	308	240	334
2007	290.6	204.1	221.5	325	327	344
2008	338.1	212.7	262.7	340	325	358
2009	96.9	72.5	72.0	296	192	357
2010	91.7	69.8	59.1	323	104	356

for Crymlyn Burrows and Marchwood, respectively (both significant at the 0.01 level).

4. Discussion

The majority of the studies exploring the relationship between incineration and health have used a simple distance metric as a proxy for exposure. Here we have provided a comparison of distance from source and emissions modelling to assess exposure to particulates emitted by two MSWIs in the UK. Our results suggest that epidemiological studies requiring an assessment of exposure to airborne pollutants from MSWIs, at a small scale level, would benefit from a dispersion modelling approach compared to a simple distance based approach. Although the use of distance as a proxy for exposure has limited data requirements, it does not account for source characteristics, the concentrations of pollutants emitted, local meteorological conditions, and topography [31, 50] all of which are incorporated in Gaussian dispersion models, such as ADMS-Urban. Dispersion models provide a different exposure assessment to distance from source. This approach is expected to be more realistic than a simple distance proxy as it tries to capture the physical processes that determine the dispersion of emissions from a point source

Table 4: Distance of the study population (all residents within 10 km) to the incinerators, Crymlyn Burrows and Marchwood.

Distance to source (km)	Crymlyn Burrow				Marchwood			
	Number of PCs	Percentage of total PCs (%)	Population count	Percentage of total population (%)	Number of PCs	Percentage of total PCs (%)	Population count	Percentage of total population (%)
0–<1	22	0.2	165	0.1	87	0.5	1677	0.5
1–<2	69	0.5	834	0.3	813	4.2	12829	3.6
2–<3	229	1.8	5067	2.0	2363	12.3	31729	8.8
3–<4	777	5.9	14590	5.9	2720	14.2	46690	12.9
4–<5	2623	20.1	38736	15.6	2969	15.5	59070	16.4
5–<6	2496	19.1	49338	19.8	2999	15.6	69784	19.3
6–<7	2365	18.1	51665	20.8	2171	11.3	48832	13.5
7–<8	1982	15.2	39467	15.9	1378	7.2	25298	7.0
8–<9	1256	9.6	25853	10.4	1611	8.4	32654	9.0
9–10	1251	9.6	23222	9.3	2055	10.7	32442	9.0
Total	13070	100	248937	100	19166	100	361005	100

PC: postcodes.

Table 5: Measure of agreement Kappa coefficient (where 0 = no agreement; 1 = perfect agreement) between modelled long-term PM_{10} concentrations and distance away from stack categorised in deciles, quintiles, and tertiles at postcode level.

	N	Type of Kappa	Deciles	Quintiles	Tertiles
Crymlyn Burrows	13069	Unweighted	0.0684	0.210	0.424
		Weighted-Equal	0.307	0.519	0.553
Marchwood	19166	Unweighted	0.0734	0.177	0.308
		Weighted-Equal	0.198	0.446	0.448

Table 6: Measure of agreement Kappa coefficient (where 0 = no agreement; 1 = perfect agreement) between population weighted modelled long-term PM_{10} concentrations and distance from the stack categorised in deciles, quintiles, and tertiles at postcode level.

	N	Type of Kappa	Deciles	Quintiles	Tertiles
Crymlyn Burrows	5269	Unweighted	0.0932	0.251	0.425
		Weighted-Equal	0.334	0.535	0.548
Marchwood	8102	Unweighted	0.0644	0.169	0.219
		Weighted-Equal	0.150	0.380	0.345

including topographic and meteorological information that influence where and how emissions are dispersed. ADMS-Urban has been successfully used and validated when assigning exposure at an individual or small area level [34–37] and is frequently used for regulatory purposes, policy support, and providing information to the public [32]. Dispersion modelling can additionally help determine the distance to which a particular source influences exposures, as shown in Figure 5, where modelled PM_{10} falls to <7% of peak concentrations at 1000 m to 2000 m away from the MSWI. The comparison between dispersion modelling and distance for the two MSWIs studied here (see Table 5 and Figure 5) reveals poor to moderate agreement only when using distance compared with dispersion modelling. Both methods assigned a decreasing exposure with an increasing distance from source (as shown by the strong spearman's correlations with continuous measures). However, when using categorical metrics (as are often employed in epidemiological studies) distance was a fairly good proxy in distinguishing highest and lowest exposure tertiles, but the dispersion model was able to capture the pattern of small area level variation in population exposure (Figures 3 and 5), which did not conform to circular dispersion around the source as would be predicted using a distance model.

The influence of stack height on the dispersion pattern was especially apparent for the Marchwood MSWI, which shows very small PM_{10} concentrations up to approximately 500 m (Figure 5(b)), after which they peak between 1000 and 2000 m, depending on the direction. This pattern was less apparent at the Crymlyn Burrows MSWI, mainly due to the lack of postcodes within 2000 m of the MSWI.

Both Figures 5(a) and 5(b) show a flattening in modelled PM_{10} concentrations beyond approximately 5 km, suggesting that, at least for the Crymlyn Burrows and Marchwood

MSWI, most variability in exposure occurs within 5 km of a MSWI and this was therefore captured well within the 10 km distance chosen in this assessment.

Model input parameters influenced both the pattern and concentration of the modelled PM_{10}, in turn affecting the modelled exposed population. It is therefore essential that the quality of the model input parameters is assessed. It was found that the model was sensitive to surface roughness length, Monin-Obukhov length, and meteorological conditions. The model output showed little relative variation in output concentrations with different input parameters with the exception of changes in meteorological station. We demonstrate here that the choice of meteorological input data is crucial. As shown in Figure 3, possible misclassification of exposure is evident from the use of different meteorological stations, particularly in the case of the south-west part of the Marchwood MSWI.

The dispersion model simulations in this study were subject to a number of limitations that would contribute to the uncertainty in the ground level exposure estimates produced. Firstly, Marchwood only had a single measure of flue gas flow, velocity, and temperature for the duration of its operation (2006 till 2010), whereas Crymlyn Burrows had quarterly measures of these flue gas metrics for most years of operation which showed substantial variation. The assumption that these flue exit parameters are constant over such long periods of time is therefore not representative of true conditions. Additionally, due to data availability, poor data quality, and completeness, the choice of meteorological sites was limited and it was challenging to find meteorological sites representative of the surrounding area. This was especially evident for Marchwood where the selected meteorological site (Solent) was located 19 km away from the MSWI. Additionally, although ADMS-Urban has been validated as a point source modelling tool in other scenarios, the long-term mean concentrations of modelled PM_{10} in this study were exceptionally low, and therefore model validation would not be possible, as they fall below the limit of detection for regulatory ambient measurements.

There are a number of disadvantages to using dispersion models, including their large input data demands, which are often unavailable, and the expertise required to successfully run and interpret the models [31]. To meet the EU Directive requirements the MSWIs in this study, along with those elsewhere in Europe, are now required to have daily measurements of particulate emissions. This allows time varying emissions to be included in modelled assessments for the first time. This is beneficial for calculating exposures linked to health endpoints with critical exposure periods, for example, trimester specific exposures for birth outcomes.

Although long-term ground level PM_{10} levels from these MSWIs were found to be approximately thousandths of regional background levels, it is hypothesised that particulates from MSWIs may possibly have different impacts on health than those from other ambient sources of particulate matter due to their metal or dioxin content, for instance. The modelled concentrations of PM_{10} may act as a proxy for the concentration fields for these and other primary emissions from MSWIs. While long-term PM_{10} concentrations from dispersion modelling may provide a good indication of ambient concentrations, this will still be an imperfect marker of personal exposure. An alternative individual level exposure could be measured by personal monitoring or collection and analysis of biomarkers. However, such personal exposure approaches, aside from being very expensive and time-consuming and (for biomarkers) potentially invasive, may not adequately capture exposures specific to MSWIs.

5. Conclusions

Using distance as a proxy measure of exposure to emissions from incinerators is a simple, quick, and cheap approach; however, when compared with dispersion modelling, there is indication of exposure misclassification. Dispersion models incorporate information on individual incinerator characteristics, emission concentrations, local meteorological conditions, and topography, all of which contribute to the observed concentrations and spatial patterns of incinerator emissions. The additional detail included in these models enables a more appropriate and informative exposure assessment from incinerators, which is important in an epidemiological context in order to reduce risk of bias in risk estimates due to exposure misclassification.

Disclaimer

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Conflict of Interests

All authors declare no conflict of interests with any trademarks mentioned in this paper.

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Research Article

Ecological Study on Hospitalizations for Cancer, Cardiovascular, and Respiratory Diseases in the Industrial Area of Etang-de-Berre in the South of France

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The Etang-de-Berre area is a large industrialized area in the South of France, exposing 300,000 inhabitants to the plumes of its industries. The possible associated health risks are of the highest concern to the population, who asked for studies investigating their health status. A geographical ecological study based on standardized hospitalizations ratios for cancer, cardiovascular, and respiratory diseases was carried out over the 2004–2007 period. Exposure to air pollution was assessed using dispersion models coupled with a geographic information system to estimate an annual mean concentration of sulfur dioxide (SO_2) for each district. Results showed an excess risk of hospitalization for myocardial infarction in women living in districts with medium or high SO_2 exposure, respectively, 38% [CI 95% 4 : 83] and 54% [14 : 110] greater than women living in districts at the reference level exposure. A 26% [2 : 57] excess risk of hospitalization for myocardial infarction was also observed in men living in districts with high SO_2 levels. No excess risk of hospitalization for respiratory diseases or for cancer was observed, except for acute leukemia in men only. Results illustrate the impact of industrial air pollution on the cardiovascular system and call for an improvement of the air quality in the area.

1. Introduction

Relationships between urban air pollution and hospitalizations for cardiorespiratory causes are well established in many studies around the world [1–3] and in France [4]. By comparison, published studies about the health effects of industrial air pollution on population living near industries are sparse, and few studies investigate the impact of industrial air pollution on cardiovascular or respiratory hospitalizations [5–7]. This paper presents the first study on the impacts of industrial air pollution on cardiorespiratory hospitalizations, in one of the largest industrial areas in France.

The Etang-de-Berre area is a large pond (0.15 km^2) surrounded by three major industrial complexes gathering several oil refineries, chemical plants, ironworks, metal plants, a waste incineration plant, an airport, and the largest French seaport [8, 9]. This industrial area located in the Provence-Alpes-Côte d'Azur region has experienced a strong economic growth since the 70s. The population has doubled between 1970 and 2000, and, today, about 300,000 inhabitants are more or less exposed to the plumes of industries.

The contribution of the Etang-de-Berre area to the regional emissions is estimated at 58% for sulfur dioxide (SO_2), 13% for particulate matter under 10 μm (PM_{10}), 23% for nitrogen oxide (NO_x), and 10% for volatile organic compounds (VOC). The main sources are the industries and and the production of energy for SO_2 and VOC emissions, industries and road traffic for PM_{10} emissions, and industries, production of energy, and road traffic for NO_x emissions [10].

SO_2 concentrations measured by the Air Quality Network in this area are still the highest observed at the regional level, even if they had decreased regularly during the last

20 years. In 2008, all monitoring stations in the area exceeded the 2005 World Health Organization (WHO) Air quality guidelines for maximum daily mean concentrations ($20\ \mu g{\cdot}m^{-3}$). None exceeded the European Council Directive 2008/50/EC of 21 May 2008 hourly limit values (hourly mean $>350\ \mu g{\cdot}m^{-3}$/more than one day) [11]. PM_{10} concentrations are relatively stable 10 years ago, but some peaks are still measured. In 2008, all the monitoring stations exceeded the WHO air quality guidelines (annual mean of $20\ \mu g{\cdot}m^{-3}$). None exceeded the 2008/50/EC limit value (annual mean of $40\ \mu g{\cdot}m^{-3}$). Nitrogen oxides (NO_x), heavy metals, and polycyclic aromatic hydrocarbons (PAH) concentrations were under the 2008/50/EC limit value, whereas benzene concentrations were slightly higher near the industrial sites. Ozone concentrations were high in summer because of the emissions of ozone precursors and the high degree of sunshine but this affects all the regional area.

Since the 1990s, environmental protection associations created by the population request an assessment of the health of population living near these polluting and potentially dangerous industries.

The administrative authorities decided to carry out quantitative health risk assessments (HRA), based on the comparison of exposure to pollutants with toxicological reference values (TRV), for the three main industrial complexes between 2006 and 2011.

The first HRA, on the oil refining area of Berre-l'Etang, began in 2006 and revealed high benzene and 1.3 butadiene fugitive emissions at the refinery [12]. Carcinogenic risks by inhalation exposure were found above the reference threshold of 10^{-5} for the population living in the city of Berre-l'Etang and in a large northern part of the study area.

Corrective measures to reduce emissions of these two compounds were then implemented on the industrial site. An updated HRA carried out in 2008 showed a decrease of the area exposed to benzene, from 30 km^2 to 10 km^2 around the industrial site. Yet, carcinogenic risks by inhalation exposure were still above the reference threshold of 10^{-5} for the population living in the north part of the study area.

An HRA on the industrial-port area of Fos-sur-Mer [13] found that SO_2 and PM_{10} modeled concentrations were higher than the air quality guidelines in all the study area. Chrome VI and 1,2-dichloroethane modeled concentrations were too high on the industrial site only. Carcinogenic risks by inhalation exposure were under the reference threshold of 10^{-5} for the entire population living near the industrial site.

The last HRA on the petrochemical area of Lavéra-La Mède [14] found that SO_2 and PM_{10} modeled concentrations were higher than the air quality guidelines in all the study area. Benzene levels were too high and dangerous for workers on the industrial site only. Carcinogenic risks by inhalation exposure were above the limit threshold of 10^{-5} for the population living in a part of the study area representing 21,000 inhabitants.

These studies have led to a complete inventory of the different pollutants emitted by the industries and have helped prioritizing actions to reduce the exposure of the population. SO_2 and PM_{10} pollutants were classified as requiring priority actions to reduce industrial emissions and population exposure, although it was not possible to assess the related health risks in the HRA, as TVR are not available for these compounds. Decreasing benzene, 1,3-butadiene, chrome VI, and 1,2-dichloroethane industrial emissions was also recommended to decrease the exposure of workers and of the population neighboring the industrial sites.

However, these studies cannot answer the main concern of the population: is the health of the people living in this industrial area worse than the health of people living in non-industrial areas?

Therefore, the administrative authorities asked the Regional office of the French Institute for Public Health Surveillance to carry out an epidemiological study. After a review of the existing studies and of the routinely available data for this area, we decided to conduct an ecological study on hospitalizations data. The objective of this ecological study was to estimate a relationship between hospitalizations ratios and SO_2 exposure levels at the district of residence. Comparison was done between exposed and nonexposed district, controlling on socioeconomic status estimated through Townsend's index and proportion of male workers in each district, which are factors potentially influencing people health and exposure.

2. Materials and Methods

2.1. Study Area. The study area is located in the Provence-Alpes-Côte-d'Azur region near the Mediterranean Sea. Its boundaries were based on modeled SO_2 concentrations, topographic criteria, and labour pool. It included 29 administrative districts (named districts afterwards) surrounding the Etang-de-Berre pond and represented 399,962 inhabitants living on a 975 km^2 area (Figure 1). 430 plants classified for environmental protection are located in the study area. Almost 50 of them have dangerous activities related to a high risk of industrial accident and are classified as "high threshold" according to the European Council Directive 96/82/EC of 9 December 1996 on the control of major-accident hazards involving dangerous substances.

These industries are grouped in 3 main complexes (Figure 2):

(i) the Lavera-la Mède area located in the district of Martigues, operating oil refining, petrochemical and organic chemical activities, and chlorine chemistry since the 1950s;

(ii) the Berre area located in the district of Berre-l'Etang operating oil storage and petrochemical industry. The first refinery was settled in 1933;

(iii) the industrial port area of Fos-sur-Mer including steel and metal working, chemicals plants, waste incineration plant, and the port for ore and oil tankers settled since the 1970s.

The Etang-de-Berre area is also crossed by a dense road network which supports a high traffic of heavy trucks related to the industrial and harbor facilities and of passenger cars commuting from home to work.

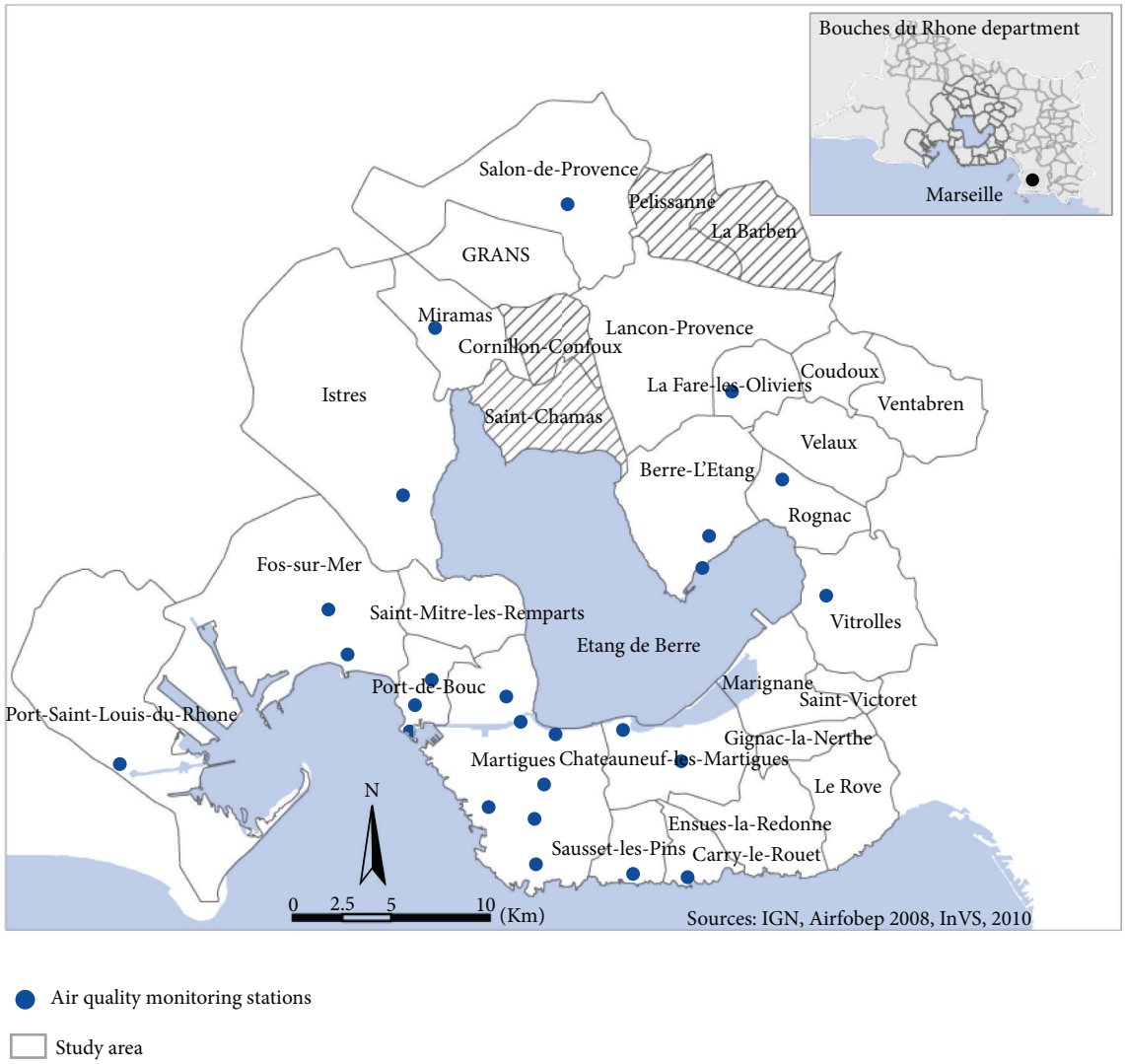

Figure 1: Study area and localization of air quality monitoring stations.

2.2. Exposure Assessment. The local Air Quality Network (Air PACA) measures air pollution levels since 1972. In 2008, 27 monitoring stations settled on the study area (Figure 1) measured continuously the following pollutants: sulfur dioxide (SO_2), ozone (O_3), nitrogen dioxide (NO_2), particulate matter (PM_{10}), carbon monoxide (CO), and benzene. For SO_2 concentrations in the study area, annual mean levels of the different monitoring stations varied between 2 and 18 $\mu g\,m^{-3}$ and maximum hourly mean levels between 83 and 831 $\mu g{\cdot}m^{-3}$ (Table 1). The highest values are measured by the industrial monitoring stations. In comparison, for the 6 stations located on the rest of the region, annual mean levels varied between 1 and 4 $\mu g\,m^{-3}$ and maximum hourly mean levels between 20 and 132 $\mu g{\cdot}m^{-3}$.

Exposure to air pollution was assessed at the district level, using SO_2 concentrations as a proxy for industrial emissions. Air PACA provided the mean concentrations of SO_2 for 2008 on a 200 m∗200 m grid using a dispersion model (ADMS4), a meteorological model and kriging. We used a geographic information system (GIS) to assign a concentration level to each district. To aggregate concentrations data, urban areas of each district were identified based on the 2006 land cover classification system. Urban areas included urbanized areas, major roads and railways, commercial, industrial, and working areas, leisure activities areas, and public gardens. For each district, the concentrations were averaged weighted on the cells proportion included in urban areas as illustrated in Figure 3.

The annual mean levels of SO_2 varied between 2.1 and 12.4 $\mu g{\cdot}m^{-3}$ depending on the district (Figure 4) and were grouped in three classes of exposure based on quartiles: reference (<4.2 $\mu g{\cdot}m^{-3}$); medium (between 4.2 and 6.4 $\mu g{\cdot}m^{-3}$), and high (>6.4 $\mu g{\cdot}m^{-3}$) values (Table 2). Reference levels were similar to the SO_2 annual mean levels measured in non-industrial districts in the regional area, varying from 1 to 4 $\mu g{\cdot}m^{-3}$.

We also investigated whether PM_{10} concentrations could be an industrial pollution indicator for this ecological study.

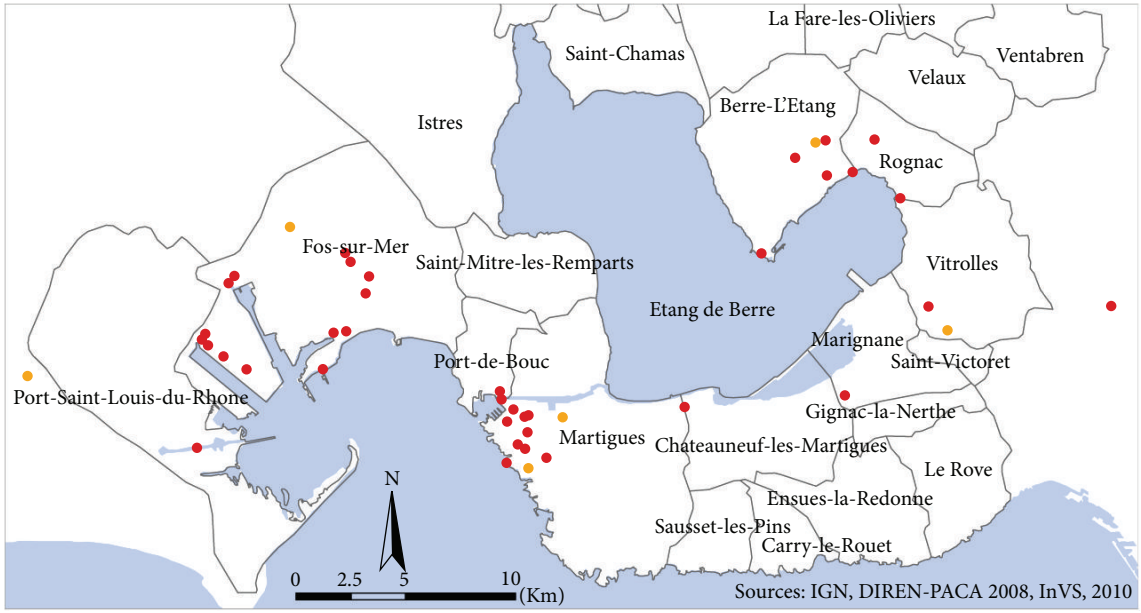

FIGURE 2: The industrial surrounding of Etang-de-Berre area. High and low level refers to the European Council Directive 96/82/EC of 9 December 1996 on the control of major-accident hazards involving dangerous substances.

Annual mean levels of the different monitoring stations varied between 27 and 33 $\mu g \cdot m^{-3}$ in the study area and were similar to those measured in the rest of the region (Table 3). With the same method used for SO_2, the estimated annual mean levels of PM_{10} varied between 27.8 and 33.6 $\mu g \cdot m^{-3}$ depending on the district. The spatial distribution of concentrations was relatively homogenous and the highest concentrations were not observed at industrial districts.

2.3. Hospitalization Data. The French programme for hospital information system (PMSI) is implemented since 1994 in public hospitals and since 1997 in private hospitals. A complete hospitalization database is available since 1998. It is a medical economic database based on the diagnosis-related group (DRG) method. Each hospitalization is registered in a local database grouped in a national database. Since 2004, a patient identification number is included to identify patients and hospital stays related to each patient.

The national hospitalization database held by the PMSI provided hospitalization data for the whole region. Hospital stays included in the analysis were selected over the study period 2004–2007 based on several selection criteria. On the first step, we excluded stays without patient identification number and stays for patient that moved outside or inside the study area between 2004 and 2007. On the second step, stays for the studied diseases were selected from the main diagnosis at the discharge, coded with the 10th revision of the International Classification of Diseases (ICD-10), and sometimes from secondary diagnosis. Finally, patients living in the study area were selected from their zip codes. The first hospitalization of each resident over the study period was retained in order to approximate a hospitalization incidence for each health indicator.

Respiratory and cardiovascular hospitalization indicators have been selected from the papers on links between air pollution and health [15–27]. The selection of cancer hospitalization indicators was based on knowledge about frequencies of different type of cancer at the regional level and on the results of two French reports on environmental cancers [28, 29]. The following hospitalization indicators were defined:

(i) all cardiovascular diseases (ICD-10: I00–I99), heart diseases (ICD-10: I00–I52), and coronary heart diseases (ICD-10: I20–I24), myocardial infarction (ICD-10: I21-I22), stroke (ICD-10: I60–I64 or G45-G46), heart rate disorders (ICD-10: I44–I49), coronary heart diseases with heart rate disorders (ICD-10: I20–I24 as main diagnosis and I44–I49 as secondary diagnosis);

(ii) all respiratory diseases (ICD-10: J00–J99), respiratory infections (ICD-10: J04–J06 or J10–J18 or J20–J22), pneumonia (ICD-10: J10–J18), asthma (ICD10: J45-J46), and exacerbations of chronic obstructive pulmonary diseases (principal indicator algorithm described in [30]);

(iii) all cancers (ICD10: C00–C97), lung cancer (ICD10: C33-C34), bladder cancer (ICD10: C97), breast cancer (ICD10: C50), multiple myeloma (ICD10: C90), malignant non-Hodgkin's lymphoma (ICD10: C82–C85), and acute leukemia (ICD10: C910, C920, C924, C925, C930, C942, C943, C950).

Table 1: Annual mean, maximum daily mean, and maximum hourly mean of SO_2 concentrations ($\mu g \cdot m^{-3}$) measured by monitoring stations located in the study area and in the remaining part of the regional area (2008 data).

Monitoring station	Type	Annual mean	Maximum daily mean	Maximum hourly mean
Study area				
Berre-l'Etang	Urban	7	66	190
Berre Magasin	Urban	4	29	160
Carry-le-Rouet	Industrial	6	41	200
Chateauneuf/La Mède	Industrial	5	74	404
Chateauneuf les Martigues	Industrial	4	28	124
Fos-sur-Mer	Urban	15	138	427
Fos-sur-Mer/les Carabins	Urban	2	33	200
Istres	Urban	5	33	125
La Fare les Oliviers	Industrial	5	22	122
Marignane ville	Urban	NA	32	221
Martigues l'île	Urban	7	43	327
Martigues La Couronne	Industrial	8	79	407
Martigues La Gatasse	Industrial	10	121	759
Martigues Lavéra	Industrial	9	88	522
Martigues Les Laurons	Industrial	18	151	412
Martigues Les Ventrons	Industrial	10	134	831
Martigues NDM	Urban	4	71	380
Martigues Le Pati	Industrial	6	36	230
Miramas ville	Urban	6	23	115
Port de Bouc La lèque	Urban	15	126	375
Port de Bouc Castillon	Industrial	11	73	292
Port de Bouc EDF	Urban	10	70	274
Port Saint Louis	Industrial	4	27	134
Rognac les Barjaquets	Industrial	4	69	350
Salon-de-Provence	Urban	4	19	83
Sausset les Pins	Industrial	10	79	433
Vitrolles	Urban	7	39	164
Remaining part of the regional area				
Arles	Urban	3	12	58
Les Pennes-Mirabeau	Urban	3	24	132
Marseille Cinq-Avenues	Urban	4	25	125
Nice Pellos	Traffic	4	18	43
Peillon	Industrial	4	10	22
Contes	Industrial	1	5	20

Table 2: Distribution of estimated SO_2 and PM_{10} concentrations by district (2008 data).

Pollutant indicator	Mean	Minimum	Centile20	Centile40	Centile60	Centile80	Maximum
PM_{10}	29.8	27.9	28.8	29.3	30.8	32.2	33.6
SO_2	4.4	2.1	3.4	4.2	4.6	6.4	12.4

The number of hospitalizations selected for the study area represented 9% of the cardiovascular and respiratory diseases hospitalizations and 7% for cancers hospitalizations registered at the regional level.

2.4. Confounding Factors. The 2006 national census held by the French national institute for statistics and economic studies (INSEE) provided data on socio-occupational groups of the working population in the study area and for the socioeconomic items included in Townsend's index. This index was built using the following socioeconomic items: proportion of unemployed person among working population, proportion of main homes with more than one person per room, proportion of main homes occupied by not owner household, and proportion of household without a car [31]. Standardized socioeconomic variables using regional values

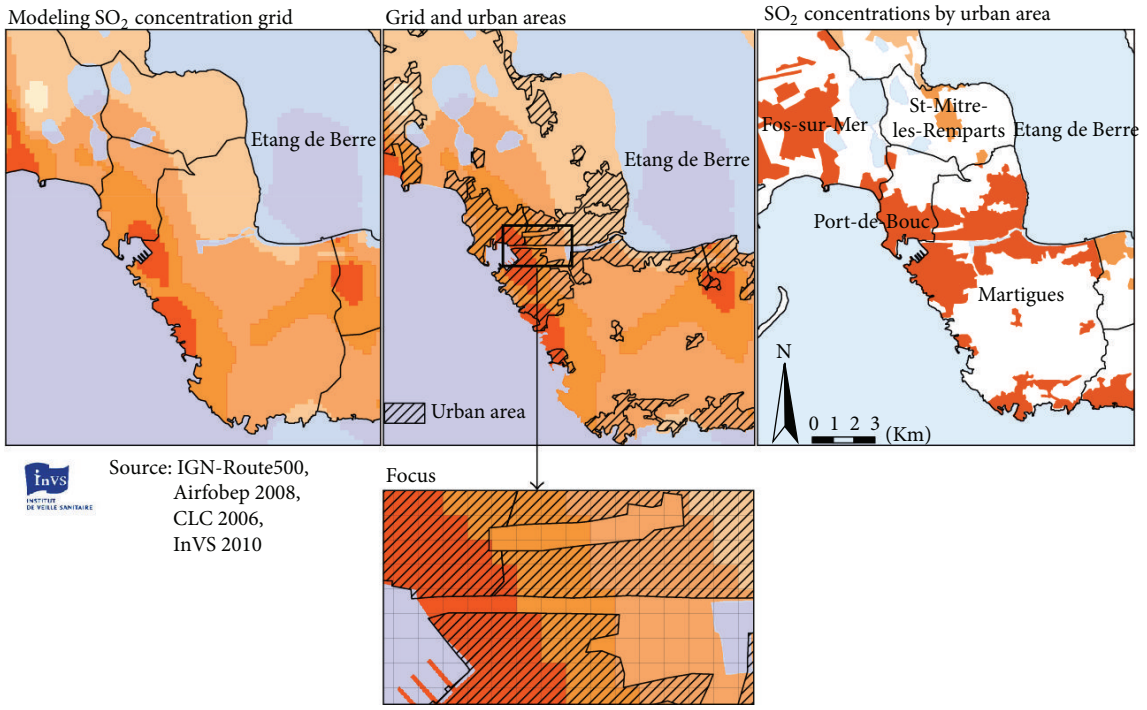

Figure 3: From SO_2 concentrations grid to urban exposure estimation.

as reference were used to build an additive scale for each district.

The proportion of male workers was retained as a confounding factor, making the hypothesis that it would be a good predictor of the industrialization of each district.

2.5. Statistical Analysis. We performed a descriptive analysis of the exposure, socioeconomic, and hospitalizations data. We calculated the expected number of cases at the district level for each health indicator by standardization method using the regional population as reference. Then standardized hospitalization ratios (SHR) were calculated as the rate of observed to expected cases.

Relative risks of hospitalization for people living in medium or high exposed districts were calculated compared to those living in the reference districts. Overdispersed Poisson regression models were fitted to assess the association between hospitalization ratios and classes of exposure to industrial pollution, taking into account potential confounding factors. The Bayesian hierarchical model developed by Besag et al. (BYM) [32] was fitted to account for this extra Poisson variability.

The first level of the BYM is a classical Poisson regression model. The second level splits the residual risk into a linear combination of covariate effects $xTi\beta$ and into random effects U_i and V_i measuring excess heterogeneity and spatial similarity, respectively:

$$\text{Log}\left(\theta_i\right) = \alpha + xTi\beta + U_i + V_i, \quad (1)$$

where the term $\exp(\alpha)$ is the overall relative risks of disease in the study area compared to the reference rate.

The vectors U and V are supposed independent, and U, that models the excess heterogeneity of the relative risks, is assumed to follow a normal distribution $U_i \sim N\ (0, \sigma_u^2)$. To model spatial similarity in residuals the Gaussian conditional autoregressive model (CAR) is used as the prior for the spatial component v:

$$\left(\frac{V_i}{V_j} = v_i,\ \ j \neq i\right) \sim N\left(\frac{\sum_{j\neq i} w_{ij} v_j}{\sum_{j\neq i} w_{ij}}, \frac{\sigma_v^2}{\sum_{j\neq i} w_{ij}}\right), \quad (2)$$

where the w_{ij}s denote weights defining which districts j are neighbors to district i (by convention $w_{ii} = 0$ for all i). We used the adjacency-based weights where $w_{ij} = 1$ if district j is adjacent to district i, $w_{ij} = 0$ otherwise are used. We have taken Gamma prior distributions for the precision parameters (reciprocal of the variance) of the heterogeneity and spatial terms. For both we have taken the noninformative Γ (0.5, 0.0005). The $\Gamma(a, b)$ denotes the Gamma distribution with expectation equal to a/b. Non-informative priors were taken for the other parameters, that is, the intercept and the regression coefficients.

In a Bayesian context, we defined the credible interval at the 5%, that is, the probability that the parameter belongs to is 95%. Analysis was done by age (children 0–14 years, adults over 15 years) and by sex for the adults with the software R and WinBUGS.

3. Results

The highest SO_2 levels (>6.4 $\mu g{\cdot}m^{-3}$) were observed in the highly industrialized districts in the South of the Etang-de-Berre area. Districts in the Northeast of the study area had the lowest levels of air pollution (Figure 3).

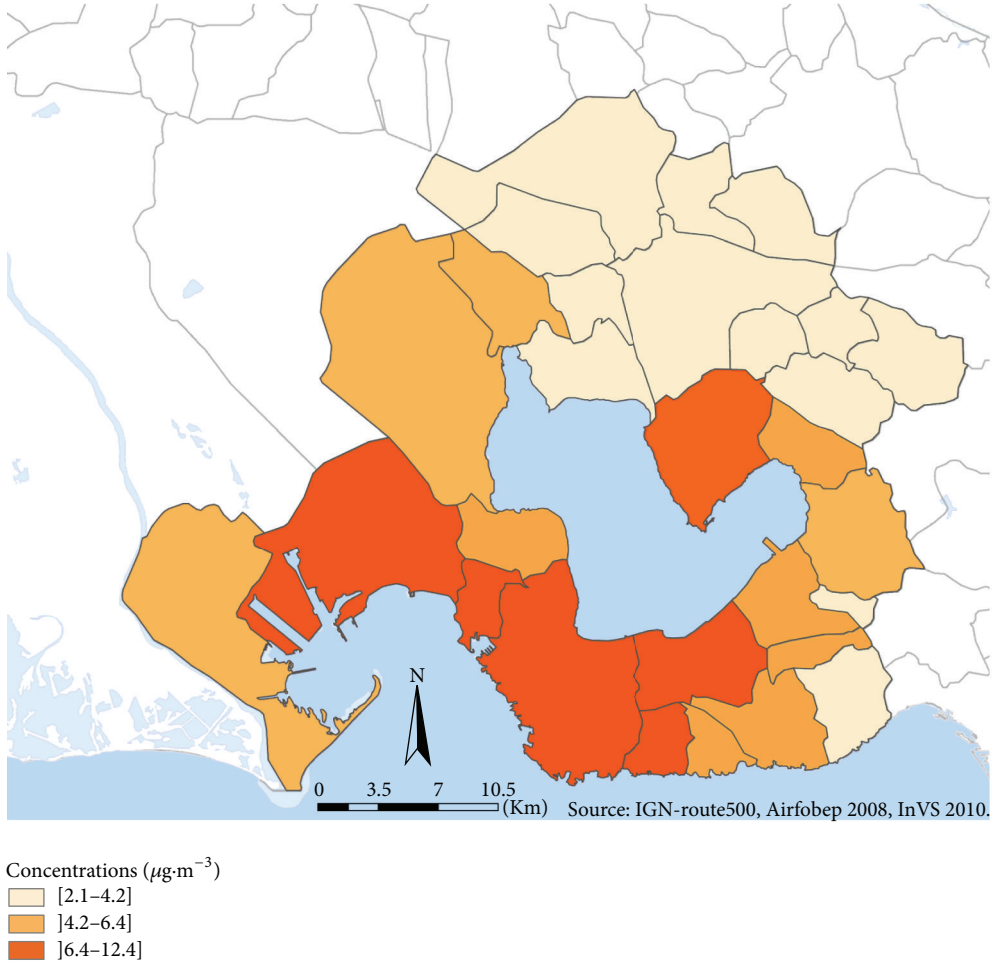

Figure 4: SO_2 exposure estimations by district (2008 data).

The Townsend's index values ranged from −3.5 to 7.9. High values are related to a low socioeconomic status (SES) and negative values to a rather high SES. Districts in the North of the study area were rather favored and industrial districts rather deprived. This index was significantly correlated with the socio-occupational group but moderately with SO_2 exposure levels (coefficient of correlation = 0.4).

Table 4 presents the number of cases by hospitalization indicators for the whole population. Cardiovascular diseases were the main causes of hospitalizations. For all indicators, the number of cases varied between districts depending on the population size.

The number of cases varied also according to sex and age. The sex ratio male/female varied from 1.2 for all cardiovascular diseases to 2.4 for myocardial infarction (MI) hospitalizations. Hospitalizations for exacerbations of COPD occurred rather in males (sex ratio = 2.5) while hospitalizations for respiratory infections, pneumonia, or asthma occurred in both sex (sex ratio from 1 to 1.2). Men were more hospitalized for acute leukemia, lung, and bladder cancer (sex ratio at 1.5, 3.3, and 5.0, resp.).

Children accounted for half of the patients hospitalized for asthma, one third for respiratory infections and 15% for pneumonia. On the other hand, children accounted for less than 1% of the patients hospitalized for cardiovascular diseases or cancer. Thus, we analyzed these indicators in adults only.

For children, the risk to be hospitalized for respiratory conditions was the same in the high or medium exposed districts and in the reference districts. The risk was slightly increased in districts with low socioeconomic status (Table 5).

For adults, and for most of the studied indicators, the risk to be hospitalized was the same in areas with medium or high exposure to industrial air pollution and in areas exposed to reference levels. However, the relative risk (RR) to be hospitalized for an acute leukaemia increased significantly to 2.6 for men living in districts with high SO_2 levels. No increase was observed for women. We found a significant increase of the risk to be hospitalized for myocardial infarction in the districts exposed to industrial air pollution, especially in women (Table 6).

Excess risk to be hospitalized for MI in women living in districts with medium or high SO_2 exposure was, respectively, 38% [CI 95% 4% : 83%] and 54% [14% : 110%] greater than women living in districts at the reference level. A 26%

Table 3: Annual mean, maximum daily mean, and maximum hourly mean of PM_{10} concentrations ($\mu g \cdot m^{-3}$) measured by monitoring stations located in the study area and in the remaining part of the regional area (2008 data).

Monitoring station	Type	Annual mean	Maximum daily mean
Study area			
Chateauneuf/La Mède	Industrial	32	102
Fos-sur-Mer/les Carabins	Urban	31	93
Marignane ville	Urban	33	106
Martigues l'île	Urban	27	84
Miramas ville	Urban	28	86
Port de Bouc La lèque	Urban	32	87
Port Saint Louis	Industrial	29	82
Rognac les Barjaquets	Industrial	27	93
Salon-de-Provence	Urban	31	94
Remaining part of the regional area			
Arles	Urban	29	90
Marseille Cinq-Avenues	Urban	29	87
Marseille Saint Louis	Urban	31	82
Marseille Thiers	Urban	27	76
Marseille Timone	Traffic	33	88
Aix Ecole d'Art	Urban	28	83
Aix jas de Bouffan	Urban	27	82
Aix Roy René	Traffic	32	86
Gardanne	Industrial	37	101
Hyères	Urban	26	74
Toulon Chalucet	Urban	28	80
Toulon foch	Traffic	38	131
Avignon Mairie	Urban	25	80
Le Pontet	Urban	31	309
Antibes Jean Moulin	Suburban	34	71
Cannes Broussailles	Urban	35	69
Nice aéroport	Observation	34	74
Cagnes sur Mer	Urban	31	74
Contes	Industrial	43	100
Peillon	Industrial	39	105

[2% : 57%] excess risk to be hospitalized for MI was observed in men living in districts with high SO_2 levels only compared to those living in districts at reference levels.

4. Discussion

This is the first ecological study on hospitalizations related to industrial air pollution near a large industrial estate in France. It highlights the cardiovascular effects of air pollution. An excess risk of hospitalizations for myocardial infarction was found for women living in the districts exposed to industrial air pollution and for men living in the highly exposed districts. These results are similar to those reported by Fung et al. in a Canadian study, where SHR for cardiovascular and respiratory diseases increased in industrial cities compared to a reference city, with higher ratios in women [5]. On the other hand, a study set in England and Wales did not show any excess risk of hospitalization for cardiovascular, cerebrovascular, and respiratory diseases among the population living near coke works [6].

The estimated excess risk of hospitalizations for acute MI was greater in women while men were mostly hospitalized for cardiovascular causes. This could be related to a higher sensitivity of women to the effects of air pollution [33] or to a better control of confounding factors in men than in women. A local study showed a correlation between the socio-occupational group and smoking in men. Daily smoking is twice as much common for workers and unemployed persons than for managers [34]. These differences by socio-occupational group are less pronounced in women. So, the adjustment of the analysis on the proportion of male workers allowed us to control partially smoking in men but not in women.

We did not find excess risk for asthma hospitalizations in children while a case crossover study found a relationship between hospitalizations or emergency visits for asthma attack and SO_2 peaks in children living near refineries (no association was found when using SO_2 daily means) [7].

The lack of significant results for respiratory diseases most probably shows that hospitalization indicators are not the best indicators to evaluate the respiratory health effects of air pollution in adults in France. Asthma hospitalization rate in adults decreased slightly since 2000, and asthma disease is mostly taken care of by ambulatory management [35]. Studies using emergency or general practitioner (GP) visits for asthma attacks could be more relevant. Moreover most of the published studies concern the analysis of asthma or respiratory symptoms prevalence in children living near industrial sites by comparison to those living in a nonexposed area [36–38]. These studies showed an increase of respiratory symptoms and asthma attacks for exposed children. Pulmonary function tests found a decrease in lung function and an increase of airway inflammation.

Regarding cancer, results reflect past exposure because of the long latency period between exposure and onset of cancer. It would have been much better to estimate patient's exposure 10–15 years ago but we had no information on their place of residence before the hospitalization. Only one significant association was found between the exposure to industrial air pollution and acute leukemia in men. This result must be considered with caution because of the small number of observed cases. However, this association observed in men may suggest a potential occupational exposure due to compounds processed or emitted by petrochemical industries. Some of them are classified as carcinogenic for human (benzene, 1.3-butadiene) or likely carcinogenic for human (1.2-dichloroethane), and benzene is commonly considered as a risk factor for acute myeloid leukemia [39, 40]. This hypothesis needs to be evaluated by local studies on the occupational exposure to these carcinogenic compounds.

The strength of this study was the estimation of the exposure to industrial air pollution using modeled SO_2 concentrations rather than a distance to the industrial source. This pollutant was the best proxy of industrial air pollution as

Table 4: Number of cases and distribution by quartiles for each hospitalization indicator between 2004 and 2007.

Hospitalization indicators	Cases	Min	Q25	Q50	Q75	Max
All cardiovascular diseases	26,108	188	397	585	1,319	3,002
Heart diseases	14,506	90	200	315	752	1,729
Coronary heart diseases	4,684	29	71	105	258	577
Coronary heart diseases with heart rate disorders	808	0	13	17	41	99
Myocardial infarction	1,545	8	19	37	93	223
Stroke	4,008	19	57	89	230	553
Heart rate disorders	2,026	10	26	47	125	267
All respiratory diseases	16,107	117	188	317	872	1,823
Respiratory infections	4,574	21	51	92	287	664
Pneumonia	2,839	15	34	57	183	394
Asthma	937	2	9	17	54	131
Exacerbation of chronic obstructive pulmonary disease (COPD)	1,213	3	13	24	69	160
All cancers	10,416	89	159	249	499	1,251
Breast cancer	1,441	14	24	34	53	183
Lung cancer	879	3	13	21	50	119
Bladder cancer	515	1	8	14	26	68
Malignant non-Hodgkin's lymphoma	311	1	5	7	15	36
Acute leukemia	138	0	2	4	7	15
Myeloma	121	0	1	2	6	18

Table 5: RR of respiratory hospitalizations and 95% credible interval (CI) in children.

Hospitalizations indicators	Exposure class	RR	IC 95%
All respiratory diseases	Reference	1	
	Medium	0.93	[0.77–1.15]
	High	0.86	[0.68–1.10]
Respiratory infections	Reference	1	
	Medium	**0.69**	**[0.53–0.90]**
	High	0.79	[0.59–1.06]
Pneumonia	Reference	1	
	Medium	0.67	[0.41–1.17]
	High	0.70	[0.38–1.36]
Asthma	Reference	1	
	Medium	0.71	[0.49–1.04]
	High	0.84	[0.54–1.35]

industrial sources provided 85% of the total SO_2 emissions in the study area. Annual mean concentrations of SO_2 were used in this study rather than hourly values for practical reasons and time consuming. Anyway, monitoring stations with the highest annual means were those with the hourly values too. Using SO_2 annual mean to model industrial air pollution rather than hourly values should not change the class of exposure of each district.

Particulate matter (PM_{10}) concentrations were emitted by many other sources, than industrial sources and could not identify correctly industrial districts. In fact, as shown by the three HRA studies, many pollutants other than SO_2 are emitted by industries in particular particles. Several studies have shown short-term effects of particulate matter (PM) on hospital admissions from cardiovascular causes [15–22], and myocardial infarctions have been shown to be susceptible to being triggered by PM [16–19]. Population living near industries is exposed to a mixture of pollutants, and particles could play a role in the observed excess of myocardial infarction hospitalizations.

In our study, exposure to air pollution, assessed as the annual average levels of modeled concentrations, depends on the parameters of dispersion and meteorological models. Corrections and adjustments were implemented at each modeling step to limit errors and bias. Using average values for each geographical unit may have resulted in a dilution effect of exposure when modeled concentrations were heterogeneous within districts. We limited this dilution effect by computing the average concentrations only in the urban area, making the hypothesis that people spent most of the time in this area during the day.

In ecological studies, the choice of exposed and non-exposed areas is usually based on the distance to the industrial site, making the hypothesis that exposure decreases as the distance increases [41–44] whereas a set estimation of exposure would be more relevant. Few studies define the study area with pollutant concentration modeling and GIS. One study used an approach based on SO_2 and nitrogen dioxides (NO_x) levels, taking only into account levels above limit values. Pollutant levels were interpolated by kriging, and a GIS was used to assign a mean concentration at residential address to each case [45]. Another study used GIS tools to assign an individual integrated score of exposure that accounts for subject's

Table 6: RR of cardiovascular, respiratory and cancer hospitalizations and 95% credible interval (CI) in adults.

Hospitalizations indicators	Exposure class	Males		Females	
		RR	CI 95%	RR	CI 95%
All cardiovascular diseases	Reference	1		1	
	Medium	1.03	[0.95–1.11]	1.01	[0.90–1.12]
	High	0.96	[0.88–1.05]	0.91	[0.80–1.04]
Heart diseases	Reference	1		1	
	Medium	1.08	[0.97–1.19]	1.13	[0.96–1.32]
	High	0.98	[0.87–1.11]	0.99	[0.82–1.19]
Coronary heart diseases	Reference	1		1	
	Medium	1.13	[0.93–1.36]	1.22	[0.87–1.65]
	High	1.07	[0.86–1.34]	1.11	[0.76–1.61]
Myocardial infarction	Reference	1		1	
	Medium	1.13	[0.94–1.37]	**1.38**	**[1.04–1.83]**
	High	**1.26**	**[1.02–1.57]**	**1.54**	**[1.14–2.10]**
Heart rate disorders	Reference	1		1	
	Medium	1.15	[0.98–1.35]	1.01	[0.81–1.31]
	High	1.16	[0.98–1.40]	1.05	[0.80–1.40]
Coronary heart diseases with heart rate disorders	Reference	1		1	
	Medium	0.94	[0.73–1.20]	1.06	[0.76–1.47]
	High	1.05	[0.73–1.52]	0.90	[0.61–1.31]
Stroke	Reference	1		1	
	Medium	0.97	[0.80–1.19]	1.07	[0.82–1.37]
	High	1.07	[0.86–1.34]	0.86	[0.60–1.15]
All respiratory diseases	Reference	1		1	
	Medium	0.97	[0.84–1.10]	1.08	[0.90–1.27]
	High	1.01	[0.86–1.20]	1.05	(0.86–1.29]
Respiratory infections	Reference	1		1	
	Medium	0.87	[0.68–1.11]	0.85	[0.65–1.09]
	High	1.00	[0.76–1.32]	0.97	[0.73–1.30]
Pneumonia	Reference	1		1	
	Medium	0.87	[0.68–1.13]	0.80	[0.63–1.03]
	High	0.95	[0.72–1.29]	0.93	[0.69–1.24]
Acute COPD	Reference	1		1	
	Medium	0.87	[0.57–1.31]	1.16	[0.77–1.80]
	High	0.80	[0.49–1.32]	0.97	(0.59–1.64]
All cancers	Reference	1		1	
	Medium	0.98	[0.89–1.07]	1.00	[0.91–1.11]
	High	0.90	[0.81–1.01]	1.03	[0.92–1.15]
Lung cancer	Reference	1		1	
	Medium	1.02	[0.81–1.29]	0.79	[0.51–1.28]
	High	1.09	[0.84–1.43]	1.05	[0.65–1.78]
Breast cancer	Reference	na	na	1	
	Medium	na	na	1.07	[0.91–1.25]
	High	na	na	0.99	[0.82–1.20]
Bladder cancer	Reference	1		1	
	Medium	0.83	[0.56–1.26]	1.07	[0.58–2.12]
	High	0.76	[0.48–1.23]	0.81	[0.38–1.70]
Acute leukemia	Reference	1		1	
	Medium	1.86	[0.87–4.13]	1.08	[0.38–3.97]
	High	**2.57**	**[1.10–6.33]**	0.94	[0.29–4.24]

Table 6: Continued.

Hospitalizations indicators	Exposure class	Males		Females	
		RR	CI 95%	RR	CI 95%
Myeloma	Reference	1		1	
	Medium	1.35	[0.54–3.61]	0.73	[0.32–1.62]
	High	1.65	[0.57–5.07]	0.40	[0.15–1.02]
Malignant non-Hodgkin's lymphoma	Reference	1		1	
	Medium	0.81	[0.52–1.23]	0.88	[0.51–1.59]
	High	0.61	[0.35–1.00]	0.86	[0.47–1.63]

Na: not available.

mobility, length of residential stay, distance to petrochemical plants, wind direction, and industrial pollution sources [46]. However, these studies were cross-sectional studies based on individual data and none of them used aggregated health data.

Regarding the design of our study, the main advantage of ecological studies is the use of aggregated data which are often routinely produced, such as hospitalization data. These data are potentially biased by coding or ranking errors that are not differential and lead rather to an underestimation of the relationship with air pollution exposure. The main error of ecological studies is the ecological bias related to heterogeneity in the geographical units due to one or more uncontrolled confounding factors that could be related to exposure and/or to health indicators.

The socioeconomic status is often seen as a source of heterogeneity between districts. Our models are adjusted on the socioeconomic status estimated by the index of Townsend and the proportion of male workers in the working population. For this local study, the index of Townsend distinguishes relatively well between the industrialized districts and the favored residential municipalities but is more variable in districts under plumes of industries. The highly exposed districts are not always the most deprived districts. For example, Fos-sur-Mer is an industrial highly polluted district but is situated in the middle class for SES.

In the literature, studies carried out on links between social deprivation, health, and air pollution use either several socioeconomic items (average annual income, proportion of people below the poverty threshold, educational level, proportion of unemployed person, proportion of workers, and marital status) or synthetic index of deprivation as those of Townsend [31], Carstairs and Morris [47], or Jarman [48]. Sometimes, synthetic indexes are specifically built from several socioeconomic variables either by a factorial [49, 50] or by an additive approach [51, 52]. These specific indexes, more representative of the local deprivation, are often used to analyze the SES modifying effect on pollution exposure. In our study we used the deprivation index as confounding factor, and Townsend's index seemed to estimate correctly deprivation at district level as reported by Declercq and Prouvost [53].

Determinants of the healthcare system can also potentially modify the relationship between exposure and hospitalizations. In France, access to healthcare is available for the quasi-totality of the population, and the very few access restrictions do not constitute a real limit in our study. On the other hand, the use of health care is linked to the socioeconomic status of the patients [54] and to the socioeconomic context of residence [55]. We did not control directly the possible heterogeneity in the use of health care because of the lack of available data at district level. However, it was indirectly taken into account through the index of Townsend and by the Bayesian hierarchical model controlling the spatial autocorrelation. This modeling allowed us to limit the bias due to variability in use of health care between districts.

Finally, in the ecological studies, the individual confounding factors such as obesity, cholesterol level, lifestyle, smoking, and alcoholism cannot be taken into account because of using aggregated data at district level.

5. Conclusion

This study underlines that, in terms of hospitalizations for respiratory diseases and cancers, the health condition of the population exposed to the industrial air pollution was similar to those of nonexposed people. However, the results illustrate the impact of industrial air pollution on the cardiovascular system.

Efforts should be done to decrease the levels of SO_2, particles, and some carcinogenic compounds emitted by the industries, by improving industrial processes and using less polluted fuels. For instance, decreasing the level of road traffic particles would require the implementation of an interurban public transport network, as well as the development of rail transport for raw materials and goods.

Prevention of the cardiovascular diseases should be a public health priority in the study area, particularly in women. General practitioners, key players in the health prevention, would have clear and useful information on harmful cardiovascular effects of air pollution.

Finally, occupational medicine should reinforce the screening of hematopoietic disorders, myelodysplasia, and acute leukaemia in workers as well as in pensioners of refineries and petrochemical plants.

Conflict of Interests

The authors declare that they have no conflict of interests.

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Research Article

The Health Profile of Populations Living in Contaminated Sites: Sentieri Approach

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SENTIERI project (Epidemiological Study of Residents in Italian Contaminated Sites) studied mortality in the sites of national interest for environmental remediation (National Priority Contaminated Sites—NPCSs). SENTIERI described mortality of residents in NPCSSs, and it specifically focused on causes of death for which environmental exposure is suspected or ascertained to play an etiologic role. The epidemiological evidence of the causal association was classified *a priori* into one of these three categories: Sufficient (S), Limited (L), and Inadequate (I). Mortality in the period 1995–2002 was studied for 63 single or grouped causes at the municipal level by computing: crude rate, standardized rate, standardized mortality ratios (SMR), and SMR adjusted for an *ad hoc* deprivation index. Regional populations were used as references for SMR calculations and 90% CI accompanied SMR values. The deprivation index was constructed using 2001 national census variables for the following socioeconomic domains: education, unemployment, dwelling ownership, and overcrowding. SENTIERI results will allow the priorities setting in remediation intervention so as to prevent adverse health effects from environmental exposure. This paper's objective is to present the rationale, methods, advantages, and limitations underlying SENTIERI project and to describe data and resources required to apply a similar approach in other countries.

1. Introduction

Human health is intimately connected to the surrounding environment. This is particularly the case of the health of people living in contaminated site(s) (CS) which is affected by the legacy of past industrialization and current industrial activities, often in absence of environmental remediation.

European Community legislation addresses the concept of CS only in the context of the Thematic Strategy for Soil Protection [1] and the Soil Framework Directive proposed by the European Commission (EC) in 2006 [2]; for details on the legal framework and definitions at EU level refer to WHO 2013 [3].

According to 2007 estimates, soil contamination requiring clean up is present in approximately 250,000 sites in the European Environment Agency (EEA) member countries [4]. Although main polluting sources may vary across Europe, industrial production and commercial activities, oil industry and waste disposal and treatment are reported to be the major ones. National reports indicate that heavy metals and mineral oils are the main soil contaminants, while mineral oils and chlorinated hydrocarbons are the most frequent pollutants found in groundwater [5].

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 groundwater, air, and food chain, resulting or being able to result in human health impacts" [3]. Given this definition, an area affected by a single chemical

contamination of a single environmental matrix (e.g., the soil contamination caused by a given pesticide) and a large area with soil, water, air, and food chain contamination by multiple chemicals (e.g., the contamination caused by long-term emissions of a petrochemical complex) can be both considered contaminated sites.

There are several approaches and methods for assessing the health impact of National Priority Contaminated Sites (NPCS). On the one hand, one can apply risk assessment techniques, where available data on the degree of contamination (typically measures of concentration of specific hazardous chemical agents) are used to quantitatively estimate the risk of occurrence of health endpoints causally associated with the agents; on the other hand, epidemiological approaches applicable to NPCSs involve the inclusive collection of available health information of resident population, and various agents and exposures. In these assessments, 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 and the potentiality to provide efficient answers. More detailed analyses can be carried out, at a higher level of definition, by collecting specific data on health outcomes and/or on exposure [3].

SENTIERI project (Epidemiological Study of Residents in Italian Contaminated Sites) [6, 7] is an example of first level descriptive approach adopting an ecological study design, looking at the aggregate population level rather than at individual level. SENTIERI project is a national project developed to evaluate the health profile of populations residing in the Italian sites of national interest for environmental remediation-National Priority Contaminated Sites (NPCS). These sites were labelled as sites of national interest 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.

This paper's objective is to present the rationale and methods underlying SENTIERI project and to describe data and resources required to apply a similar approach in other countries.

2. Rationale

When studying how the environment can adversely affect human health, it is usually very difficult to identify clear cause-effect relationships because they are characterized by multicausality 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 exposure level and disease development. 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 multistep procedure described in the following sections. A selection of epidemiologic terms are defined in Glossary to facilitate the reading of the paper.

3. The Study of the Health Profile of Residents in NPCSs: What to Do and Why

3.1. Site Selection. As a first step, NPCSs to be studied should be chosen, and the criteria adopted to define NPCS/NPCSs are clearly indicated. The NPCS selection will depend on the aims of the study to be undertaken, on the availability of the NPCCs-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, and media pressure. It is advisable that the criteria used throughout this phase are clearly stated.

3.2. Environmental Data. In most instances NPCSs are characterized by the presence of numerous and different environmental sources of contamination possibly leading to human exposures. 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.

3.3. Study Population. Criteria to define populations affected by contamination may vary. Populations at risk can be identified as people living in the neighborhood of NPCSs sources or living in areas defined as contaminated. Typically, the distance from the areas affected by contamination is used, but also dispersion modelling results are used. In the latter case, the definition of the areas most affected by contamination, and the consequent identification of at-risk populations, depends on the accuracy of the model. There are several models used to evaluate the areas affected by contaminants; their implementation and improvement depend on the available information on several parameters. For example, in the case of emissions into the air from oil refineries, the parameters to be considered should be characteristics of emission sources: for example, height, flow rate, composition of emissions, exit temperature, local orography, and meteorological conditions [8]. Areas characterised by contamination processes different from direct industrial emissions require other parameters. In the case of landfills many early disposal sites did not have liners to trap rainwater that percolate through the landfill, and some newer landfills have liners that leak. The percolating water leaches toxic chemicals (e.g., from batteries, electronic equipment, and discarded household chemicals) that can contaminate soil and groundwater in ways that make it difficult to adequately identify the population at risk. Furthermore, in 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 food chain.

3.4. 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 considering two different needs: (1) it should 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) it should be sufficiently numerous to obtain stable reference rates also for rare diseases. These two needs have opposite requirements, as the first one is usually negatively correlated with the dimension of the population, while the second one is positively correlated with the dimension of the population. The reference populations should be selected balancing these two needs. Usually one or two populations among the following are selected as reference population: national, and regional, local (i.e., a population composed of populations residing in the neighbourhood of the contaminated area).

3.5. Outcome Selection. The aims of the study will imply a sound outcomes selection to include the ones for which environmental exposure/s (see environmental data) is 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, and so forth. General considerations about the quality of available information and data as well as intrinsic limitations of the selected outcome measures 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, and 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.

3.6. Small-Area Studies. Small-area studies investigate the role of neighbourhood level [9]. 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 the larger and more widely spread populations [10].

The smallest territorial unit that can be used in small area studies depends on data availability that may vary in different countries. For example, in Italy small area studies can be carried out at the census tract (average of 200 residents) and municipality levels. In 2001 about 70% of the Italian municipalities included less than 5,000 residents; this compares with Great Britain, where small area studies can be carried out at the following levels: enumeration districts—400 residents, electoral wards—5,100 inhabitants, and postcode sectors—6,600 people [11].

3.7. Socioeconomic Confounding. In geographical studies of environment and health, confounding from social and economic factors may occur. To control such confounding effect, standardisation 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.

Deprivation can be defined as "a state of observable and demonstrable disadvantage relative to the local community or the wider society or nation to which an individual, family, or groups belong" [12]. Deprivation indices are area-based measures of material and social disadvantageous circumstances, that is, indicators of relative deprivation at population level. A detailed discussion on the use and critical aspects of the application of DI in small area studies of environment and health can be found in an open access systematic review [11].

3.8. A Priori Evaluation of the 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 basis of statistical significance. As an example, SENTIERI dealt with the complexity of the relation between area contamination and health effects. For each NPCS studied the project focused on those causes identified *a priori* from the epidemiological evidence of their association with selected environmental exposures. This is the basic key aspect of the SENTIERI approach.

It is suggested that researchers use environmental contaminants information considering the available level of details. In SENTIERI possible relevant exposures were abstracted from Legislative Decrees, that is, 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 heterogeneous level of environmental characterization. While for some NPCSs information on specific chemical contaminants was 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.

When studying factors that determine changes in the occurrence of a given health condition or its predictive factors, it should always be kept in mind that most diseases have a multiple etiology. Therefore also exposures different from those specifically present in NPCSs should be considered, as well as every known cause or risk factor, such as smoking habits, alcohol consumption or other sources independent from those at study, that is, socioeconomic factors and occupational exposures, and air pollution due

to combustion of fuels for transport activities and domestic heating. The latter aspects are particularly relevant when studying complex industrial settings close or overlapping to urban highly populated areas.

Once the environmental exposures of interest identified, 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 kinds of publications are collected: handbooks, original articles, letters to scientific journals, multicentric studies, editorials, reviews, meta-analyses, and so on.

Therefore, the first decision to be taken is about the "relevance" to give to the collected material and how to use it to define the strength of the association between the specific health outcome and the environmental exposure/s that characterize/s the NPCSs.

SENTIERI study group defined a hierarchy in the literature sources. Sources expressing the epidemiological community consensus, evaluating scientific evidence by means of standardized criteria, and weighting the study design and the occurrence of biased results were considered most important (i.e., IARC monographs, WHO publications, European Environment Agency reports, handbooks of environmental, and occupational medicine). 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.

This process was performed considering not only the environmental exposures, but also those risk factors previously mentioned (smoking habits, alcohol consumption, air pollution, socioeconomic aspects, and occupational exposures). 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 the strength of the causal association for each cause-exposure combination was classified (matrix of *a priori* evidence evaluation).

The complexity of the described approach requires a multidisciplinary group of researchers. Expertise in environmental and occupational epidemiology, statistics, and public health clinical medicine, toxicology, and analytical chemistry are needed to tackle this complex environmental issue.

4. The Study of the Health Profile of Residents in NPCSs: SENTIERI Project

4.1. Site Selection. As indicated previously, the location of NPCSs should be identified. All data about contamination sources and characterization of contamination should be collected and examined to identify the contamination diffusion and finally define the areas and populations possibly affected by contaminants. SENTIERI project studied populations residing in the sites of national interest for environmental remediation (National Priority Contaminated Sites—NPCSs).

4.2. Environmental Data. In SENTIERI the production activities and sources of contamination listed in the Decrees defining the sites' boundaries were used as a proxy for environmental residential exposures; they are coded as chemical industries, petrochemicals and refineries, steel plants, power plants, mines and/or quarries, harbour areas, and asbestos or other mineral fibres, landfills, and incinerators. For each NPCS contamination data were collected, both from the national and local environmental remediation programmes.

4.3. Study Population. The study population comprised residents in 44 NPCSs; each one included one or more municipalities, a total of 5.5 million inhabitants in the 44 NPCSs, about 10% of the Italian population at the time of 2001 Census.

4.4. Reference Population. In SENTIERI project the Italian 2001 standard population was used as a reference to calculate crude and standardized rates. Regional populations were used as reference in the indirect standardization.

4.5. Outcome Selection. Mortality for 63 causes (or group of causes) for the period 1995–2002.

SENTIERI approach can be applied considering different health outcomes. Each outcome and cause analysed should be characterized to define its specific contribution in evaluating the possible health impact of contamination. For this aim, mortality, morbidity (e.g., hospital discharge records), cancer incidence, and congenital malformations prevalence could be of major interest. As described in the previous section, for each outcome a matrix of *a priori* evaluation should be built. Each outcome can be considered usable for the SENTIERI approach if its validity is previously verified, and appropriate epidemiological parameters can be estimated.

4.6. Small-Area Statistics. Briefly, SENTIERI studied mortality in 44 NPCSs using data at municipality level (1995–2002), calculating indicators such as crude and standardized rates (Italian 2001 standard population as reference) and standardized mortality ratio (SMR), using regional comparison rates, both crude (SMR) and adjusted for an *ad hoc* deprivation index (SMR ID).

4.7. Socioeconomic Confounding. To control for confounding from social and economic factors an *ad hoc* Deprivation Index was built and applied to the SMR estimates in SENTIERI project (SENTIERI DI). The deprivation index was constructed using the 2001 national census variables representing the following socioeconomic domains: education, unemployment, dwelling ownership, and overcrowding.

4.8. A Priori Evaluation of the Evidence. The epidemiological evidence was examined on the basis of explicit criteria to build a matrix of the *a priori* epidemiological evaluation of the strength of the causal association for each combination of selected outcome and environmental exposure. For details concerning the *a priori* evaluation see Section 3.

The procedure to develop such matrix can be summarized as follows.

Firstly a multidisciplinary group of researchers (see the previous section) draws up the list of causes to be submitted to the evidence evaluation.

Secondly, the epidemiologists classify the strength of the causal association of each outcome/exposure combination.

To complete this phase in SENTIERI project, the epidemiologists developed a procedure to examine the epidemiological literature published from 1998 to 2009 on the health risk of populations living in NPCSs. For details refer to Section 3 and [6].

The epidemiologists examined each cause of death/exposure combination (mortality was the first outcome to be analyzed) in terms of strength of causal inference. "Environmental exposures" were distinguished from "other exposures" in NPCSs. The former were fixed on the basis of the possible sources of contamination in NPCSs listed in the Decrees that defined each site boundaries (e.g., chemical industry, steel plants); the "other exposures" were the environmental, lifestyle and occupational most important known etiological factors: air pollution, active and passive smoking, alcohol intake, occupational exposures, and socioeconomic status. The procedure finally led to classify the evidence of the causal association into three categories: Sufficient to infer the presence of a causal association, Limited to infer the presence of a causal association, and Inadequate to infer the presence or the absence of a causal association.

The criteria adopted for the classification are reported in Table 1.

At the end of the second phase, a matrix of epidemiological *a priori* evidence about the strength of each outcome-cause/*environmental exposure* or outcome-cause/"other exposure" causal association was prepared (example in Table 2).

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

Sufficient (S) Sufficient to infer the presence of a causal association	(i) the Sufficient evaluation relies on one or more *primary sources* or on the data they provide for such evaluation or (ii) Quantitative meta-analyses provide data for an evaluation classifiable as Sufficient
Limited (L) Limited but not sufficient to infer the presence of a causal association	(i) 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 a Sufficient evaluation, or they do not provide data for such evaluation
Inadequate (I) Inadequate to infer the presence or the absence of a causal association	(i) some *primary sources* study the causal association but they disagree about the evaluation (conflicting evidence) or (ii) some quantitative meta-analyses/reviews/multicentric studies/two or more single studies analyze the association but they disagree about the evaluation (conflicting evidence) or (iii) 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 or (iv) the available studies are not consistent (conflicting evidence) or (v) only one single study analyzing the causal association is available

5. The Study of the Health Profile of Residents in NPCSs: SENTIERI Project—Main Findings and Results for a Single Site and for All NPCSs Combined

Specific causes with a certain level of strength of causal association with the environmental exposures present in each NPCS were reported and discussed in detail in SENTIERI. In order 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, ameliorate the level of knowledge, reducing scientific uncertainties about the heath impact of contamination and facilitating the process of identification and implementation of remediation interventions.

When more than one NPCS are studied, a homogeneous way of presenting and discussing results can make the study results clearer and more readable.

SENTIERI study group prepared a form to present each NPCS at study. It included a summary description of population and contamination data: specific sections dedicated to (a) results by gender (general health profile and specific, *a priori* selected causes); (b) previous studies carried out in the investigated area; and (c) a conclusive paragraph with suggestions for further scientific and/or remediation priorities as well as recommendations for public health interventions.

In single sites examples of recommendations aimed at a better description and clarification of the observed health effects include the investigation of the respiratory diseases prevalence in children, the conduction of occupational and residential cohort studies, and health surveillance activities as well as exposure assessment and biological monitoring investigations.

Table 2: SENTIERI projectmatrix of epidemiological *a priori* evidence evaluation for *environmental exposures* in National Priority Contaminated Sites (NPCSs) and "other exposures" for some selected causes adapted from [6].

(a) Environmental exposures in NPCSs

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

(b) Other exposures

Cause of death	Air pollution	Active smoking	Passive smoking	Alcohol	Socioeconomic status	Occupation
All ages						
Malignant neoplasms of trachea, bronchus, and lung	S	S	S	I	S	S
Malignant neoplasms of pleura	L					S
Diseases of the respiratory system	L onset/S wors	S onset/wors	L onset/wors	S	L	S
Asthma	L onset/S wors	S onset/wors	L onset/wors	L	L	S
Up to 14 years old						
Asthma			S onset/wors		L	

An example is the one of Sassuolo-Scandiano NPCS presented in a following paragraph.

5.1. Main Findings of SENTIERI Project. Some NPCS-specific results are noteworthy. The presence of asbestos or asbestiform fibres was the motivation for including six NPCSs in the "national environmental remediation programme." In five of these sites increases in malignant pleural neoplasm mortality were observed; in four of them the excess was in both genders. In four out of six other sites where in addition to asbestos other sources of environmental pollution were reported, mortality from malignant pleural neoplasm was increased in both genders. Asbestos and pleural neoplasm represents a unique case. Unlike mesothelioma, most causes of death analyzed in SENTIERI have multifactorial etiology; furthermore in most NPCSs multiple sources of different pollutants are present, sometimes concurrently with air pollution from urban areas: in these cases, drawing conclusions on the association between environmental exposures and specific health outcomes might be a hard task.

Notwithstanding these difficulties, in a number of cases an etiological role could be attributed to some environmental exposures. The attribution could be possible on the basis of the increases observed in both genders and in different age classes, and the exclusion of a major role of occupational exposures was thus allowed (in Italy most of the workforce in industrial setting is still represented by males). For example, a role of emissions from refineries and petrochemical plants was hypothesized for the observed increases in mortality from lung cancer and respiratory diseases in two NPCSs; a role of emissions from metal industries was suggested to explain increased mortality from respiratory diseases in two other sites. In six NPCSs an etiological role of air pollution in the raise of congenital anomalies and perinatal disorders was suggested, and a causal role of heavy metals, PAH's, and halogenated compounds was suspected for mortality from renal failure in six sites.

5.2. Sassuolo-Scandiano: An Example for a Single SENTIERI Site. According to the 2001 Census, the NPCS Sassuolo-Scandiano includes 6 municipalities with a 102,811 overall population.

The perimetration Decree of this NPCS lists the presence of pottery manufacturing plants, an environmental exposure that SENTIERI qualifies as "C" (plants producing chemicals and/or chemical products).

SENTIERI results among the main causes of death show in this NPCS some excesses for all causes and circulatory and

respiratory systems diseases in men. Some excesses are also observed for digestive system diseases in women (Table 3). For the causes of death with an *a priori* Sufficient or Limited evidence of causal association with the environmental exposure in this NPCS, an excess for respiratory diseases and asthma was observed in men (Table 4), and for congenital anomalies (malformations) in all age classes, both genders (Table 5).

Previous studies in this NPCS showed that lead, a metal used in the pottery production, polluted subsoil, surface, and ground waters. Notwithstanding a decrease in occupational exposure between the beginning of the Seventies and half of the Nineties, in 1995, the lead levels remained high. At the beginning of the Eighties, lead exposure levels in children were high; during the second half of the Nineties a sharp decrease was observed, and blood concentrations were lower than the 10 μg/100 mL limit. According to SENTIERI, the evidence of the causal association between occupation and respiratory system diseases and asthma was classified as Sufficient.

Since silicosis was not separately analyzed in SENTIERI and its risk is known to increase in pottery production, as observed in the cohort study of workers compensated for silicosis in Italy, it was probably conducive to the observed respiratory diseases excess in this NPCS.

The occupational exposure to lead in pottery production might have contributed to the mortality excess due to Parkinson's disease and hypertension. SENTIERI observed an excess in men (SMR = 160 (90% C.I. 111–224), SMR ID = 168 (90% C.I. 117–234)) and similarly in women (SMR = 110 (90% C.I. 69–167), SMR ID = 110 (90% C.I. 69–166)). A hypertension excess was pointed out for both genders (men: SMR = 192 (90% C.I. 166–221), SMR ID = 190 (90% C.I. 164–219); women: SMR = 206 (90% C.I. 184–230), SMR ID = 196 (90% C.I. 176–219)).

In conclusion, data acquisition for the appraisal of the present lead environmental pollution and occupational exposure is suggested. Individual epidemiological investigations are recommended to study asthma prevalence.

5.3. Results for All NPCSs Combined. SENTIERI project assessed also the overall mortality profile in all the NPCSs combined. The mortality for causes of death with *a priori* Sufficient or Limited evidence of causal association with the environmental exposure showed, for the period 1995–2002, 3,508 excess deaths for all causes, corresponding to 439 deaths/year; the number of excess deaths was 1,321 for respiratory diseases, 898 for lung cancer, and 588 for pleural neoplasms. When considering excess mortality with no restriction to causes of death with *a priori* Sufficient or Limited evidence of causal association with the environmental exposure, the number of excess deaths for all causes was 9,969 (SMR 102.5, about 1,200 excess deaths/year); the excess was 4,309 for all neoplasms (about 538 excess deaths/year), 1 887 for circulatory system diseases, and 600 for respiratory system diseases.

6. Discussion

The ecological approach used in SENTIERI does not allow to draw firm conclusions on the causal relationships between residential exposure and health status in residents in a contaminated site; furthermore, 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. This has 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 [7]. Another aspect which could increase the persuasiveness of environmental-related health effects is the identification of raised health risks in children living in contaminated sites. In the 44 combined NPCSs, among children 0-1 year old, mortality from all causes and from perinatal conditions was, respectively, 4% (3,328 cases) and 5% higher (1,903 cases) than the Italian reference population, and the overall mortality was significantly increased in one or more age groups (0-1, 0–14, and 0–19 years) among children living in 11 (25%) NPCSs [13].

The value of an ecological study like SENTIERI should be measured, as recently suggested [14], 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. Events such as the explosion of Seveso in 1976 [15] and Bhopal in 1984 belong to this category [16]. More frequently the environment has been progressively and perhaps surreptitiously contaminated by a heterogeneous mixture of pollutants originating from industry (often a variety of industrial activities) or waste treatment/disposal activities. In this case 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 quantitatively overtime. Often, the available exposure information is indirect and qualitative. For example, in SENTIERI project the sources of environmental exposures were abstracted from the legislative Decrees defining sites' boundaries, and chemical industry, petrochemicals and refineries plants, steel plants, power plants, mines and/or

Table 3: Mortality for the main causes of death. Number of observed cases (OBS), standardized mortality ratio crude (SMR), and adjusted for deprivation (SMR DI), 90% CI, 90% confidence interval; regional reference (1995–2002). Males and females.

Cause	NPCS: SASSUOLO-SCANDIANO					
	Males			Females		
	OBS	SMR (90% CI)	SMR DI (90% CI)	OBS	SMR (90% CI)	SMR DI (90% CI)
All causes	3677	105 (102–108)	106 (103–109)	3131	102 (99–105)	102 (99–105)
All neoplasms	1241	101 (96–106)	102 (97–107)	818	93 (88–99)	95 (90–101)
Diseases of the circulatory system	1402	109 (105–114)	110 (105–115)	1416	103 (99–108)	102 (98–107)
Diseases of the respiratory system	261	118 (107–131)	120 (108–133)	160	102 (89–116)	105 (92 –120)
Diseases of the digestive system	145	106 (92–122)	107 (93–123)	149	119 (103–136)	120 (104–137)
Diseases of the genitourinary system	35	95 (70–126)	95 (71–126)	39	116 (87–151)	117 (88–152)

quarries, harbour areas, asbestos or other mineral fibres, landfills, and incinerators subsequently coded. Such data are insufficient to give a full picture of space and time distribution and variability of the exposures. 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, due to many factors (e.g., concentration of contaminants and their diffusion to soil and water, distance of residence from polluting sources). The possible consequences of such nondifferential exposure misclassification are complex, and direction of the resulting bias is not predictable [17].

An additional limitation in exposure ascertainment 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.

Each vital statistics is able to provide information only about the events that is designed to record, and databases need to be validated for use in epidemiological studies.

IIn 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 [18]. In Italy mortality data are available for the whole country, and validity of cause of death certification has been documented for specific diseases [19–22].

In most European countries Hospital Discharge Records (HDRs) are indicators of hospital activity, and their main use is for administrative purposes [23]: validity when employed in ecologic studies has not been systematically evaluated. Some Italian reports [24, 25] 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 Italy in the context of contaminated sites congenital anomalies have been used in a descriptive study [26] and the investigation of cancer incidence has been planned [27].

Mortality statistics and hospital discharge statistics have been using the succeeding versions of the International Classification of Diseases (ICD) that guarantees homogeneity and comparability of results obtained in different places. However, particularly for cancer, the resolution power of the ICD is far lower than that of classifications based on pathological diagnosis such as the succeeding versions of the International Classification of Diseases for Oncology (ICD–O). Some associations between environmental agents and cancer are limited to specific pathological variants of the disease (e.g., wood dust and adenocarcinoma of the nose and nasal sinuses); for populations served by cancer registries where the histological type of cancer is systematically recorded this problem is solved.

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 [11]. To account for deprivation in SENTIERI project mortality data were analyzed both crude and adjusted [28] based on an *ad hoc* deprivation index (SENTIERI DI).

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 present paper referred as a common thread to SENTIERI project, in its main components of mortality study and *a priori* evaluation of the epidemiological evidence. The main limitations of the overall approach have been listed. Its major strengths are the standardization of the mortality analysis and NPCSs classification in terms of environmental exposure

Table 4: Number of observed cases (OBS), standardized mortality ratio crude (SMR), and adjusted for deprivation (SMR DI); 90% CI, 90% confidence interval; regional reference (1995–2002). Males and females. Causes with Sufficient or Limited evidence of association with the *environmental exposures* in SASSUOLO-SCANDIANO NPCS (chemical industry).

Cause	NPCS: SASSUOLO-SCANDIANO											
	Males			Females			*Environmental exposures* in the NPCS*	*Other exposures*				
	OBS	SMR (90% CI)	SMR DI (90% CI)	OBS	SMR (90% CI)	SMR DI (90% CI)		Air pollution	Active smoking	Passive smoking	Alcohol	Occupation
Malignant neoplasm of stomach	118	106 (90–124)	103 (88–121)	70	94 (76–114)	89 (72–109)	C	I	S	I	I	I
Malignant neoplasm of colon and rectum	113	91 (77–106)	92 (78–107)	79	78 (64–94)	81 (66–97)	C	**	I	I	S	I
Diseases of the respiratory system	261	118 (107–131)	120 (108–133)	160	102 (89–116)	105 (92–120)	C	L ons/S wor	S ons/wor	L ons/wor	S	S
Asthma	10	216 (117–367)	206 (112–349)	7	147 (69–275)	151 (71–284)	C	L onss/S wor	S ons/wor	L ons/wor	L	S

IPS *environmental exposures*: C: production of chemical substances, P&R: petrochemical plant and/or refinery, S: steel plant, E: electric power plant, M: mine or quarry, HA: harbour area, A: asbestos or other mineral fibres, L: landfill, I: incinerator.

Legend of the evaluation of the evidence: S: Sufficient to infer the presence of a causal association, L: Limited but not sufficient to infer the presence of a causal association I: Inadequate to infer the presence or the absence of an association, S ons/wor: sufficient onset and worsening, L ons/S wor: limited onset/sufficient worsening, L ons/wor: limited onset and worsening, *sufficient or limited evidence, **not applicable.

Table 5: Number of observed cases (OBS), standardized mortality ratio crude (SMR), and adjusted for deprivation (SMR DI); 90% CI, confidence interval; regional reference (1995–2002). Causes with Sufficient or Limited evidence of association with the *environmental exposures* in SASSUOLO-SCANDIANO NPCS (chemical industry).

Cause (age groups)	NPCS: SASSUOLO-SCANDIANO								
					Other exposures				
	OBS	SMR (90% CI)	SMR DI (90% CI)	*Environmental exposures* in the NPCS*	Air pollution	Active smoking	Passive smoking	Alcohol	Occupation
Congenital anomalies (all ages)	25	138 (96–193)	144 (100–201)	L	l	**	L	L	I
Certain conditions originating in the perinatal period (0-1)	14	74 (44–115)	74 (45–115)	C, L	L	**	S	I	I
Asthma (0–14)	<3			C	L ons/S wor	**	S ons/wor	**	**

IPS *environmental exposures*: C: production of chemical substances, P&R: petrochemical plant and/or refinery, S: steel plant, E: electric power plant, M: mine or quarry, HA: harbour area, A: asbestos or other mineral fibres, L: landfill, I: incinerator.
Legend of the evaluation of the evidence: S: Sufficient to infer the presence of a causal association, L: Limited but not sufficient to infer the presence of a causal association I: Inadequate to infer the presence or the absence of an association, S ons/wor: sufficient onset and worsening, L ons/S wor: limited onset/sufficient worsening, L ons/wor: limited onset and worsening, *sufficient or limited evidence, **not applicable.

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.

7. Concluding Remarks

The SENTIERI approach allows the description of the health status of populations living in the Italian NPCSs. Furthermore, it is suitable for an overall analysis of data from different NPCSs and comparative analysis of data from NPCSs with the same contamination sources.

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 [3]. 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.

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, occupation, and socioeconomic factors such as poverty and level of education. Identifying these relationships is therefore challenging; however, the effort is often worthwhile as it may help to redefine priorities and unlock resources [29].

Other strengths of the SENTIERI approach are that the *a priori* evidence evaluation and mortality analysis can be updated [30]; other health outcomes in addition to mortality can be analyzed, for example, cancer incidence [27], morbidity, and adverse reproductive effects; also the *a priori* evaluation can be carried out for *environmental exposures* different from the ones in SENTIERI project.

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 inasmuch as this becomes a permanent system of epidemiological observation on health of residents in NPCSs.

Glossary

Attribute: a factor that is an intrinsic characteristic of the individual person, animal, plant, or other type of organism under study (e.g., genetic susceptibility, age, sex, breed, and weight).

Contaminated site: area hosting or having hosted human activities which have produced or might produce environmental contamination of soil, surface or ground water, air, and food chain, resulting or being able to result in human health impacts.

Cause of disease: a risk factor (e.g., characteristic, behavior, or event) that directly influences the occurrence of a disease. Reducing such a factor among a population should reduce occurrence of the disease.

Determinant: any factor that brings about change in a health condition or in other defined characteristics.

Deprivation: a state of observable and demonstrable disadvantage relative to the local community or the wider society or nation to which an individual, family, or groups belong.

Ecological study design: an approach that looks for associations between exposures and outcomes in populations rather than in individuals.

Environmental remediation: the process of removing pollution or contaminants from environmental media such as soil, groundwater, sediment, or surface water for the general protection of human health and the environment.

Exposure: having come into contact with a cause of, or possessing a characteristic that is a determinant of, a particular health problem.

Health indicator: any of a variety of measures (e.g., mortality rate) that indicate the state of health of a given population.

Incidence: a measure of the frequency with which new cases of illness, injury, or other health condition occur among a population during a specified period.

Meta-analysis: a systematic method that uses statistical techniques for combining results from different studies to obtain a quantitative estimate of the overall effect of a particular intervention or variable on a defined outcome. It produces a stronger conclusion than can be provided by any individual study.

Morbidity: the incidence of a particular disease.

Mortality rate: a measure of the frequency of occurrence of death among a defined population during a specified time interval.

Multicentric study: a study conducted at more than one research or medical centre.

Outcome: any or all of the possible results that can stem from exposure to a causal factor or from preventive or therapeutic interventions; all identified changes in health status that result from the handling of a health problem.

Population: the total number of inhabitants of a geographic area or the total number of persons in a particular group (e.g., the number of persons engaged in a certain occupation).

Risk assessment: a method to characterize the nature and magnitude of health risks to humans (e.g., residents, workers, and recreational visitors) and ecological receptors (e.g., birds, fish, and wildlife) from chemical contaminants and other stressors that may be present in the environment.

Risk factor: an aspect of personal behavior or lifestyle, an environmental exposure, or a hereditary characteristic that is associated with an increase in the occurrence of a particular disease, injury, or other health condition.

Systematic review: a critical assessment and evaluation of all research studies that address a particular clinical issue. A set of specific criteria is used in an organized method of locating, assembling, and evaluating a body of literature on a particular topic.

Standardized mortality ratio: ratio between the observed number of deaths in a study population and the number of deaths expected, based on the age- and sex-specific rates in a standard population and the age and sex distribution of the study population.

Validity: the degree to which a measurement, questionnaire, test, or study or any other data-collection tool measures what is intended to measure.

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Review Article

Contaminated Sites in Europe: Review of the Current Situation Based on Data Collected through a European Network

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Under the European Union (EU) Thematic Strategy for Soil Protection, the European Commission has identified soil contamination as a priority for the collection of policy-relevant soil data at European scale. In order to support EU soil management policies, soil-related indicators need to be developed which requires appropriate data collection and establishment of harmonized datasets for the EU Member States. In 2011-12, the European Soil Data Centre of the European Commission conducted a project to collect data on contaminated sites from national institutions in Europe using the European Environment Information and Observation Network for soil (EIONET-SOIL). This paper presents the results obtained from analysing the soil contaminated sites data submitted by participating countries. According to the received data, the number of estimated potential contaminated sites is more than 2.5 million and the identified contaminated sites around 342 thousand. Municipal and industrial wastes contribute most to soil contamination (38%), followed by the industrial/commercial sector (34%). Mineral oil and heavy metals are the main contaminants contributing around 60% to soil contamination. In terms of budget, the management of contaminated sites is estimated to cost around 6 billion Euros (€) annually.

1. Introduction

Soil contamination creates a significant risk to human health. For instance, heavy metals from industrial waste contaminate drinking water, soil, fodder, and food [1]. Also, the large volume of waste and the intense use of chemicals during past decades have resulted in numerous contaminated sites across Europe. Contaminated sites could pose significant environmental hazards for terrestrial and aquatic ecosystems as they are important sources of pollution which may result in ecotoxicological effects [2].

Emissions of hazardous substances from local sources could deteriorate soil and groundwater quality. Management of contaminated sites aims at assessing the adverse effects caused and taking measures to satisfy environmental standards according to current legal requirements. Additionally, the impact of soil contamination to health and more specifically the main epidemiological findings relevant to CS are briefly presented below.

The implication of soils to human health is direct such as ingestion, inhalation, skin contact, and dermal absorption. Some epidemiological examples include geohelminth infection and potentially harmful elements via soil ingestion, cancers caused by the inhalation of fibrous minerals, hookworm disease, and podoconiosis caused by skin contact with soils [3]. Elliott et al. (2001) [4] have found small excess risks of congenital anomalies and low and very low birth weights in populations living near landfill sites.

Soil contamination is mainly located close to waste landfills, industrial/commercial activities diffusing heavy metals, oil industry, military camps, and nuclear power plants. As European society has grown wealthier, it has created more and more rubbish. Each year in the EU, 3 billion tonnes of solid wastes are thrown away (some 90 million tonnes of them are hazardous). This amounts to about 6 tonnes of solid waste for every man, woman, and child (Eurostat, Environmental Data Centre on Waste [5]).

The main anthropogenic sources of heavy metals exist in various industrial point sources, for example, present and former mining activities, foundries, smelters, and diffuse sources such as piping, constituents of products, combustion of by products, and traffic related to industrial and human activities [6].

In the US, the army alone has estimated that over 1.2 million tons of soils have been contaminated with explosives, and the impact of explosives contamination in other countries in the world is of similar magnitude [7]. In recent years, growing concerns about the health and ecological threats posed by manmade chemicals have led to studies of the toxicology of explosives, which have identified toxic and mutagenic effects of the common military explosives and their transformation products [8]. Papp et al. (2002) [9] have studied the significant radioactive contamination of soil around a coal-fired thermal power plant.

Different contaminants have different effects on human health and the environment depending on their properties. The contaminant effect depends on its potential for dispersion, solubility in water or fat, bioavailability, carcinogenicity, and so forth. Chlorinated hydrocarbons (CHCs) are used mainly for the manufacturing of synthetic solvents and insecticides. They are environmental contaminants that bioaccumulate and hence are detected in human tissues. Epidemiological evidence suggests that the increased incidence of a variety of human cancers, such as lymphoma, leukemia, and liver and breast cancers, might be attributed to exposure to these agents [10].

Mineral oil large-scale use and various applications lead in many cases to environmental contamination [11]. Such contamination may be a consequence of petroleum transport, storage and refining, or accidents [12]. From a quantitative perspective, mineral oil is probably the largest contaminant in our body. That humans can tolerate this contaminant without health concerns has not been proven convincingly. The current Editorial of the European Journal of Lipid Science and Technology concludes that this proof either has to be provided or we have to take measures to reduce our exposure (from all sources, including cosmetics and pharmaceuticals) and the environmental contamination.

Polycyclic aromatic hydrocarbons (PAHs) are semivolatile, chemically stable, and hydrophobic organic compounds which are ubiquitous in the environment and good markers of urban activities. PAHs are related with anthropogenic toxic element contamination [13].

Heavy metals have been used by humans for thousands of years. Although several adverse health effects of heavy metals have been known for a long time, exposure to heavy metals continues and is even increasing in some parts of the world, in particular in less developed countries, though emissions have declined in most developed countries over the last 100 years [14]. Any metal (or metalloid) species may be considered a "contaminant" if it occurs where it is unwanted, or in a form or concentration that causes a detrimental human or environmental effect. Metals/metalloids include lead (Pb), cadmium (Cd), mercury (Hg), arsenic (As), chromium (Cr), copper (Cu), selenium (Se), nickel (Ni), silver (Ag), and zinc (Zn). Other less common metallic contaminants include aluminium (Al), cesium (Cs), cobalt (Co), manganese (Mn), molybdenum (Mo), strontium (Sr), and uranium (U) [15].

According to WHO, priority should be given to the pollutants on the basis of toxicity, environmental persistence, mobility, and bioaccumulation [16]. Many of the heavy metals such as cadmium, arsenic, chromium, nickel, dioxins, and PAHs are considered to be carcinogenic, based on animal studies or studies of people exposed to high levels [17]. In addition to carcinogenicity, many of these substances can produce other toxic effects (depending on exposure level and duration) on the central nervous system, liver, kidneys, heart, lungs, skin, reproduction, and so forth.

The toxicity and fate of phenolic pollutants in the contaminated soils are associated with the oil-shale industry [18]. Phenol has been shown to cause liver and kidney damage, neurotoxic effects, and developmental toxicity in laboratory animals (Environment Agency, 2009).

The most common source of cyanide contamination is former gas work sites. However, cyanide contamination is also associated with electroplating factories, road salt storage facilities, and gold mining tailings [19]. Cyanide toxicity results from inhibition of cytochrome oxidase thereby limiting the absorption of oxygen at the cellular level. The central nervous system is a major target of acute cyanide toxicity, with a short period of stimulation evidenced by rapid breathing, followed by depression, convulsions, paralysis, and possibly death [20].

Benzene, toluene, ethylbenzene, and xylene (BTEX) are classified as hazardous air pollutants (HAPs) [21]. Exposure to HAPs can cause a variety of health problems such as cancerous illnesses, respiratory irritation, and central nervous system damage [22].

The objective of relevant EU policies is to achieve a quality of the environment where the levels of manmade contaminants on sites do not give rise to significant impacts or risks to human health and ecosystems. The most recent developments in soil policy at European level are the introduction of the thematic strategy for the protection of soils [23] and the proposed soil framework directive [24]. Soil contamination is recognised as one of the eight soil threats expressed in the thematic strategy and the proposed directive. As there was not a consensus for the establishment of the soil framework directive, legal requirements for the general protection of soil have not been agreed at EU level and only exist individually in most Member States. However, the integrated pollution and prevention control directive [25] requires that operations falling under its scope do not create new soil contamination. Other EU directives such as the water framework directive [26] and the waste directive [27], not aimed directly at soil protection, provide indirect controls on soil contamination [28]. Notwithstanding these controls, some significant new site contamination still occurs as a result of accidents [29] and illegal actions. While the creation of new contaminated sites is constrained by regulation, a very large number of sites exist with historical contamination that may present unacceptable risks and these sites require management. One example is the environmental disaster following flooding by red sludge in the Ajka region in Hungary [30]. However, the research and political arena regarding land contamination no

longer consider only a few incidents that lead to severe soil contamination, but rather look at it as a wide spread environmental problem.

In 2001, the European Environment Agency (EEA) in cooperation with EEA affiliated countries started to develop a core set of policy relevant indicators, among which the indicator "Progress in the Management of Contaminated Sites" (CSI015) was the only one related to soil. Since then, data collections in relation to this indicator were launched four times by EEA [31], the last one in 2006, with contribution from member countries of the European Environment Information and Observation Network (EIONET) [32]. In the period 2011-2012, the European Soil Data Centre (ESDAC) [33] organized a similar campaign in order to update the CSI015. This indicator quantifies the progress in the management of local contamination, identifies sectors with major contribution to soil contamination, classifies the major contaminants, and finally addresses issues of budgets spent for remediation. The indicator is very important for policy makers as it tracks progress in the management of contaminated sites and the provision of public and private money for remediation. With this indicator, a number of activities causing soil pollution can be clearly identified across Europe. The indicator also supports the implementation of existing legislative and regulatory frameworks (integrated pollution prevention and control directive, landfill directive, water framework directive) as they should result in less new contamination of soil.

The present study presents an overall picture in Europe concerning contaminated sites and does not focus on individual countries. Instead, there are many other studies, such as the one of Ferguson (1999) [34], that present the inventories of contaminated sites for individual countries. The overall objective of this paper is to make an overview of the current situation of contaminated sites in Europe. Specifically, the study intends to

(i) focus on contaminated sites caused by industrial activities;

(ii) review the type of sources;

(iii) respond to the main policy questions addressed in the indicator CSI015.

2. Materials and Methods

The study makes an assessment of the data collected through EIONET and then focuses on the data related to contamination as a consequence of industrial activities.

2.1. EIONET-CSI Data. The contaminated sites data (denoted as EIONET-CSI from now on) were collected and managed by the European Soil Data Centre (ESDAC). The data were collected in 2011-2012 through the EIONET network which consists of representative organizations from 38 European countries for a number of environmental themes [35]. The appointed organisations for the theme "soil" are lead institutions in the soil domain at national level, and they provide official country data on specific requests related to soil by ESDAC.

The geographical coverage of EIONET includes 27 Member States of the European Union together with Iceland, Liechtenstein, Norway, Switzerland, Turkey, and the West Balkan cooperating countries: Albania, Bosnia, Herzegovina, Croatia, the former Yugoslav Republic of Macedonia, Montenegro, and Serbia as well as Kosovo under the UN Security Council Resolution 1244/99. Similar data on contaminated sites have been collected in 2001, 2002, 2003, and 2006. The data were collected through a standard questionnaire and then compiled in a centralized database. The questionnaire was designed such that received data could feed the compilation of the indicator, the CSI015 indicator. There is no legal obligation for the EIONET member countries to submit data, and their contribution is on a voluntary basis.

2.2. Terms and Definitions. In order to minimize the differences in interpretation by individual countries of certain terms used in the questionnaire, ESDAC provided the following definitions according to EEA [31].

(i) "Contaminated site" (CS) refers to a well-defined area where the presence of soil contamination has been confirmed and this presents a potential risk to humans, water, ecosystems, or other receptors. Risk management measures (e.g., remediation) may be needed depending on the severity of the risk of adverse impacts to receptors under the current or planned use of the site.

(ii) "Potentially contaminated site" (PCS) refers to sites where unacceptable soil contamination is suspected but not verified, and detailed investigations need to be carried out to verify whether there is unacceptable risk of adverse impacts on receptors.

(iii) "Management of contaminated sites" aims to access and, where necessary, reduce to an acceptable level the risk of adverse impacts on receptors (remediate). The progress in management of CS is traced in 4 management steps starting with preliminary study, continuing with preliminary investigation, followed by site investigation, and concluding with implementation of site remediation (reduction of risk).

There is an important definition in terminology which allows the readers of the article to distinguish between "estimated" and "identified" sites. The questionnaire asked the countries to provide estimations on how many CSs and PCSs may be situated in their territory. Data on estimated CS and PCS is based on studies or expert judgment. The questionnaire also asked for identified number of CS and PCS. In this case, the countries report data for which they actually posses available information about local soil properties and hydrology.

2.3. Other Datasets. For a more comprehensive assessment, a number of auxiliary official Eurostat datasets [35] were used such as the countries' populations, the surface area, the gross domestic product (GDP), and the number of enterprises in the industrial/services sectors. Those datasets are used for developing statistics with parameters that include the surveyed population, the surveyed area, the density of CS and

PCS, the contribution (%) of various industrial sectors to contamination, and the proportion of budget spent for management of CS.

2.4. Methodology. The study is based on the received data from the countries that participated in the survey, replying to the questionnaire available in the European Soil Portal [36]. The questionnaire has a user-friendly format as a Microsoft Excel file and contains 5 main sections: "management of contaminated sites," "contribution of polluting activities to local soil contamination," "environmental impacts," "expenditures," "remediation targets and technologies." Each section includes between 1 and 5 questions requesting the "user" to submit the data for each of the available options. The questionnaire was requesting numerical values (not classes or vague responses) which allowed making aggregations depending on the policy question that was to be addressed. Two example questions are the following: percentage (%) of sites, where risk reduction measures are completed; expenditures in million euro per capita per year. As a support, a guidelines document was available with detailed explanation for each of the questions and the possible options plus example responses based on previous data collection exercises.

Each country represented by its designated EIONET National Reference Centre for soil provided its best assessment based on available data. The data collection campaign was launched in October 2011 and ended in February 2012.

3. Results

Even if the questionnaire included other data and information, this paper mainly focuses on the local contamination analysis, the type of contamination (which sectors are contributing the most), the distribution of the main contaminants, and the budget spent for remediation. The management of CS will not be analysed in detail as each country follows a different approach concerning the management steps. The analysis is performed in the study area as a whole and not at country level. It should be noted that quite different interpretations of the abovementioned definitions have been applied by individual countries.

3.1. Extent of Local Contamination in Europe. Data on soil contamination per country is a necessary input in order to estimate the scale of soil contamination in Europe. The majority of the addressed countries (33 out of 38 countries), corresponding to 80% of the total population, have responded with data on the identified number of PCS and CS (Figure 1(a)). The missing five countries were Bosnia, Herzegovina, Poland, Portugal, Slovenia, and Turkey. According to Figure 1(a), around 1,170,000 PCSs have been identified in Europe till 2011. More than 10% of them or around 127,000 have been identified or confirmed as CSs. The ratio of remediated sites (RSs) to CSs is around 45% as more than 58,000 CSs have already been remediated (Figure 1(a)). The data gap for the 5 missing countries can be covered by employing the density of PCS (2.4 PCS/1,000 capita) and CS (2.62 CS/10,000 capita) (Table 1). Applying the average of 2.4 identified PCS per 1,000 capita for the 5 missing countries, the identified PCS for the whole Europe (38 countries) is estimated to be around 1,470,000. Applying the average of 2.62 identified CS per 10,000 capita (Table 1, column (a)) for the missing 5 countries, the identified CS can be raised to 160,000.

Apart from the identified PCS and CS, countries have been asked to provide their estimations for those 2 figures. A subset of 12 countries out of the 33 participating ones has provided estimations about the PCS (Table 1, column (b)). As a rule of thumb, the estimations are greater than the identified ones. According to their estimations, 740,000 PCSs may exist in their territory with a density of 4.2 PCS/1,000 capita. Those 12 countries have reported 520,000 PCSs which result that the ratio "*identification to estimation*" for PCS is around 70%. Two types of extrapolations can be performed in order to estimate the total number of PCS. In the first one, the average value of 4.2 PCS/1,000 capita is applied to the total population of the 38 countries, and the total number of estimated PCS is then around 2,553,000 (Figure 1(b)). In the second extrapolation method, the ratio "*identification to estimation*" for PCS (70%) is applied to the countries which were unable to provide estimations; then the approximate number of PCS can be estimated to be 2,087,000.

Another subset of 11 countries (not a sub group of the previous 12) covering 10% of total population has provided estimations about CS. They estimated more than 32,000 CSs with a density of 5.7 CS/10,000 capita (Table 1, column (c)). Those 11 countries have reported 10,036 identified CSs which result that the ratio "*identification to estimation*" for CS is 30.7%. The first method of extrapolation is to apply the average density to the rest of the population (90%), where data does not exist. According to this estimation, the number of CS in Europe is estimated to be around 342,000 which accounts for 14% of the total estimated PCS (Figure 1(b)). In the second extrapolation method, the ratio "*identification to estimation*" for CS (30.7%) is applied to the whole population, and the estimated number of CS becomes more than 516,000. When comparing to the last survey of 2006, the estimated number of PCS was around 3 million, and the estimated number of CS was around 250,000.

The high variability of the data reported can be seen in Figure 2. The huge differences in the density rates represent the situation of PCS per country and how countries interpret the term of "potential contamination." Interpreting the metadata that come with the received data, PCSs are understood in a different way. For instance, Luxemburg, Belgium, Netherlands, and France include potentially polluting activities in their PCS figures, and this is the reason for high density of PCS in those countries (Figure 2). Other countries such as Austria, Hungary, and Norway include in their PCS figures only the sites where there is an evidence of potential contamination. Another factor contributing to this high variability is the granularity of a site. Some countries report sites which are important at national level, while others include also small sites such as storage tanks.

3.2. Sectors Contributing Most to Soil Contamination. Soil contamination is the result of various sectors and activities. The countries were asked to allocate a percentage of contribution of each sector to local soil contamination based on

Table 1: Estimated and identified PCS and CS.

	Identified PCS and CS (a)	Estimated PCS (b)	Estimated CS (c)	Total (d)
Countries	33	12	11	38
Surveyed population	487,152,449	177,412,672	57,568,148	612,117,243
Surveyed surface area (km^2)	4,460,305	1,552,984	833,188	5,772,075
Surveyed of total population	79.6%	29.0%	9.4%	
Surveyed of total area	77.3%	26.9%	14.4%	
PCS	1,169,649	739,968		2,553,000*
PCS/1000 capita	2.4	4.2		
CS	127,475		32,601	342,000*
CS/10,000 capita	2.62		5.7	
Remediated sites (RSs)	58,336			
RS/10,000 capita	1.20			

*Based on extrapolated data.

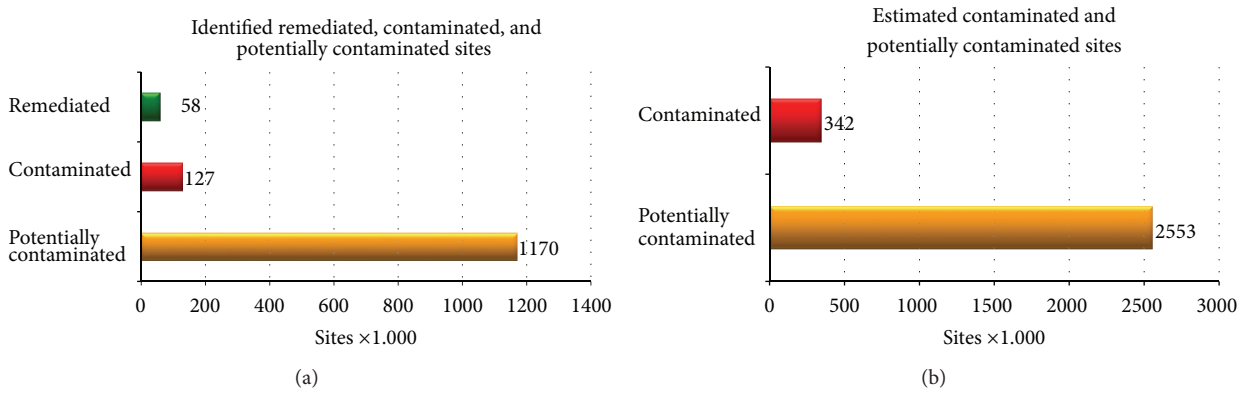

Figure 1: (a) Number of identified remediated (RS), potentially (PCS), and contaminated Sites (CS) reported by 33 countries. (b) Number of estimated potentially (PCS) and contaminated sites (CS) extrapolated to 38 countries.

the occurrence of incidents. The following seven categories of activities were proposed:

(i) waste disposal (municipal waste disposal and industrial waste disposal).

(ii) industrial and commercial activities (mining, oil extraction and production, and power plants).

(iii) military (military sites and war affected zones).

(iv) storages (oil storage, obsolete chemicals storage, and other storages).

(v) transport spills on land (oil spill sites and other hazardous substance spills sites).

(vi) nuclear.

(vii) other sources.

Responses related to contributing sectors were received from 22 countries which correspond to circa 53% of the total study population. Waste disposal and treatment contribute to more than 37% of soil contamination. Inside this category, municipal waste and industrial waste contribute to similar shares. The industrial and commercial activities contribute to 33.3% share, followed by storage (10.5%), while of the rest have a contribution of 19.1%. Nuclear operations contribute only 0.1%, but contamination from major nuclear players (e.g., scores from nuclear power stations) was not taken into account by some countries. The data cannot be compared to 2006 survey as the sample of countries that responded is dissimilar.

A special focus is given to the industrial and commercial sectors causing soil contamination. The countries were asked to assign percentages in each specific industrial sector which contributes to soil contamination. The responses of 17 countries covering 44% of the total study population suggested that the production sector contributes to around 60% of soil contamination, while the service sector has a share of 33% and the mining sector contributes to around 7% (Figure 3).

A closer look at the production sector reveals that the textiles, leather, wood, and paper industries are of minor importance for local soil contamination (circa 5%), while metal industries are most frequently reported to be important sources of contamination (13%) followed by chemical industry (8%), oil industry (7%), and energy production (7%) that sum up the 35% of the production sector, while all of the rest

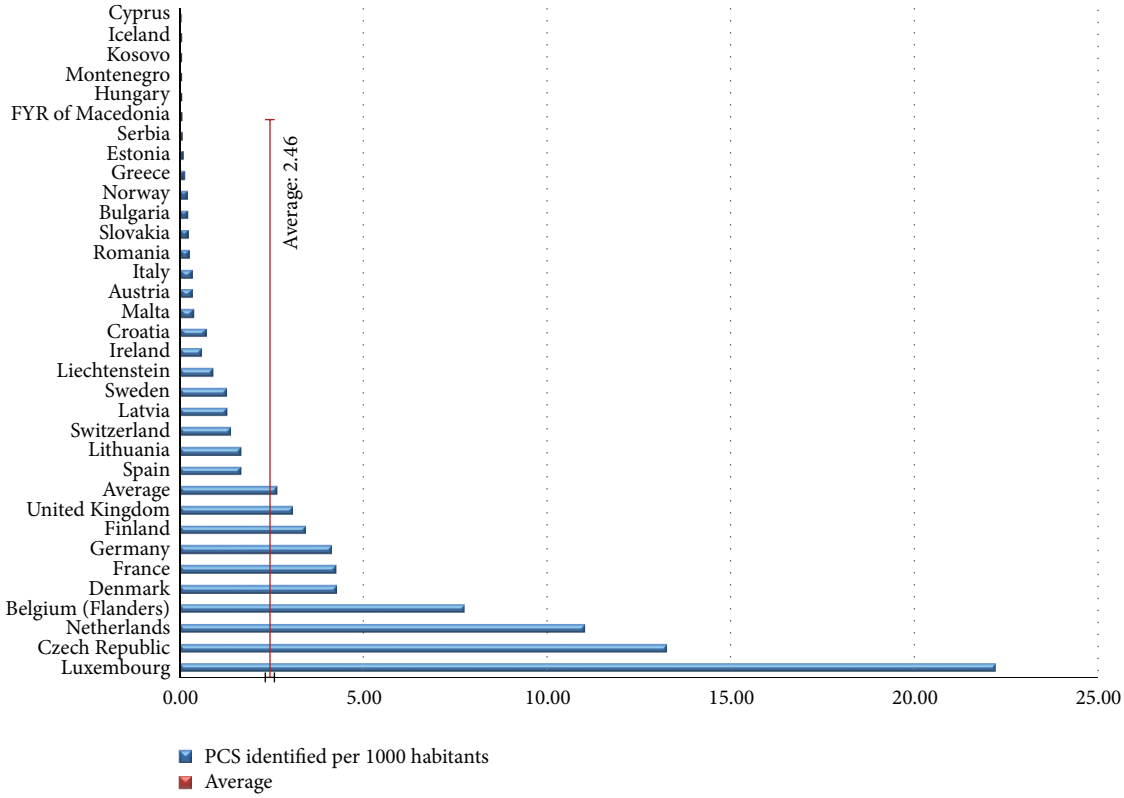

Figure 2: Density (identified PCS/1,000 capita) in 33 countries.

(25%) are distributed in 6 categories. For the service sector, gasoline stations are the most frequently reported sources of contamination (15%) followed by the car service stations (around 6%).

The Eurostat data on sectoral breakdown of manufacturing (NACE [37]) sums up the total number of enterprises in the EU to 2.041 million. The Eurostat industrial sectors do not correspond one-to-one with the industrial production sectors considered in the EIONET-CSI questionnaire (Table 2, column (a)). Some grouping of the Eurostat sectors (plus sign in column (c)) has taken place to make the correspondence. Note that the Eurostat data for the mining sector was embedded in the Eurostat category "other manufacturing." From the values in columns d and b, a new value (column (e)) is computed that expresses how many enterprises of an industrial sector contribute to 1 percent of the local contamination coming from that sector. The smaller the number, the more one site contributes to industrial contamination. The resulting figures show for instance that mining sites are individually heavier polluters compared to other sectors. Instead, the electronic industry enterprises pollute less compared to the shown sectors (Table 2).

3.3. Main Contaminants. The countries were asked to allocate a percentage for the proposed contaminant categories based on the occurrence of soil contamination. Distinctions were made between contaminants affecting the solid matrix (soil, sludge, and sediments) and the liquid matrix (groundwater, surface waters, and leachate). The following eight categories of contaminants were proposed both for solid and liquid matrices:

(i) chlorinated hydrocarbons (CHCs).

(ii) mineral oil.

(iii) polycyclic aromatic hydrocarbons (PAHs).

(iv) heavy metals.

(v) phenols.

(vi) cyanides.

(vii) aromatic hydrocarbons (BTEX: benzene, toluene, ethyl benzene, and xylene).

(viii) others.

The responses were received from 16 countries which correspond to about 40% of the total study population. The analysis based on these responses is of key importance for research and development, the remediation market, and related industries. For instance, if a specific compound is known to be a major soil contaminant, it may be worthwhile to develop new detection methods (i.e., in situ detection) and more efficient remediation techniques.

The distribution of the contaminants affecting soil is similar to the one of groundwater. The main contaminant categories are heavy metals and mineral oil contributing jointly to around 60% in soil contamination and 53% of the groundwater contamination (Figure 4). On the contrary, the phenols

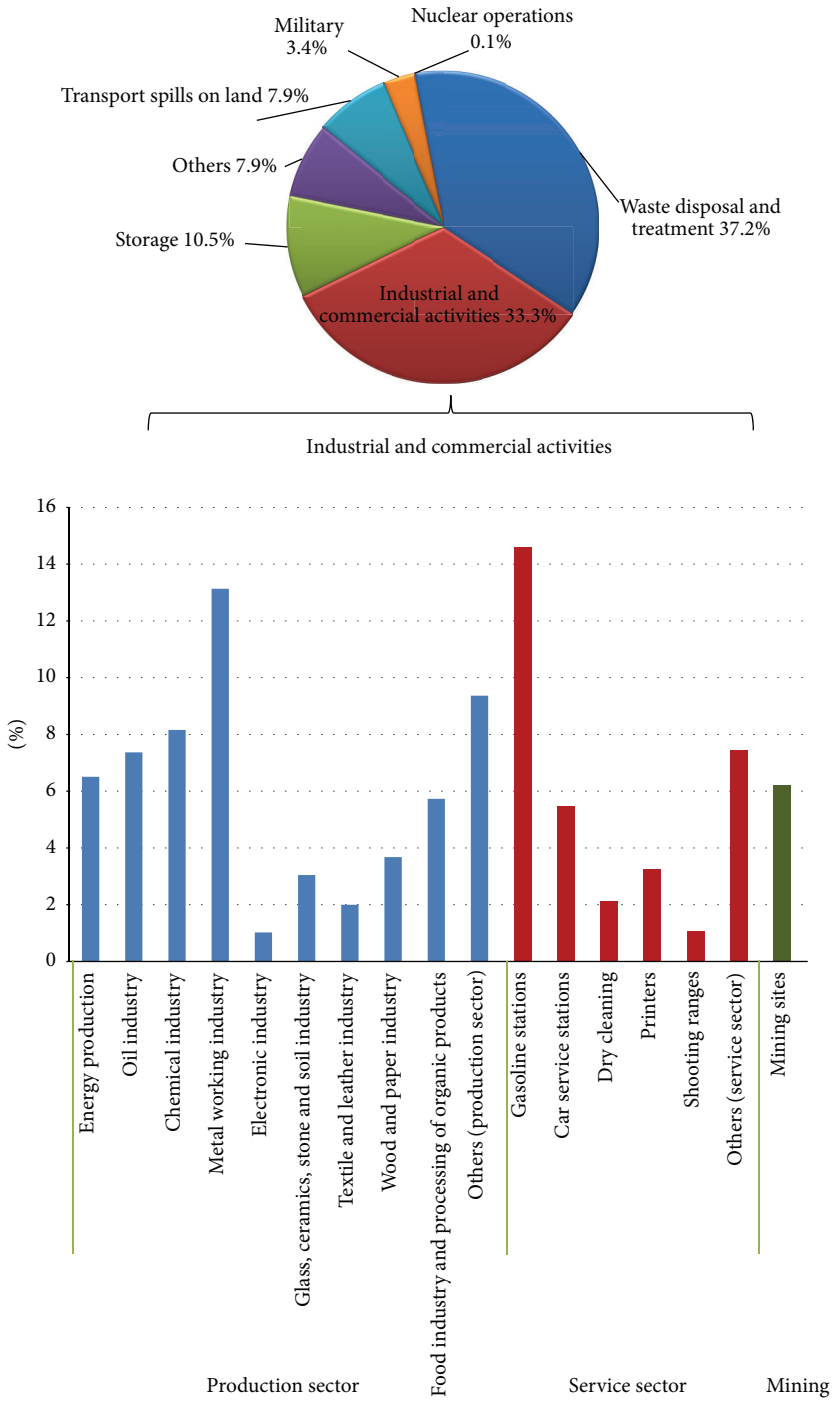

Figure 3: Distribution of sectors contributing to soil contamination in Europe with special focus to industrial/commercial activities.

and cyanides have an insignificant contribution to total contamination. The remaining four categories (BTEX, CHC, PAH, and others) have similar contributions to soil contamination varying between 8 and 11% and summing up to 40%. In the groundwater contamination, their contribution is around 45% ranging from 6% for PAH to 15% for BTEX. The current distribution is similar to the one proposed after the analysis of the 2006 surveyed results.

3.4. Budget Allocated. The cost of managing the CS is an important element taken into account by policy makers. The questionnaire included parts to investigate annual estimation of expenditures, share of private/public money, and share of total expenditure. This is a very important aspect as one of the most criticised issues in the proposed European soil framework directive [24] was the required estimate of annual cost for management of CS. According to the impact

Table 2: Comparison of sectoral contribution to industrial contamination against the total number of enterprises.

Industrial/service sector	Sector contribution to industrial contamination (production)	Manufacturing sector	Number of enterprises (1,000)	Number of enterprises (1,000) contributing to 1% of industrial contamination
(a)	(b)	(c)	(d)	(e)
Chemical industry	8.2%	Chemicals plus rubber and plastic products	97.2	11.9
Metal working industry	13.1%	Basic metals plus fabricated metal products	381.2	29.1
Textile and leather industry	2.0%	Textiles plus wearing apparel plus leather	225.4	112.7
Wood and paper industry	3.7%	Wood and paper	191.8	51.8
Food industry and processing of organic products	5.7%	Food products plus beverages	273.8	48.0
Electronic industry	1.0%	Computer, electronic, plus electrical equip.	94.1	94.1
Mining sites	6.2%	Mining	18.2	2.9
Total	39.9%	Total	1281.7	

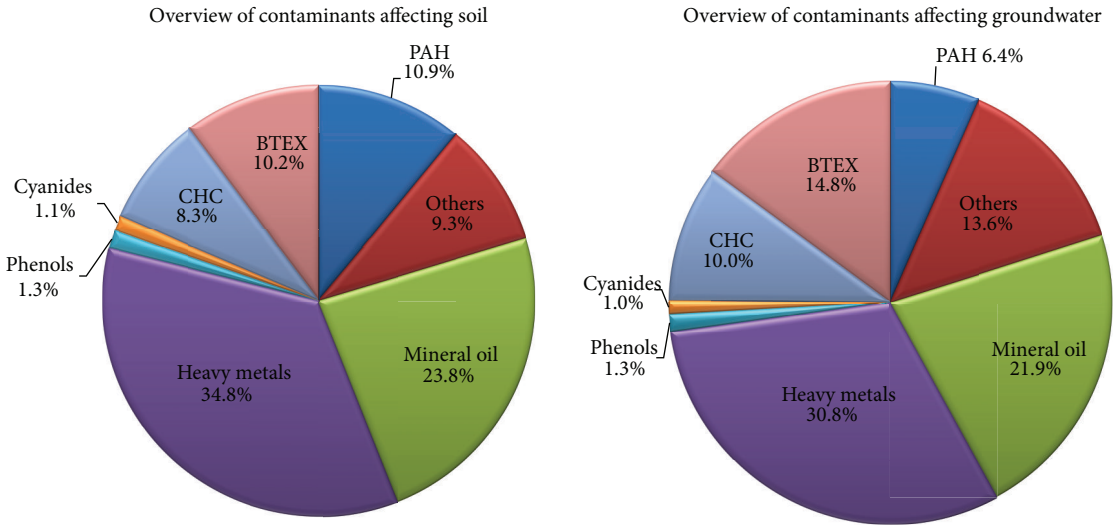

Figure 4: Distribution of contaminants affecting soil and groundwater in Europe.

assessment of the proposed directive, there was a wide-ranging estimate from 2.4 to 17.3 billion Euros.

According to the responses of 11 countries covering 23% of the total population (139 million out of the 612 million inhabitants for the total area), 1,483.2 million euros (€) were spent annually for the management of CS in these countries. In absolute terms, this is around 10.7€ per capita or 0.041% of the gross domestic product (GDP) for the 11 countries. The reported data show a small decrease in expenditure for management of CS compared to 2006 (12€ per capita).

If this sample of 11 countries is considered representative for the whole Europe, then the management of contaminated sites can be estimated to be 6,526 million euros (€) per year. Compared to the impact assessment of the proposed soil framework directive, this amount of money is probably a more precise estimate of the cost of the management of all identified CSs (including remediation).

Regarding the share of private/public money, 42% of the total expenditure comes from public budgets while the 58% from private investments. Another interesting aspect of the study is the share in the total expenditures for the management of CS for the different management steps. The vast majority (80.6%) is spent for the remediation measures while 15.1% is spent in site investigation and only 4.3% in after care measures and redevelopment of the sites. When considering the budget spent on remediation and the number

or remediated sites (RSs) in the 11 reported countries, it is calculated that the average amount spent per RS annually is around 37.1 thousand euros (€) in a range varying from 7.5 thousand € to 232 thousand € annually. As the remediation of sites has a duration of more than 1 year, the majority (40%) of the reported remediation projects fall in the range 50,000 to 500,000€, while a considerable 26.5% of the reported cases fall in the range between 5,000 and 50,000€.

4. Discussion and Conclusions

In terms of estimations, around 1,170,000 PCSs have been identified which are circa 45% of the total estimated PCSs. Also, around 127,000 CSs have been already identified which are circa 27% of the total estimated 342,000 CSs. Moreover, around 46% of the total identified CSs have been remediated (58,300 RSs). The identified figures for CS, PCSs and RS are based on reported data from 33 countries, while the estimated CSs and PCSs have been extrapolated based on data from a limited sample (11 or 12 countries).

Notwithstanding the positive outcomes of the EIONET-CSI data collection, it could be noted that the data submitted were not homogeneous since there are differences in the way that countries interpret the terms of contaminated sites. As shown in Figure 2, there is a high variability between the data submitted by countries. This variability is explained by the large uncertainty both in terms of methodology and data. Some countries run their own CS management system which may not fit perfectly to the definition of the CSI015 indicator, and this contributes to methodology uncertainty. Moreover, the reported data are usually based on expert judgement which includes a high degree of uncertainly. The countries may interpret the data specifications in different ways, and this increases the heterogeneity in the data reported. The reported data on CSI015 indicator are based on the exceed of limits in concentrations of hazardous chemicals. However, common limits are unlikely to be established at the European level since they may be strongly influenced by local soil and geological properties.

An adequate response to the high data variability could be to make a pan-European training event with the participation of competent national EIONET authorities, with the objective to apply the same terminology in all countries in subsequent data collections. The heterogeneity of responses can also be decreased if the provided documentation is taken into account.

In general, there are difficulties in getting the data on soil contamination, but improvement in data availability and data quality over the years can be observed. At this moment, the resulting dataset is the best "picture" that can be achieved based on national data. The EIONET-CSI data collection has taken place 5 years after the previous one of 2006. This 5-year period between data collections seems to be more appropriate than the 2-year period applied in the past, since the data on CS are not changing considerably in such a relative short time.

The direct and indirect costs to a country for dealing with the problem of CS depend on the amount and characteristics of CS in its territory. Generally, the presence of CS can affect company profits, business confidence, and attractiveness to investors. It may also affect aspects of public health and ecosystem protection. The remediation cost of CS, even if only a very little percentage of GDP, seems to be a major issue, and investments to improve the land quality through remediation are not readily made. Countries should weigh the costs of dealing with local land contamination against benefits to public health, improvement of the environment (e.g., water quality), land regeneration, and sustainable use of soil.

Restrictions set by privacy law in Europe are a major obstacle to identification and management of land contamination. Status and data on private land are not easily accessible to public authorities as this may have some implications for the land owner. However, the situation of his land is affecting public health, water quality, and ecosystem services. In cases of proven soil contamination, public authorities could be allowed for intervention or even raise public awareness. The conflicts between public interest and privacy regarding land and in general environmental problems should be resolved at a legal basis.

The EIONET-CSI dataset will be supplemented with heavy metals data at European level. In 2009, 22,000 soil samples were taken in European Union countries during a soil survey named LUCAS [38]. Those soil samples have been analysed for some of the most important soil attributes such as soil organic carbon, and the results assist to estimate better the overall situation in Europe [39]. Currently, these soil samples are analysed for heavy metals, and the expected output results will facilitate better assessment of soil contamination in European Union. The LUCAS heavy metals dataset will face the issue of privacy which can overcome with the application of digital soil mapping for the development of interpolated maps. The combination of LUCAS heavy metals with EIONET-CSI will be an important step in assessing soil contamination in Europe.

The proposed datasets and the current study can be considered by public health professionals for epidemiological assessments. The study of human exposure pathways is a key issue on contaminated sites, and certainly the integration of EIONET-CSI datasets with epidemiological data would be a very important step forward in this direction. Moreover, as the majority of food is growing in soil, biomonitoring and other research should investigate the pathways and routes from producers to consumers.

Conflict of Interests

The authors confirm and sign that there is no conflict of interests with networks, organisations, and data centres referred in the paper. In specific, ESDAC is the European Soil Data Centre and is an integral part of the Joint Research Centre of the European Commission, to which the authors are affiliated. Moreover, the ESDAC is operated by the authors themselves, so there cannot be any conflict of interests whatsoever. Also, the authors have published the paper relevant to ESDAC [33]. European Environment Information and Observation Network for soil (EIONET-SOIL) is the network of soil organizations officially designated by the European countries that deliver, on request by ESDAC and on a voluntary basis, data on soil related topics, in this case,

contaminated sites. Therefore, there cannot be any conflict of interests. Note that the contributing organizations of the EIONET-SOIL are explicitly acknowledged in the paper. Also, the authors have published a paper relevant to another data collection (soil organic carbon) in the past [32].

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Review Article

A Review of Exposure Assessment Methods in Epidemiological Studies on Incinerators

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Incineration is a common technology for waste disposal, and there is public concern for the health impact deriving from incinerators. Poor exposure assessment has been claimed as one of the main causes of inconsistency in the epidemiological literature. We reviewed 41 studies on incinerators published between 1984 and January 2013 and classified them on the basis of exposure assessment approach. Moreover, we performed a simulation study to explore how the different exposure metrics may influence the exposure levels used in epidemiological studies. 19 studies used linear distance as a measure of exposure to incinerators, 11 studies atmospheric dispersion models, and the remaining 11 studies a qualitative variable such as presence/absence of the source. All reviewed studies utilized residence as a proxy for population exposure, although residence location was evaluated with different precision (e.g., municipality, census block, or exact address). Only one study reconstructed temporal variability in exposure. Our simulation study showed a notable degree of exposure misclassification caused by the use of distance compared to dispersion modelling. We suggest that future studies (i) make full use of pollution dispersion models; (ii) localize population on a fine-scale; and (iii) explicitly account for the presence of potential environmental and socioeconomic confounding.

1. Introduction

Incineration is one of the most common technologies for waste disposal [1]. The number of incineration plants in Europe has been constantly rising in the last years, in the effort to manage and treat an ever-increasing waste production according to the EU directives and minimizing landfill disposal [2]. As waste incineration releases in the atmosphere chemicals that are potentially toxic [3], there is increasing public concern about the possible adverse effects on human health caused by this waste management technology [4, 5].

The literature on health effects of waste incinerators is extensive and can be essentially classified into two groups: observational studies (i.e., epidemiological analyses) and simulation studies (i.e., health risk assessment). The first group includes studies that make use of a variety of statistical techniques to describe the potential relationship between the *observed* health status of the population and the exposure level from incinerators. The second group includes studies aimed at estimating the *expected* impact, in terms of health risk and/or number of sanitary cases, of a measured or simulated exposure to environmental contaminants [6–8].

Available epidemiological studies have been well reviewed in many published papers [9–11] and reports published by international agencies [12, 13]. However, the lack of a common framework for study designs makes the results of the different investigations on the health impacts hardly comparable and thus inconclusive. Poor exposure assessment is claimed as one of the main reasons of inconsistency of results in published studies [3, 9, 10, 13].

Exposure is generally defined as the contact between a stressor and a receptor and can be characterized either by direct (e.g., personal monitoring and biological markers) or indirect methods (e.g., environmental monitoring,

modelling, and questionnaires) [14]. Although direct measures of exposure can be considered the best measures for assessing the effect of a specific substance on the target population, indirect measures of exposure (e.g., simulations of atmospheric dispersion) have greater utility for source emission assessment and control, since they are capable of linking population health to specific pollution emission sources [14]. These indirect methods have rapidly evolved in the last years [15], especially due to the increasing diffusion of the use of Geographical Information Systems (GIS) [16] and computer models to simulate atmospheric dispersion [17].

The aims of the present work were twofold: first, we wanted to investigate what methods and approaches are commonly used in the published literature to characterize exposure levels from waste incinerators; second, we wanted to assess, through a computer simulation study, how the classification of the expected exposure level may change as a function of the method used to estimate it.

The analysis was performed by using the literature database gathered within a project supported by the Emilia Romagna Region (North Italy) between 2007 and 2012 (MONITER Project) [18], to standardize environmental monitoring and health surveillance methods in areas characterized by the presence of incinerators and to evaluate the health status of populations around the eight incinerators of the region.

Although the focus of the present work was on waste incinerators, the results of our analysis can be extended to any point source of atmospheric pollution [19] or more generally to contaminated sites, where the presence of multiple sources has to be taken into proper account.

2. Material and Methods

2.1. Literature Review. We analyzed papers referenced in previously published reviews on incinerator health effects [9–13, 20] and, additionally, searched for further references on MEDLINE, PubMed, Scopus, and Google Scholar by using a number of keywords combinations (e.g., "epidemiology," "incinerator," "adverse effect," etc.). We focused our analysis only on observational epidemiological studies. Human biomonitoring [21, 22] and risk assessment studies [7, 8, 23] were not considered here. We excluded also studies on incinerator's workers [9] as the exposure pathway and levels can be completely different from those experienced by the population living around the incinerator plants.

The studies reviewed, rather than defining a relationship between environmental pollution and human health, aimed at evaluating the possible association with a specific industrial source of pollution (i.e., incinerators). The conceptual model for the emission-exposure pathways is sketched in Figure 1. Waste incineration epidemiological studies usually focus on gas stack emissions from the combustion process, while other possible sources of pollution (water discharges, ashes, smell emission, traffic, etc.) are not generally investigated [3]. After the emission from the incineration stack, pollutants dispersion in the atmosphere depends upon a number of physical and environmental variables such as stack height,

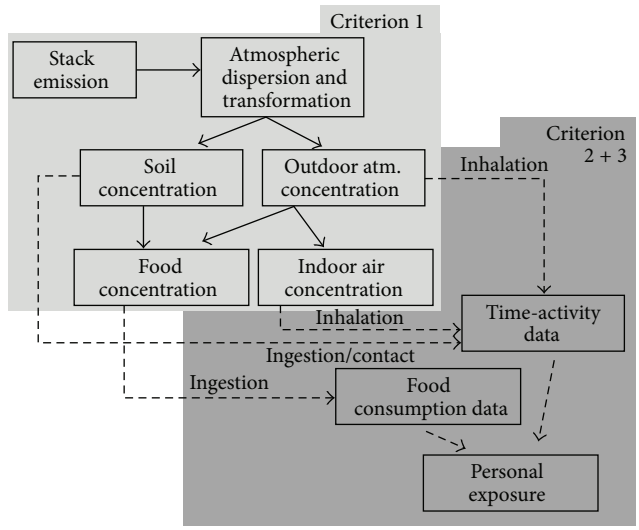

Figure 1: Conceptual model representing the principal impact pathways that determine exposure to atmospheric emissions from an incinerator. Contamination of drinking water is not represented.

wind speed and direction, temperature, and atmospheric stability. Some gases may undergo various chemical transformations, and part of the contaminants may eventually settle down on a variety of surfaces such as soil, vegetation, and water. Concentrations in the atmosphere and in soil may be either directly inhaled, ingested, or absorbed through dermal contacts or they can enter the agricultural food chain [24]. The actual exposure to potentially hazardous contaminants is thus determined by the time spent by various sectors of the population in different environments (outdoor, indoor at home, or at work) and could be due to inhalation, ingestion of contaminated water or food, and dermal contact with contaminated vectors (e.g., soil, water) [25]. Since incinerators are potential sources of persistent pollutants (e.g., dioxins, heavy metals, etc.) [3], ingestion can represent a relevant exposure pathway.

Exposure to pollutants has conceptually at least three dimensions, namely, (i) the intensity of exposure, which depends among the other things upon the concentration level of contaminants in different media; (ii) space, as both population density and concentration of contaminants are spatially heterogeneous; (iii) time, which is the duration and variability of exposure, as this determines the total amount of contaminant that has been eventually ingested, inhaled, or absorbed through dermal contacts [14]. Exposure assessment reconstructs the relationship between receptors and locations and between locations and the presence and amount of a certain risk factor. Accordingly, we reviewed the selected literature focusing only on the approaches used to define the exposure level and classifying them on the basis of three criteria (Table 1):

(1) the approach used to define the intensity of exposure to the emission source (3 categories);

(2) the scale at which the spatial distribution of the exposed population was accounted for (3 categories);

Table 1: Classification of exposure assessment methods.

Category	Description
	Criterion 1: definition of exposure intensity
1	Qualitative (e.g., presence/absence of the source/contamination in an area)
2	Distance from the source (e.g., linear distance)
3	Dispersion models (e.g., average annual atmospheric concentration)
	Criterion 2: definition of population distribution
1	Municipality/community/postcode sector
2	Census unit/full postcode
3	Exact residential address location
	Criterion 3: temporal variability
1	Time-invariable (i.e., fixed) exposure
2	Time-variable exposure (e.g., residential history and/or variability in emissions from the source)

(3) whether temporal variability in exposure was considered or not in the published study (2 categories).

The combination of all categories can result in a total of 18 possible methods of exposure assessment and was hereafter referred to as "$x.y.z$," where x represents the method used to estimate expected intensity, y the method used to estimate population distribution, and z whether the exposure was variable or not in time. For example, a published study classified as "2.3.1" means that the exposure level was evaluated as a function of the distance from the source, population distribution in the territory was assessed by using exact residential address location, and exposure was fixed in time.

Exposure assessment methods were categorized only on the basis of the exposure variables actually used in the epidemiological model. As discussed afterward, some studies reported additional information (such as measured concentrations of pollutants in various media) useful to interpret or support exposure model outcomes, even though this information was not used in statistical calculations.

Another important element of the exposure assessment process is the control of confounding factors, that is, variables that may hide or enhance the measure of effect [26, 27]. These factors can be socioeconomic (e.g., people living in industrial areas near incinerators may be more deprived) or environmental (e.g., frequently incinerators are located in areas with high pollution from other industrial sources and traffic).

For each reviewed study we analysed also whether and how confounding factors were accounted for. Since evaluation of confounding factors can follow a variety of approaches, we decided not to include this aspect as a fourth criterion in our classification scheme. Nevertheless we thoroughly comment on the role of confounding factors as well as their importance in epidemiological studies in the discussion.

2.2. Case Study: Parma. To understand how the choice of one or another approach of Table 1 may ultimately affect the estimated exposure, we run a simulation case study based on real data from an epidemiological surveillance program for a new incinerator that is under construction in the city of Parma (Italy).

The data used to simulate the effect of alternative methods of exposure assessment were as follows:

(i) location of the stack of the incinerator;

(ii) exact location of the address of residence for 31,019 people living around the incinerator (circle of 4 km of radius);

(iii) boundaries of the 2001 Italian census blocks for the area, as defined by the Italian National Institute of Statistics;

(iv) the results of an atmospheric dispersion model for PM_{10} emitted from the incinerator.

Geographic coordinates of addresses were provided by the local registry office. Atmospheric dispersion was simulated using the ADMS Urban model [28], a second generation quasi-Gaussian model already employed in other studies on health effects of incinerators [29–31]. Since the study area is located in a flat plane, this model was judged suitable to compute long-term average concentration and deposition [32].

We used PM_{10} as a tracer for the complex mix of pollutants emitted by the incinerator, after a test on various types of pollutant. The aim of the simulation was to determine a geographic gradient of exposure inside the study area: this spatial gradient is mainly determined by the incinerator's characteristics and atmospheric conditions, while it is only poorly dependent on the pollutant's properties.

We used five years of hourly meteorological data (2005–2010) from the nearest meteorological station (about 4 km from the plant) and source characteristics from the authorized project (i.e., stack height: 70 m; gas temperature: 150°C; PM_{10} emission flux: 231 mg s^{-1}) to calculate average hourly concentrations at ground level (ng m^{-3}) and average hourly deposition (ng m^{-2} h^{-1}) of PM_{10} over the period 2005–2010 on a regular 200 m receptor grid. Calculated concentrations were interpolated (using quadratic inverse distance weighting) to obtain continuous maps (Figure 3).

For each individual, we evaluated residential time-invariant exposure to the incinerator using the following methods:

(1) distance between census block centroid and incinerator (CBDI, method 2.2.1);

(2) distance between exact address location and incinerator (ADDI, method 2.3.1);

(3) average concentration and deposition inside the census block of each address (CBCO and CBDE, method 3.2.1);

(4) concentration and deposition at the address location (ADCO and ADDE, method 3.3.1).

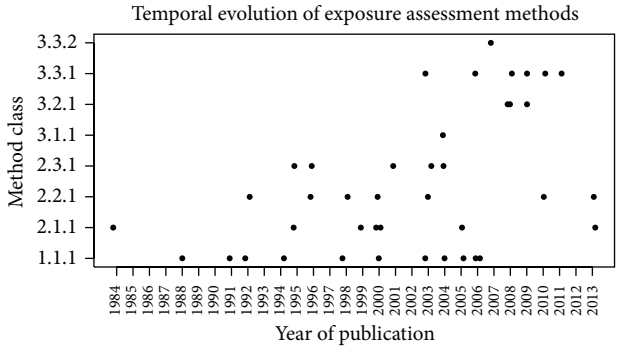

Figure 2: Temporal evolution of exposure assessment methods. Methods are classified according to Table 1 and sorted in the y-axis from the less precise to the best one.

We then contrasted the results of using alternative approaches for the assessment of the exposure level for each individual in the sample. Exposure variables were categorized in 5 classes (i.e., 1: lowest exposure, 5: highest exposure) using quintiles of each variable distribution. Thus, each exposure class contain approximately the same number of subjects. Only for address distance from the incinerator we defined also a second categorization using regular buffers, as done in the majority of published studies [33–35].

Concentration and deposition estimates based on dispersion models are affected by their own degree of uncertainty and should be possibly ground trued with field measurements and/or experiments. A previous validation study conducted in France [32] demonstrated that this kind of models provide a reliable proxy for incinerator exposure in simple terrain such as the area under study: we here assumed that simulated concentrations represent the closest estimate to the actual exposure.

Therefore we evaluated the degree of exposure misclassification using two-way tables and Cohen's kappa test of agreement [36, 37]. Cohen's kappa was calculated using quadratic weighting to assign less importance to misclassification between adjacent classes and higher importance to other misclassifications.

3. Results

3.1. Literature Review. A total of 41 studies published between 1984 and January 2013 were identified by the literature search. Table S1 in Supplementary Material available online at http://dx.doi.org/10.1155/2013/129470 (Supplementary Information) reports the resulting categorization of exposure methods and other relevant information for each study. The column "covariates" lists the confounding factors that were evaluated in each study.

Figure 2 represents the evolution of methodologies in time, based on the year of publication. Methods on the y-axis are sorted from the less precise to the best one.

With reference to the first classification criterion, that is, method used to assess exposure intensity, 19 studies (46%) used a measure of distance, both on a continuous scale and more commonly by defining concentric areas with arbitrary radius. In some cases [38–41] also wind direction was used to introduce some spatial anisotropy in exposure. Lee and Shy [42] used distance to define exposed communities but developed also a longitudinal study using daily PM_{10} measurement from fixed air monitors. One study [43] analysed spatial clustering of disease cases: since the analysis was based on the position of the community of residence, we classified this method as 2.1.1. One study [41] presented multiple assessment methods: presence/absence of the incinerator, distance from the plant, and an exposure index based on distance, wind direction, and time spent outdoor by people.

11 studies (27%) used atmospheric dispersion models to define population exposure. Generally models were used to estimate long-term average atmospheric concentrations at ground level, although one study used cumulated depositions [44]. Two studies [29, 45] used also heavy metals as indicator of exposure, while all the others used dioxins.

The remaining 11 studies (28%) used a qualitative definition of exposure to contrast the health status of communities/municipalities with and without incinerators. One study [46] developed quantitative indicators to classify municipalities, using emission inventories for dioxin from incinerators.

All the published studies used the residence as the place where exposure to atmospheric pollution occurs (criterion no.2). Nevertheless, different levels of detail were used in defining residence location. The majority of the papers (n = 19, 46%) considered the municipality or community of residence (e.g., postcode sector, school, hospital, etc.), 12 studies (29%) used the exact geographic coordinates of the address of residence, and 10 (24%) used the full postcode or census unit.

Finally, all the published literature, with one exception [47], defined exposure proxies that did not account for temporal variability in population spatial distribution and incinerators' emissions (criterion 3) that is, they considered the residence at the time of diagnosis, at enrolment, or the longest residence of the subject. Residential histories and changes in exposure intensity (e.g., as a consequence of changes in combustion and gas depuration technologies) were not accounted for in the other examined studies.

Overall, Figure 2 shows a trend of improvement in the quality of exposure assessment during the examined years, although three studies published after 2010 still used linear distance as the exposure proxy.

3.2. Results of the Simulation Case Study in Parma. Figure 3 reports the map of the census blocks around the incinerator under construction in Parma, its location (the star), the location of the sample of resident people used in the present study (small black dots), the expected PM_{10} concentration as simulated with the ADMS model, and the regular, 800 m wide, circular buffers around the emission source. Figure 4 contrasts the results of alternative approaches to assess exposure level in terms of intensity (simulated concentration versus distance from the emission sources) and accuracy in residence location.

Table 2: Evaluation of the agreement between concentration maps and other exposure assessment methods. Quadratic weighted Cohen's kappa and percentages of subjects classified in the same exposure class or in different classes.

Comparison exposure	Weighted kappa[a]	Matching subjects	Misclassification in adjacent categories	Misclassification in >1 class apart
ADCO versus ADDE	0.91	69.6%	29.3%	1.1%
ADCO versus CBCO	0.97	89.2%	10.5%	0.3%
ADCO versus CBDE	0.90	70.0%	27.8%	2.2%
ADCO versus $ADDI_1$	0.61	38.9%	45.1%	16.0%
ADCO versus CBDI	0.60	40.2%	44.5%	15.3%
ADCO versus $ADDI_2$	0.35	25.4%	39.8%	34.8%

ADCO: address concentration (quintiles), ADDE: address deposition (quintiles), CBCO: census block concentration (quintiles), CBDE: census block deposition (quintiles), $ADDI_1$: address distance (quintiles), $ADDI_2$: address distance (regular 800 m buffers), CBDI: distance between census block centroid and incinerator. [a]all kappa with $P < 0.001$.

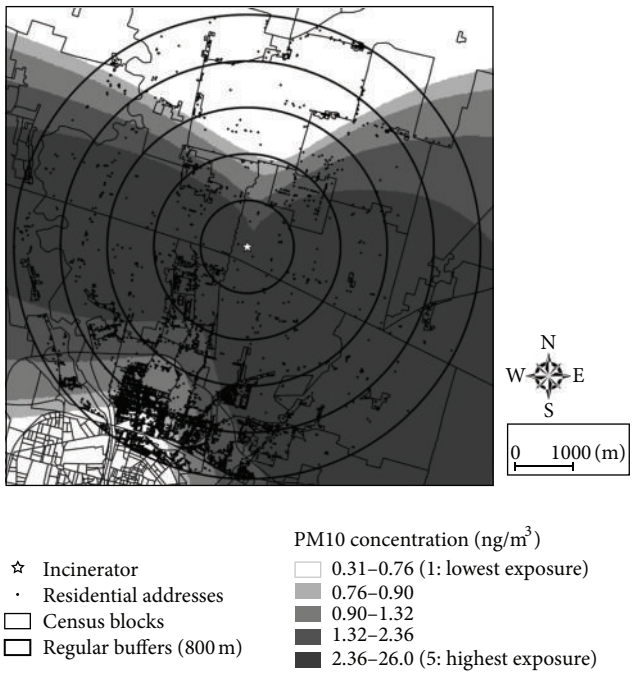

Figure 3: Representation of the area considered in the case study of Parma.

Table 2 shows Cohen's kappa indices of agreement between concentration maps and other exposure assessment methods. The table reports also the share of individuals over the 31,019 samples assigned to the same class of exposure, the share of individuals classified in an adjacent exposure class, and that of individuals classified into two or more classes apart. High kappa values are encountered when concentrations and depositions are considered, while comparison between concentration and distance approaches gave worst results when distance is categorized on regular concentric circles.

4. Discussion

4.1. Evaluation of Exposure Intensity (Criterion 1). The majority of the papers reviewed in the present study appear to suffer from poor exposure characterization. A relevant part of these papers (28%) used qualitative definitions of exposure (e.g., presence/absence of the source or anecdotic presence of pollution). These methods cannot account for the complexity of impact pathways described in Figure 1 nor for the heterogeneity in the exposure level that is normallyv expected as a consequence of the uneven distribution of the resident population and of the anisotropic dispersal of pollutants in the atmosphere. For instance, in the simulation case study we ran in Parma, the use of method 1.1.1 (presence of the incinerator in the municipality) would not allow us to discriminate between different levels of exposure and, therefore, all the 30,019 people in our sample (as well as the remaining 158,660 inhabitants of Parma) would be all classified as highly exposed, which would probably not be the case.

Epidemiological analyses carried out on a significant number of municipalities still represent a valuable instrument for public health tracking since they can evidence disease clusters in some regions that must be studied further. Even though any departure of disease incidence in large communities from background levels has to be taken very seriously, it is very difficult to use this type of evidence to infer about the role of specific emission sources (i.e., an incinerator), as many other potential confounding factors might exert a significant effect, particularly in highly urbanized areas. Moreover, the risk of false positive and, to a greater extent, false negative results, common to all exposure assessment methods, can be exacerbated when epidemiological data are averaged out on a vast territory with large internal differences in the exposure levels, as in method 1.1.1.

Almost half of the studies used distance to measure exposure. This is certainly a substantial improvement with respect to just an absence/presence evaluation, as contamination from an atmospheric emission source (e.g., air, soil, and locally produced food) is generally expected to decrease with distance. However, the assumption of isotropy in atmospheric dispersion of contaminants could lead to remarkable errors in exposure assessment. Many features of the emission source (e.g., stack height, gas flow temperature and velocity, and pollutant concentration) and of the local environment (e.g., local meteorology, topography, and land use) determine where and how far stack emissions disperse and how ultimately enter different environmental compartments.

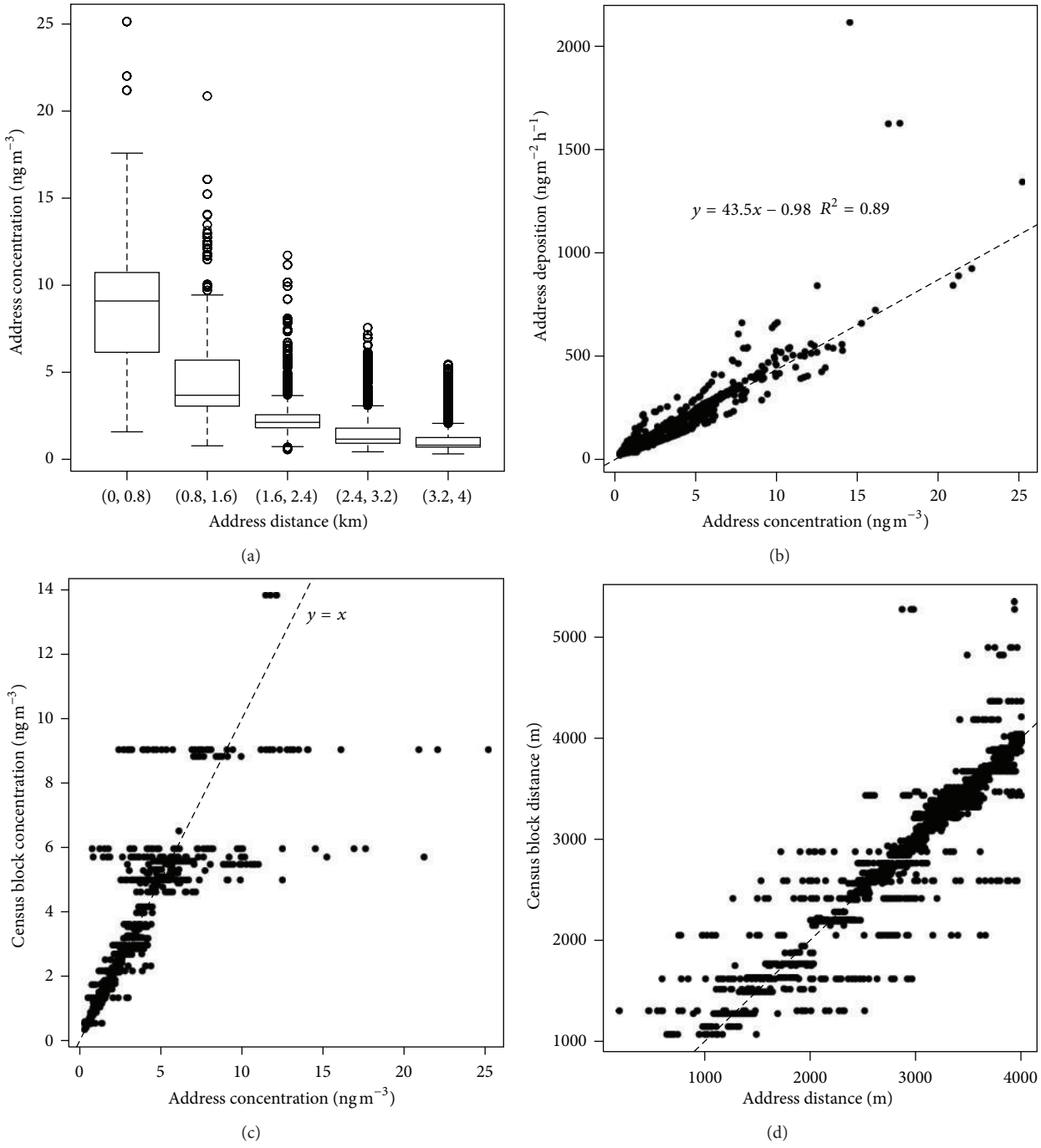

Figure 4: Results of exposure assessment by using different methodologies. (a) Variability of residential address concentration (ADCO) inside each regular 800 m buffer. Boxes represent the interquartile range (IQR), the horizontal line inside the box is the median value, and the whiskers extend to 1.5 times the IQR from the box. (b) Relationship between ground concentration (ADCO) and deposition (ADDE) at addresses location. The line represents the linear regression model. (c) Relationship between simulated concentrations evaluated at exact address (ADCO) and at census block level (CBCO). The line represents the 1 : 1 relationship. (d) Relationship between distance of the exact address ($ADDI_1$) and distance of the census block centroid (CBDI). The line represents the 1 : 1 relationship.

In our simulation study carried out for the Parma incinerator, the distance method assigns the same exposure level to people resident in the northern and eastern parts of the territory around the emission stack, even though simulations showed that concentrations are expected to be higher along the east-west direction than to the north-south one (Figure 3).

Because of the anisotropic dispersion of pollutants in the atmosphere, the expected PM_{10} concentrations at the residence address vary wildly inside each 800 m wide buffer

around the incinerator (Figure 4(a)). Consequently, the use of distance from the emission source as a proxy of actual concentrations could cause a high degree of misclassification (Table 2).

The use of well-tuned atmospheric dispersion models allows a substantial improvement in the estimation of exposure level, especially if carried out along with a fine scale estimation of the spatial distribution of the vulnerable population. Anyway, atmospheric pollution models are themselves affected by a considerable level of uncertainty [48] depending upon assumptions on actual atmospheric conditions, reconstruction of wind fields, and type of dispersion processes, including the possibility of simulating chemical transformation which are known to be highly relevant for the formation of tropospheric ozone and secondary fine particulate matter.

A significant number of the published papers analysed in the present study provided only a limited information on the atmospheric model: generally there was no discussion about the type of model used, the type and source of meteorological data, model adequacy to represent complex morphological natural or urban landscape and/or wind calms, and the assumptions made about pollutant's emission rates and physical-chemical properties.

Only few studies explicitly acknowledged limitations in the modelling approach used. For example, instead of adopting a different dispersion model as suggested by the same authors in a previous study [32], in Viel et al.'s [49] a part of the study area was excluded because dispersion model results were judged unreliable in that area. Another study [50] used maps of ground level concentrations estimated on the basis of emissions and meteorological data, but no dispersion model was cited. Almost all the studies used dioxins as an impact indicator: dioxins represent a family of 210 congeners, each one with different physical-chemical characteristics: no study clearly explained how these chemicals were treated in the model (e.g., using 2,3,7,8-TCDD congener properties). Moreover, some studies did not report a clear definition even of the most basic variables used to measure exposure, that is; averaging time for concentrations [31, 45, 51] or distinction between concentrations and depositions to ground [31]. As shown in our case study ground level atmospheric PM_{10} concentrations and depositions from a point source have very similar patterns with some significant departure, nevertheless the choice of one or the other measure of exposure should be at least discussed, related to the main route of exposure considered. All these pieces of information are important to judge the quality of the exposure assessment process, its uncertainties, and to allow comparability and reproducibility of methods.

Regardless of how detailed, accurate and advanced the model to simulate atmospheric dispersion is, it is still only a part of the impact pathways described in Figure 1. All the studies implicitly assumed that inhalation represents the principal exposure pathway, while no published literature measured or modelled the possible exposure through ingestion of contaminated food or contact with contaminated soil.

No study used measured levels of pollution in different media (e.g., atmosphere, soil, and food) as the exposure variable in the epidemiological model, except for one work [42] that used also measured 24 h average PM_{10} concentrations in each community as a predictor for pulmonary function, although there were no differences in average levels between communities defined *a priori* as exposed and not exposed. Many studies presented information on measured levels of pollution [43, 52–54], but these data were not included in the statistical model. This is not surprising, as it is very difficult to discriminate the contribution of single-point sources to the observed concentrations levels. The latter, in fact, invariably depend the contribution of several other confounding emission sources [55, 56], especially if they are located in urbanized areas with intense traffic or industrial activities. Thus, indirect measures of exposure obtained through modelling represent a valid alternative useful to identify the possible role of a specific emission source.

4.2. Evaluation of Receptor's Exposure (Criteria 2 and 3). The actual exposure of an individual to the pollutants emitted by an incinerator may occur in different environments and last a variable amount of time. All published studies used the residence as the place where exposure to atmospheric pollution occurs (criterion 2). Notably, one study [57] considered also the location of workplace of studied subjects.

Residence location can be determined with various degrees of precision. The majority of revised studies (48%) used community level to determine residence location (i.e., town, municipality, postcode sector, and school). In this way the same exposure level is assigned to large groups of population, but this assumption was rarely discussed and no measures of exposure variability inside groups were reported. Thus, it was impossible to evaluate the degree of ecological bias [58] that is, how well the variation in risk between groups with different average exposure applies to the variation in risk between individuals.

Some studies used census block or full postcode for determining residence position. The dimension of these blocks may vary greatly depending on the location: normally these blocks are smaller in populated areas but may become very large in other rural zones. Moreover, no information was generally given about blocks extension, and it was difficult to compare very different blocks types like Small Area Health Statistic Unit (SAHSU) [35], UK census postcode system [59], or UK Lower Layer Super Output Areas (LSOA) [60]. In our case study census blocks had an average area of 0.4 km^2 (min: 968.4 m^2; max: 6.3 km^2) and contained on average 26 addresses (min: 1; max: 130): both address distances and concentrations vary widely inside some census blocks (Figures 4(c) and 4(d)). This was true especially for more exposed areas, since the incinerator is located in a less densely populated area with large census blocks. This aspect could lead to different degree of errors in exposure assignment, that increase with the level of pollutant or proximity to the incinerator.

The most precise way to locate residences is to address geocoding: this procedure assigns a couple of geographic coordinates to each address. Errors in address positioning

depend on the quality of the database used but is generally in the order of tens to hundreds meters [61, 62], thus small in comparison with the use of census blocks or full postcode.

In future studies maximum disaggregation of data, to maximise information and minimize potentially differential ecological biases [63], is thus recommended.

The use of residence as exposure location is a very common assumption in environmental epidemiology since it is easily derived and there is evidence that people normally spend a great part of their time inside their residences, for example, on average 69% [64] and 80% [65]. Nevertheless, home location may not well represent total exposure because people may experience shorter but more intense exposures outside home, and residence is a proxy only for inhalation exposure and does not account for indirect pathways [66] (Figure 1). Although this technique has well-known limitations, it is often the only method available, particularly for large populations or for reconstructing historical exposures.

Temporal variability in exposure is an issue rarely explored in the reviewed studies. Temporal variability may result both from changes in source emissions over time or from residential mobility of the population and may be a cause of incorrect exposure assignment [67, 68]. Only one published study [47] explicitly accounts for historical exposure variability by reconstructing residential histories and evolution of dioxin emissions from the sources considered. However the exposure indicator chosen (i.e., the average exposure over time) may introduce some bias: since emissions from the sources considered were progressively reduced starting from the 1990s, the average exposure value decreases with the increase of exposure duration. A better indicator could have been cumulative exposure, that is, the sum of the annual exposure concentration over the exposure duration. One study [29] considered the modification of incinerator emissions over time indirectly, without considering changes in the final statistical model, but evaluating how the morphology of fallout maps was similar in time.

Although difficult to achieve because of data unavailability, especially for studies on old incinerators, in future studies efforts should be developed in reconstructing residential histories and variability in incinerator's emission over time, at least as a sensitivity analysis for the model.

4.3. Exposure Misclassification and Confounding Factors. Almost all papers used categorical definitions of exposure (i.e., exposure classes). One issue rarely discussed is the rationale behind the choice of cut-off values used to classify continuous variables. In the absence of toxicological reference values for this type of exposure, in our case study we used a criterion expected to make the results of the statistical analysis more stable and reliable, that is, having roughly the same number of exposed individuals in each class. In reviewed studies *a priori* cutoffs of exposure were generally chosen without an explicit justification [33–35, 51].

When categorical exposure variables are measured with error, they are said to be misclassified. Misclassification can be differential or nondifferential with respect to disease status of an individual person [26], the latter being more probable in reviewed studies and generally leading to risk estimations biased toward the null. Nevertheless, in presence of more than two exposure categories, non-differential misclassification can move estimates of risk away from null and disrupt exposure-response trends [69].

Our case study showed that

(i) for exposure measures based on distance a relevant part of the population may be classified in the wrong exposure category (assuming that dispersion model better represents real exposure), with relevant percentages of subjects moving by more than one category;

(ii) the use of census blocks to identify the residence may introduce a certain degree of differential misclassification since the error is higher in more exposed areas and lower for less exposed.

Both these factors may bias risk estimates away from the null or modify exposure-response trends.

Sometimes, the degree of error in exposure assessment can be evaluated with a validation study [70], that is, comparing modelled exposure with "gold-standard" measurement of exposure collected for a random subsample of the population, such as direct measurement of individual exposure. In practice, since no such gold standard is generally available, we recommend researchers to conduct sensitivity analyses on exposure assessment [71] and discuss the magnitude of error that may be present in their data.

Another issue that is only partially dealt with in reviewed literature is confounding. Confounding occurs when a risk factor different from the exposure variable under study causes bias in the estimation of association between exposure and disease, due to its differential distribution in exposed and non exposed groups [72]. Various confounding factors may affect a study on incinerators' health effects, that is, socioeconomic differences (e.g., poverty, occupation), personal lifestyles (e.g., alcohol, smoke), and presence of other sources of pollution.

Many reviewed studies did not account for any confounder in the epidemiological model [33, 47, 59, 73–77]. Some studies collected information about personal lifestyles or socio-economic status directly through questionnaires [38–40, 51, 78, 79]. Unfortunately the use of questionnaires and surveys is unfeasible for large populations; thus a large part of the studies did not consider personal lifestyles but included socio-economic indicators (e.g., deprivation indexes) evaluated at municipality/census block of residence [29, 30, 35, 44, 45, 49, 80, 81]. These indexes are generally constructed based on census statistics.

Of particular concern is the general lack of information about environmental confounding. Many of the pathologies under study have been associated with various atmospheric pollutants (e.g., PM_{10}, NO_x, etc.) or specific anthropogenic sources (e.g., road traffic, industrial emissions). Often, waste incinerators are located inside industrial areas or near other major sources of pollution. In our case study, for example, the incinerator is located inside the industrial area of Parma, at about 200 m from a national highway that crosses the

study area east-west (i.e., the prevalent wind directions). As a result, most exposed subjects, as identified by the dispersion model, were also more exposed to other sources of pollution. It will be difficult to correctly identify the possible health effect of this incinerator, unless we have some information about the difference in population exposure to other sources between the exposed and nonexposed groups. Only few studies included information about environmental confounders. Biggeri et al. [79] used measured particulate depositions from the nearest monitoring station, Cordier et al. [45] used proxies for the presence of industrial activities and road traffic at community level, and two studies [31, 44] used proxies for traffic and industrial pollution at census block level. Notably, one recent study [29] used atmospheric dispersion models to estimate pollution concentrations at the address of residence from other local sources of atmospheric pollution (road traffic, industrial plants, and heating). This represents a notable improvement since the confounding factor was evaluated with the same spatial resolution as exposure to the incinerator.

As the quantitative contribution of well-managed modern incinerators to total pollution levels in a study area and to baseline health risks is expected to be low, we suggest to draw a careful attention to other local sources of pollution and to implement multisite studies on large populations where feasible.

5. Conclusions

We reviewed 41 articles from the literature with the main aim of retrieving information for the definition of an exposure assessment protocol to be used in a large study on health effects of pollution due to incinerators (MONITER project).

Overall, our analysis showed a trend of improvement in exposure assessment quality over time, with a massive use of dispersion models in exposure assessment after year 2003.

Nevertheless, the lack of a common framework for exposure assessment is demonstrated by the use of a variety of methods, also in recent papers, with different quality of epidemiological findings and difficulties in comparisons of results.

In most of the selected studies the characterization of exposure can be significantly improved by using more detailed data for population residency and better simulation models. Recent development of informative systems and high availability of environmental and demographic data suggest the use of dispersion models of pollutants emitted from a source, combined with precise methods of geographic localizations of people under study, as the state of the art method to assess exposure of population in epidemiological studies. Considerations about residential mobility, temporal variations in pollution emissions, latency period of investigated diseases, and treatment of environmental and sociodemographic confounders can improve exposure assessment accuracy.

All these aspects of exposure assessment are particularly relevant as most of environmental conflicts usually arise from the evaluation of the contribution of the various pollution sources to the overall contamination.

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Review Article

A Review of the Epidemiological Methods Used to Investigate the Health Impacts of Air Pollution around Major Industrial Areas

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We performed a literature review to investigate how epidemiological studies have been used to assess the health consequences of living in the vicinity of industries. 77 papers on the chronic effects of air pollution around major industrial areas were reviewed. Major health themes were cancers (27 studies), morbidity (25 studies), mortality (7 studies), and birth outcome (7 studies). Only 3 studies investigated mental health. While studies were available from many different countries, a majority of papers came from the United Kingdom, Italy, and Spain. Several studies were motivated by concerns from the population or by previous observations of an overincidence of cases. Geographical ecological designs were largely used for studying cancer and mortality, including statistical designs to quantify a relationship between health indicators and exposure. Morbidity was frequently investigated through cross-sectional surveys on the respiratory health of children. Few multicenter studies were performed. In a majority of papers, exposed areas were defined based on the distance to the industry and were located from <2 km to >20 km from the plants. Improving the exposure assessment would be an asset to future studies. Criteria to include industries in multicenter studies should be defined.

1. Introduction

Industrial areas are characterized by a high density of industries, sharing common infrastructures, such as transport networks, waste water treatment plants, and waste incineration plants. These areas cluster at-risk activities and pollution sources. They have historically attracted, and may still attract, hundreds of employees who have settled in the vicinity of the plants. With extensive urbanization, industrial areas have been embedded in the urban landscape, increasing the nuisances and the exposure of the population. For instance, in the South of France, the industrial area of l'etang de Berre hosts 430 industries classified for the protection of the environment and more than 60% of the Seveso II (referring to the European directive 96/82/CE) plants of the region. About 16 towns representing more than 300,000 inhabitants are exposed to the plumes produced by these plants [1].

People living near major industrial areas are facing complex situations of exposure: occupational and environmental exposure, multiexposure to chemicals combined with exposure to noise, dusts, visual pollution, stress, and so forth The possible associated health risks are of the highest concern to the population.

Quantitative health risk assessments, based on the comparison of a hypothetical exposure (assessed through measured or modeled concentrations in different matrices combined with scenarios of exposure) to toxicological reference values or to regulatory values, have been extensively used for regulatory purposes. They can point out problems with specific pollutants or route of exposure. For instance, several risk assessments around large French industrial areas found that the levels of some compounds, including benzene, particulate matter (PM), and SO_2, could be considered too high [2, 3]. They confirmed that the concerns of the population were legitimate and triggered actions to reduce those specific pollutions. Yet, quantitative health risk assessments can neither tell if and how many people are actually suffering because of the pollution, nor they can take into account the integrated burden of the multiexposure to the chemical,

physical, and perceived industrial pollution. The answers to these questions belong to epidemiologists and raise several methodological issues: what kind of study should be used, which health outcomes should be investigated, how to assess exposure, and how to control for confounding factors?

In this paper, we performed a literature review of the published studies investigating the health of population exposed to industrial air pollution around major industrial sites. The objectives were (1) to identify the reasons why studies were performed, (2) to list the health outcomes that have been investigated, (3) to describe the study designs that have been used, and (4) to describe and discuss the exposure assessments. The objectives were not to perform a systematic review but to collect a representative sample of the different practices that can be used in that field.

2. Methods

The work focused on studies investigating the chronic effects of air pollution from large industrial areas and major complexes grouping several plans or multicenter studies involving similar types of industry that could be or not part of larger industrial complexes.

Papers published between 1980 and 2012 were searched based on the Scopus database that includes PubMed and other relevant literature database. As an initial research using key words referring to industry retrieved very few papers, we searched epidemiological studies on the impacts of air pollution around point sources. On a second step, papers dealing with industries were selected based on the title and abstracts.

The initial search equation was ((“Air Pollutants” [MeSH] OR “Air Pollution” [MeSH]) AND “epidemiology” [Subheading]) OR ((Air pollution [Title/Abstract] OR Air pollutants [Title/Abstract]) AND (epidemiology OR epidemio* OR “Case control study” OR cohort OR “cross sectional study” OR prevalence OR incidence OR Surveillance OR survey OR “Health risk” OR “Risk assessment” OR health OR “Health effects” OR Exposure OR “Health impact*” OR Mortality OR “Adverse effects”)) AND (industry OR industrial) AND (residents OR Residential OR inhabitants OR neighborhood* OR vicinity OR “living area” OR “living near” OR surrounding* OR populations).

Papers were analyzed focusing on the types of industries, the study design, the health indicators, and the exposure assessment. The objectives were to identify the methods but not to discuss the results reported by each paper. To do so, reviews focusing on specific industries would be more relevant.

3. Results

From the initial search 230 papers in English or French were selected based on their title. Based on the abstracts, 155 papers were excluded (58 environmental studies only, 35 looking at exposure through water, soil, or food and not air directly, 36 using industrial areas as one source among other air pollution sources, 10 description of the health of a population without links to exposure, 8 on nuclear installations, 4 toxicological studies, 3 studies focusing on acute exposure after an accident, and 1 literature review). Two reports from the grey literature were added, but no specific search was performed to identify such reports on a larger scale.

77 papers were finally included in the review, published between 1989 and 2011. While papers were available from many different countries, a majority of papers came from 3 European countries: the United Kingdom, Italy, and Spain (Table 1). One paper may provide results for several studies, and 27 studies were focusing on cancer, 25 on morbidity, 9 on biomonitoring, 7 on mortality or birth outcome, and 3 on mental health. Studies for each of these health outcomes are described below.

3.1. Cancers

3.1.1. Reasons for Performing Studies on Cancers. The 27 studies on cancer are detailed in Table 2. 12 studies were multicenter studies, ranging from 4 sites to 452 sites.

The reasons for doing an epidemiological study on cancer near a major industrial area were frequently concerns from the population, explicitly quoted by 7 studies [1, 7, 12, 15, 17, 25, 27]. Few studies gave details on the social background, showing that the health issues crystallized the concerns of the population. For instance, Bhopal et al. states that “[⋯] *the controversy was such that the health concerns were central issues in a public inquiry, and received extensive media coverage. Our study was requested by the local authority, to help resolve this controversy*”. Sans et al. reports that their “*study was undertaken in response to concerns of a local pressure group based* [⋯] *about an alleged cluster of cancer, especially of the larynx, and leukaemia among children* [⋯] *there was also concern about several deaths among teachers and pupils at the nearby comprehensive school*”. In 11 other studies, concern of the population is not mentioned, but the authors justified their study with references to an overincidence of cancers or mortality observed in the area by previous investigation [4–6, 8, 9, 14, 16, 19, 26, 28, 31].

By contrast, multicenter studies refer to the literature and possible etiology in relation to the emissions to justify their choices [20–22, 24], although geographical variations of the incidence of the cancers investigated are also used as a justification for focusing in a specific region or on a specific cancer [10, 18, 23].

3.1.2. Industries Involved in the Studies on Cancers. Study areas vary from very rural areas with about 2,000 inhabitants [17] to highly populated areas with several hundred thousand people [1, 4, 12]. The industries involved in the studies are highly heterogeneous and usually have been operating since several decades before the study period, with areas sometimes industrialized since the 19th century. Six studies were on refineries [6, 16, 17, 26, 28], including one multicenter study in the United Kingdom [14], and 3 on petrochemical plants [15, 27], including one multicenter study in Louisiana [7]. Larger sites gather a variety of different industries. For instance,

Table 1: Summary of the papers in the literature review.

Country	Total number of papers	Health outcome (several health outcomes may be described in 1 paper)					
		Cancer	Morbidity	Biomonitoring	Mortality	Birth outcome	Mental health
United Kingdom	15	5	5	2	4	0	1
Italy	9	3	3	2	1	0	0
Spain	8	7	0	1	1	0	0
Taiwan	7	4	0	0	0	3	0
Israel	6	1	3	0	8	1	0
United States	6	1	0	1	0	2	2
Canada	5	1	4	0	0	0	0
Sweden	4	1	1	2	0	0	0
France	2	2	1	0	0	0	0
Thailand	2	0	2	0	0	0	0
Countries with 1 study only		Finland, Lithuania	Argentina, Australia, Brazil, India, Romania, South Africa	Korea			
Total number of studies (several studies may be described in 1 paper)		27	25	9	7	7	3

Teesside includes iron, steel industries, chemical, and heavy engineering industries. By 1945 it was the largest single chemical production complex in the world [8]. In France, a site like Etang de Berre involves oil refining, oil storage, petrochemical and organic chemical activities, chlorine chemistry, steel and metal working, waste incineration plant, and the port for ore and oil tankers [1].

Among the multicenter studies, industrial sites of different natures were involved in a study in Italy [4, 5] and in Spain [24]. Wilkinson et al. studied 11 petrol refineries corresponding to 7 industrial areas [14]. In a study investigating the petrochemical industries in Louisiana, Simonsen et al. used three different criteria to aggregate the industries: (1) all sites were considered as a whole, without regard to specific emissions; (2) sites were classified on the basis of their Standard Industrial Classification code as either belonging to the petrochemical industry or not; (3) sites were classified on the basis of the International Agency for Research on Cancer (IARC) carcinogen rating assigned to their specific chemical releases [7].

European registries of polluting industries were extensively used in Spain [10, 18, 20–24, 32, 33] to perform the multicenter studies. In some cases [10, 23, 24], all sites were included. For instance, the study by Cambra et al. included 66 sites, aggregated into 6 categories: 4 energy production plants, 28 metalworking industries, 8 cement industries, 44 chemical industries, and 17 others [24]. In other cases, only the industries corresponding to one activity, for example, metal production [20, 22] or paper, pulp, and board industries [18], were included.

3.1.3. Type of Studies Investigating Cancers. Most of the studies (20/27) used a geographical ecological design, based on standardized mortality or morbidity ratios, searching for a possible overincidence of the mortality or the morbidity. Poisson regression and similar statistical designs were used to assess a relationship between health indicators and exposure, taking into account confounding factors (mostly socioeconomic) (Table 2).

Seven studies were case-control studies [4–10]. For instance, Zambon et al. included 172 cases of sarcoma and 405 controls in their study [4]. Biggeri et al. collected data from 755 cases of lung cancer and 755 controls [5]. The multicenter design was used either for case-control studies [4, 5, 7, 10] or for standardized incidence or mortality ratio studies [14, 18, 20–24, 31].

Lung cancer was the most commonly studied [1, 5, 7–10, 15, 16, 18, 19, 21, 24, 25, 28, 34], based on registries, mortality data, or hospitalizations data [10]. Other cancers investigated were leukemia [6, 15, 20, 25–27], digestive cancers [22], non-Hodgkin's lymphoma [23] and sarcoma [4], either based on mortality or registry data.

The latency of cancer was usually taken into account as the number of years of residence in the area before deaths. It varied from at least 1 year (e.g., [9]) to 10 years (e.g., [8]) and was sometime unspecified.

3.1.4. Exposure Assessment in the Studies Investigating Cancers. Distance was used as the method to assess the exposure in 19 of the studies. The use of distance is seen as a way to overcome the lack of measurement data, but also to reduce the latency problem, as clearly stated by Pless-Mulloli et al. : *"areas closest to steel and chemical plants at the time of study were also close 40 years earlier, an important consideration given the long latency of lung cancer"* [19]. However, this requires the

Table 2: Studies investigating cancer.

Reference	Country	Industrial background	Health outcome	Epidemiological design	Exposure assessment
Zambon et al., 2007 [4]	Italy	Industrial waste incinerators, Municipal solid waste incinerators, Medical waste incinerators, thermal power plants, oil refinery industrial plants for the production of primary aluminium	Visceral and extravisceral sarcoma	Case control (72 cases and 405 controls)	Dispersion modeling (Industrial Source Complex Model in long-term mode, version 3 (ISCLT3))
Biggeri et al., 1996 [5]	Italy	Shipyard, iron foundry, incinerator, and Trieste city center	Lung cancer (mortality)	Case-control study (755 case-control pairs)	Distance and angle from each subject location to each pollution source
Yu et al., 2006 [6]	Taiwan	Oil refinery	Leukemia	Case control (171 cases and 410 controls)	Distance, based on previous studies (3 km radius from the geographic centroid of any of the four petrochemical complexes)
Simonsen et al., 2010 [7]	United States	Petrochemical industries	Lung cancer (registry)	Case control (455 cases and 437 controls)	Distance (0.5 miles, 1 mile, and 2 miles)
Edwards et al., 2006 [8]	United Kingdom	Iron and steel, chemical, and heavy engineering industries	Lung cancer (registry)	Case-control study (204 cases and 339 controls)	Distance, guided by a validation study using data from historical records
Petrauskaite et al., 2002 [9]	Lithuania	Production of mineral fertilizers, aluminum fluoride, and sulfuric acid	Lung cancer (mortality)	Case-control study (410 cases 410 controls)	Distance, based on measurements of sulfuric acid and the prevailing wind (6 km)
Lopez-Cima et al., 2011 [10]	Spain	23 industrial installations reporting to the EPER	Lung cancer	Case-control study (626 case, 626 controls)	Distance
Pascal et al., 2011 [1]	France	Oil refining, oil storage, petrochemical and organic chemical activities, chlorine chemistry, steel and metal working, chemical plants, waste incineration plant, port	All cancers, lung cancer, bladder cancer, breast cancer, multiple myeloma, malignant non-Hodgkin's lymphoma, and acute leukemia (hospitalisations)	Standardised incidence ratio	Coupling of a dispersion model (ADMS4), a meteorological model and kriging to assess the SO_2 levels
Viel et al., 2011 [11]	France	13 municipal solid waste incinerators	Non-Hodgkin's lymphomas (registry)	Standardised incidence ratio	Dispersion model (Atmospheric Dispersion Model System version 3—ADMS 3) for each category of pollutants (dioxins, metals, and dusts)
					Perceived exposure areas (criteria not

Table 2: Continued.

Reference	Country	Industrial background	Health outcome	Epidemiological design	Exposure assessment
Bhopal et al., 1994 [12] Bhopal et al., 1998 [13]	United Kingdom	Coke ovens (66 from 1980)	Cancer (registry)	Standardised incidence ratio	specified), modeled exposure (model not specified) 24-hour mean daily measures of SO_2 and smoke over 56 months (1987–91)
Wilkinson et al., 1999 [14]	United Kingdom	11 oil refineries	Lymphohaematopoietic malignancy	Standardised incidence ratio	Distance (0–2 km, 0–7.5 km, and eight bands around refinery perimeters)
Axelsson et al., 2010 [15]	Sweden	Industrial complex including a large cracker producing ethylene and propene	Leukemia, lymphoma, cancers of the lung, liver, and central nervous system, all cancers taken together (registry)	Standardised incidence ratio	Models (unspecified) of ethylene levels
Eitan et al., 2010 [16]	Israel	Petroleum refineries, oil-fired power plant, and several large petrochemical, chemical, and agrochemical industries	Lung cancer, bladder cancer, and non-Hodgkin's lymphoma	Standardised incidence ratio	Spatial interpolation of SO_2 and PM10 routine monitoring data
Schechter et al., 1989 [17]	Canada	Two natural gas refineries	Cancer (registry)	Standardised incidence ratio	Unclear
Monge-Corella et al., 2008 [18]	Spain	18 EPER-registered paper, pulp, and board industries	Lung cancer (mortality)	Standardised incidence ratio	Distance (≤5 km from a paper, pulp, and board industry, ≤5 km from any other industrial installation, towns having no EPER-registered industry within 5 km of their municipal centroid (reference level))
Pless-Mulloli et al., 1998 [19]	United Kingdom	Teeside	Lung cancer (mortality)	Standardised mortality ratio	Distance (0.1–2.7 km, 1.5–4 km, and farther)
García-Pérez et al., 2010 [20]	Spain	118 integrated pollution prevention and control (IPPC) category 2 metal production and processing installations which report their emissions to the EPER	Leukemia (mortality)	Standardised mortality ratio	See Monge-Corella
García-Pérez et al., 2009 [21]	Spain	57 combustion installations which report their emissions to the EPER	Lung, larynx, and bladder cancer (mortality)	Standardised mortality ratio	See Monge-Corella
García-Pérez et al., 2010 [22]	Spain	118 integrated pollution prevention and control (IPPC) category 2 metal production and processing installations that reported their releases to air and water in 2001	Tumours of the digestive system (mortality)	Standardised mortality ratio	See Monge-Corella

Table 2: Continued.

Reference	Country	Industrial background	Health outcome	Epidemiological design	Exposure assessment
Ramis et al., 2009 [23]	Spain	452 industries reporting releases to air to the EPER, grouped by industrial sector	Non-Hodgkin's lymphomas (mortality)	Standardized mortality ratio	Distance (1, 1.5, and 2 km).
Cambra et al., 2011 [24]	Spain	284 industries declaring to the EPER emissions of pollutants	Lung cancer (mortality), haematological tumours (mortality)	Standardised mortality ratio	Distance (<2 km, >2 km)
Michelozzi et al., 1998 [25]	Italy	A large waste disposal site (one of the largest in Europe), a waste incinerator, and a petrochemical refinery	All cancers, laryngeal cancer, lung cancer, liver cancer, kidney cancer, and lymphatic and haematopoietic cancers (mortality)	Standardised mortality ratio	Distance (3, 8, 10 km, 10 concentric circles with a radius increasing from 1 to 10 km to define nine bands)
Pekkanen et al., 1995 [26]	Finland	Refinery	Leukemia, hematological cancers, all cancers (registries)	Standardised mortality ratio	Distance (4,4–7.9, 8–11.9, 12–15.9, and >16 km)
Sans et al., 1995 [27]	United Kingdom	Petrochemical processing: alcohols, styrene, olefins, benzene, vinyl chloride monomer, and polyvinyl chloride (PVC)	Cancer incidence and mortality for all cancers, leukaemias, and cancer of the larynx	Standardised mortality ratio	Distance (0–3 km, 7–5 km, and eight bands between circles of radii 0.5, 1–0, 2–0, 3–0, 4–6, 5–7, 6-7, and 7–5 km)
Yang et al., 2000 [28]	Taiwan	Kaohsiung oil refinery	Lung cancer (mortality)	Standardised mortality ratio	Distance
Pan et al., 1994 [29]	Taiwan	Kaohsiung oil refinery	Cancer in children (mortality)	Standardised mortality ratio	Distance
Tsai et al., 2009 [30]	Taiwan	Petrochemical industries	Bladder cancer (mortality)	Standardised mortality ratio	In each district, the number of employees of the industries divided by the population, in three clases

assumption that people were also living in the same area 40 years earlier.

Several options were used for the distance (Table 2), for instance,

> exposed group ("near") ≤ 5 km from a metal production plant, intermediate ≤ 5 km from any industrial installation other than metal production and processing, unexposed group ("far"), consisting of towns having no EPER-registered industry within 5 km of their municipal centroid (reference level) [18],
>
> distance: 0–2 km, 0–7.5 km, and eight bands around refinery perimeters with outer limits at 0.5, 1, 2, 3, 4.5, 5.6, 6.6, and 7.5 km [14],
>
> three concentric circles with radii of 3, 8, and 10 km for descriptive purposes and 10 concentric circles with a radius increasing from 1 to 10 km to define nine bands [25].

Additional refinement may be added, taking into account, for instance, the residential history [7]. Bhopal et al. made an original combination of different metrics to characterized exposure: perceived exposure areas (criteria not specified), modeled exposure (model not specified), and the 24-hour mean daily measures of SO_2 and smoke over 56 months [12]. In Finland, the exposure area was based on distance, but that distance was chosen based on measurements of sulfuric acid and the prevailing wind directions [9]. Edwards et al. also mentioned that their choice of the distance was guided by a validation study using data from historical records and measurements [8].

Another example of a complex exposure assessment initially relying on distance is given by Yu et al.: to account for the effects from monthly prevailing wind, they defined exposure wedges for each month by the monthly prevailing wind direction. Only addresses located within the exposure wedges were considered exposed during the particular month, and the exposure opportunity scores for these residences were

assigned by the inverse of distance to the relevant petrochemical complexes [6].

Although reference sites are usually defined as the farthest to the plant, some studies include a further subclassification taking into account proximity to traffic, urban, semiurban, and rural areas. The definition of these areas may vary between studies. For instance, the industrial area can be defined based on the distance between the subject's residence and an industrial installation (industrial distance), as the area defined by the first decile of industrial distance [10].

Models were used by only 5 studies. The Industrial Source Complex Model in long-term model was used by Zambon et al. [4], and Atmospheric Dispersion Model System version 3-ADMS 3 was used in France [1, 31]. The other two models were not detailed [12, 15]. In the Etang de Berre study, results from the models were combined with measurements to obtain a map of the annual mean levels of SO_2, which were then grouped in three classes of exposure based on quartiles [1]. Viel et al. derived two indicators from the air pollution model, corresponding to different hypotheses about the mode of exposure: the concentrations alone represented exposure from inhalation only; the number of years the plant had operated and the degradation speed in soils provided a cumulative ground-level concentrations since the start of the activity [31].

The lack of emission data is a key limitation to modeling, acknowledged by some authors [16]. In France, Viel et al. used a complex process to recreate emissions based on exposure judgment in order to be able to complete the dispersion modeling [31].

Measures alone were used by one study only, taking advantage of a relatively dense air quality monitoring network for SO_2 and PM_{10} [16]. More frequently, measures were used to describe areas previously chosen based on distance or modeling, and measurements were not input in the statistical models. For instance, in the case of Stenungsund in Sweden, models (unspecified) of ethylene levels based on the emissions of year 2000 were used to classify a low and a high exposure area. Measurements were performed in the high exposure areas (ethylene, propylene, benzene, 1,3-butadiene, 1,2-dichloroethane (EDC), and vinyl chloride) in 2001-2002 and 2006-2007. They were used to perform ahealth risk assessment but not directly in the epidemiological study [15]. In the area of Teesside , abundant routinely available air quality data, *"reflecting long standing concerns about air pollution there,"* [13] were used to check the validity of the selection of study areas based on residential proximity to industry as a proxy for exposure [13].

3.2. Morbidity. Studies on morbidity are detailed in Table 3. Again, there is a great diversity of the industries involved in the studies, similar to those described for cancer.

3.2.1. Reasons for Performing Studies on Morbidity. Concern was a major motivation quoted by 12 studies [1, 12, 35, 36, 38, 41, 46, 48, 51, 54, 57]. For instance, Bhopal et al. stated that *"one of the major concerns among the residents* [⋯] *was an apparent increase in the incidence of asthma in the area"* [12]. Reference to previous studies showing over-incidences of cancer, mortality or asthma are also quoted by 11 studies [37, 40, 42, 45, 48, 49, 52, 53, 56]. For instance, in the area investigated by Halliday et al., *"the prevalence of childhood asthma* [⋯] *was approximately twice that of a control area* [⋯]*"* [42]. One study mentioned that an acute episode had severe impacts, resulting in hospitalizations [57].

3.2.2. Health Outcome and Type of Studies Investigating Morbidity. A majority of the studies focused on the respiratory health of children (17 studies), using questionnaires specifically defined for the study or standardized questionnaires such as the ISAAC questionnaire from the International Study of Asthma and Allergies in Childhood [39, 45, 47, 54], or the questionnaire from the American Thoracic Society (ATS) [40, 43]. Few studies used additional data from general practitioners (GPs) [12, 13, 49, 59]. Studies involved from 200 to 500 children [41, 43, 47] to more than 3000 children [59]. 6,399 adults were also interviewed in Teesside [12], while in India the respiratory health of 2573 women was investigated [38]. Several studies also involved measurements of the lung function. One study in Thailand investigated short-term memory dysfunction in children through questionnaires [57] (Table 3). One study focused on odor annoyance, based on the observation that *"odors from industrial sources, such as the petrochemical plants in Sarnia, have been shown to considerably impact general health and well-being by affecting both the physiological and psychosocial status of people"* [58].

3.2.3. Type of Studies Investigating Morbidity. Two studies were intervention studies. Câra et al. compared GPs information on the respiratory health of 874 children for two periods: when the industry was operating and after its closure [49]. Stenlund et al. investigated the influence of a measure taken to reduce air pollution (predominantly dust and soot) on perceived pollution, risk perception, annoyance, and health symptoms through interviews of 684 people [46].

Five studies used an ecological approach to study standard rates ratio based on hospital admissions or disease incidence. Two studies quantified the relationship between symptoms and measurements through a time-series analysis [12] and a case-cross over analysis [52].

3.2.4. Exposure Assessment in the Studies Investigating Morbidity. Participants of the cross-sectional surveys were selected based on their city of residence (or school), and distance was again the preferred method to define the exposed versus nonexposed cities. In most studies, a finer exposure assessment was performed for the participants, based on information collected through the questionnaires, modeling, or measurements. When measurements were available, they were not always used to assess exposure. For instance, Moraes et al. mentioned that concentrations were available for several pollutants (PM, NOx; SO_2, O_3, benzene, toluene, and xylenes) but used them for descriptive purposes only (in comparison to the World Health Organization air quality standards) [47].

Table 3: Studies investigating morbidity.

Reference	Country	Industrial background	Health outcome	Epidemiological design	Exposure assessment
Fung et al., 2007 [35]	Canada	Sarnia "Chemical Valley"	All hospital admissions, admissions with a primary diagnosis of respiratory diseases and cardiovascular diseases	Standardized admissions ratio	Comparison of three cities, annual averages of SO_2, NO_2, and O_3
Pascal et al., 2011 [1]	France	Oil refining, oil storage, petrochemical and organic chemical activities, chlorine chemistry, steel and metal working, chemical plants, waste incineration plant, port	Hospitalisations for cardiovascular and respiratory diseases	Poisson regression models	Coupling of a dispersion model (ADMS4), a meteorological model and kriging to assess the SO_2 levels
Kosatsky et al., 2004 [36]	Canada	industrial area in Montreal	Hospitalisations for cardiovascular and respiratory diseases	Standardised admissions rates	O_3, NO_x, SO_2, and PM measurements
Bhopal et al., 1994 [12] Bhopal et al., 1998 [13]	United Kingdom	Coke ovens (66 from 1980)	GPs activity: data on consultations, chronic conditions, hospital admissions, and current drug treatments. Lung function, Self-reported respiratory, and nonrespiratory health including asthma	Age and sex standardised rates and ratios, questionnaires (6399 adults, 1888 children) time series	Perceived exposure areas (criteria not specified), modeled exposure (model not specified) 24-hour mean daily measures of SO_2 and smoke over 56 months (1987–91)
Aylin et al., 2001 [37]	United Kingdom	Coke works	Hospital admissions for respiratory and cardiovascular diseases	Standardised admissions rates	Distance (7.5 km)
Patel et al., 2008 [38]	India	Vapi industrial area, dyes, chemical plants	Respiratory health, lung function	Questionnaires (2, 573 women)	Distance (<2 km, 2-3 km, 3-4 km, and farther)
De Marco et al., 2010 [39]	Italy	Largest chipboard industrial park	Respiratory and skin diseases	Questionnaires (ISAAC (1998), ECRHS (2002), SIDRIA, MM040NA and MM080 standardized questionnaires, 3854 children)	Distance (no wood factories <2 km from home and school ("unexposed" group) at least 1 low emission factory (but no chipboard industries) <2 km from home or school (group "at low exposure"), at least 1 chipboard industry <2 km from home or school (group "at high exposure")
Dubnov et al., 2007 [40]	Israel	Major coal-fired power station	Health status, pulmonary function tests (PFT), forced vital capacity (FVC) and forced expiratory volume during the first second (FEV1)	Questionnaires (ATS and National Heart and Lung Institute) (1492 children)	$NO_x * SO_2$ during acute episodes (NO_x and SO_2 measurements above 0.125 and 0.070 ppm, respectively, during 30 mn), based on a map interpolated from 12 monitoring stations
Ginns and Gatrell, 1996 [41]	United Kingdom	Cement works	Respiratory health	Questionnaire (362 children)	Distance (near the industry versus area 9 to 19 km away)

Table 3: Continued.

Reference	Country	Industrial background	Health outcome	Epidemiological design	Exposure assessment
Halliday et al., 1993 [42]	Australia	Power stations	Asthma, general symptoms, measurement of lung function, bronchial reactivity, and skin test atopy was	Questionnaire (851 children)	Distance (near the industry versus area 40 km away)
Peled et al., 2005 [43]	Israel	2 power plants	Health status, lung function (peak expiratory flow)	Nested cohort study (285 children), questionnaire based on the American Thoracic Society's (ATS) ATS-DLD-78	PM10 and PM2.5 daily measurements at 6 stations
Pignato et al., 2004 [44]	Italy	Petrochemical industries and oil refineries	Self-reported asthma, asthma-like symptoms, and allergic rhinitis	Questionnaires (1180 children)	Annual mean NO_2 measurements
Rusconi et al., 2011 [45]	Italy	Biggest high complexity refinery in the Mediterranean Sea and largest European liquid fuel gasification plant	Asthma, respiratory symptoms in children, FENO, and lung function measurements	Questionnaires (ISAAC)	Measurement of weekly concentrations of SO_2, benzene, NO_2, O_3
Stenlund et al., 2009 [46]	Sweden	Steel industry	Self-reported health symptoms bronchitis- and asthma-like, and neurasthenic	Interventional, population-based questionnaire study (684 adults)	distance (two areas relatively close and relatively distant)
De Moraes et al., 2010 [47]	Brazil	Petrochemical complex	Wheezing	Questionnaires (ISAAC) (209 children)	Cities in a 5-kilometer radius, communities established downwind of the petrochemical complex and thus, under greater influence of its dispersion plume (A, B, C), were classified as "exposed communities" (ECs) Those upwind of the plant and thus less exposed to its dispersion plume (D, E) were used as reference communities (RCs)
Jadsri et al., 2006 [48]	Thailand	50 chemical industries	Respiratory diseases	Spatial regression analysis	Dispersion of SO_2, NO_x, and TSP
Câra et al., 2007 [49]	Romania	Iron, steel, and coke factory	Wheezing	Comparison of two periods before and after the closure of the factory (GPs information for 874 children)	Distance (near the industry and 10 km away)
Pless-Mulloli et al., 2000 [50] Pless-Mulloli et al., 2001 [51]	United Kingdom	Opencast coal mining sites	Respiratory illnesses	Questionnaires (3216 children) and GPs records (2442 records)	Distance (5 cities near industries and 5 referent cities further away)

Table 3: Continued.

Reference	Country	Industrial background	Health outcome	Epidemiological design	Exposure assessment
Smargiassi et al., 2009 [52]	Canada	Refinery	Emergency visits and hospital admissions for asthma in children	time stratified case-crossover	Distance (0.5–7.5 km) and daily SO_2 measurements, at-home estimates of daily exposure based on a dispersion model (AERMOD)
Howel et al., 2001 [53]	United Kingdom	Opencast coal mines	Respiratory health	GP data, respiratory events (2442)	Distance, PM10 measurements
White et al., 2009 [54]	South Africa	Petrochemical refinery	Respiratory health	Questionnaire (ISAAC) (2361 children)	Distance, wind direction, and speed
Wichmann et al., 2009 [55]	Argentina	Petrochemical industries	Respiratory health, lung function (standard spirometry)	Questionnaires (1191 children)	Distance, near petrochemical industries, near heavy roads, and 2 relatively nonpolluted areas, PM and VOCs measurements
Yogev-Baggio et al., 2010[56]	Israel	Coal-fired power plant	Respiratory health, lung function (forced expiratory volume)	Questionnaires (1181 children)	$NO_x * SO_2$ during acute episodes (NO_x and SO_2 measurements above 0.125 and 0.070 ppm, respectively, during 30 mn), based on a map interpolated from 12 monitoring stations
Aungudornpukdee et al., 2010 [57]	Thailand	15 chemical industries	short-term memory dysfunction	Weschsler intelligence scale for children, questionnaires (2955 children)	Distance to major air pollution sources (industries, roads, etc.)
Atari et al., 2009 [58]	Canada	Sarnia "Chemical Valley"	General health status, odour annoyance	Telephone interviews (804)	Land use regression (LUR) modeling based on SO_2 and NO_2 measurements

White et al. reported that they did not have the budget for a model and that concentration and emissions data were missing. Therefore, they add that they rely on a meteorologically estimated exposure index based on wind direction and speed [54]. Aylin et al. also explained that they had to use distance because input data for the dispersion modeling were missing [37].

Fung et al. selected the participating cities based on the annual averages of SO_2, NO_2, and O_3 and mentioned that the reference area *"is polluted but considered 'clean' compared to the two more polluted other cities*" [35].

Pless-Mulloli et al. proposed two indicators to characterize the long-term versus short-term exposure: short-term exposure was assessed through PM_{10} measurements, and long-term exposure was defined as living near an active site [59]. Regarding short-term, acute exposure, Dubnov et al. developed a complex indicator for episodes when NOx and SO_2 concentrations were high. For each episode, they computed an integrated concentration value (ICV) as NOx multiplied by SO_2 summarized the results over the entire study period (3 years) [40].

One study compared the associations between emergency department visits and SO_2 concentrations obtained from fixed monitors and from an air dispersion modeling and found some differences increasing with the distance [53].

3.2.5. Mortality (from Other Causes Than Cancer). Studies on mortality are detailed in Table 4. They were all geographical ecological studies, distance being used as the exposure indicator except in one study relying on SO_2 dispersion modeling [60]. Sarov et al. investigated perinatal mortality and used odors complaints to define the distance [61]. One study was multicentric, focusing on 10 coke works operating in England and listed in the Coke Oven Managers Association [62].

Table 4: Studies investigating mortality.

Reference	Country	Industrial background	Health outcome	Epidemiological design	Exposure assessment
Hodgson et al., 2007 [60]	United Kingdom	Runcorn: chlor alkali plant, power stations	Mortality from renal diseases	Standardised mortality ratio	Dispersion of mercury (ADMS)
Hodgson et al., 2004 [63]	United Kingdom	Runcorn: chlor alkali plant, power stations	Mortality, hospital admissions for kidney diseases	Standardised mortality ratio, standardized admissions rate	Distance
Dolk et al., 1999 [62]	United Kingdom	Coke work	Mortality for cardiovascular and respiratory causes	Standardised mortality ratio	Distance (2 km, 7.5 km, bands of 0.5, 1, 2, 3, 4.6, 5.7, 6.7, and 7.5 km).
Triolo et al., 2008 [64]	Italy	Industrial settlement	Mortality (all causes, cancers, cardiovascular, respiratory, diabetes, injuries, etc.)	Standardised mortality ratio	Distance: 3 concentric zones of 5 km around the industries, dispersion model (CMPM98) for SO_2, O_3, and SO_2 measurements
Cambra et al., 2011 [24]	Spain	284 industries declaring the EPER emissions of pollutants	Mortality all causes, ischaemic heart disease, cerebrovascular diseases, chronic lower respiratory tract diseases	Standardised mortality ratio	Distance (<2 km, >2 km).
Sarov et al., 2008 [61]	Israel	17 plants: chemical, pharmacochemical, and heavy industry	Perinatal mortality	Standardised mortality ratio	Distance up to 20 km based on odors complaints
Bhopal et al., 1994 [12] Bhopal et al., 1998 [13]	United Kingdom	Coke ovens (66 from 1980)	Mortality	Age and sex standardised rates and ratios, Questionnaires (6399 adults, 1888 children) Time series	Perceived exposure areas (criteria not specified), modeled exposure (model not specified) 24 hour mean daily measures of SO_2 and smoke over 56 months (1987–91)

3.3. Birth Outcome

3.3.1. Reasons for Performing Studies on Birth Outcome. Studies are summarized in Table 5. Seven studies on birth outcomes were identified, with three focusing on the same petrochemical area in Taiwan [28, 65, 66]. The main sites were those already investigated for other health issues, such as Teesside . Again, concerns of the population were the main reason for investigation in the studies focusing on a single area [12, 13, 67], while results from the literature and etiology were the reasons for the three multicenter studies [68–70]. In Taiwan, studies were justified on observed excess cancer mortality among women [28, 71].

3.3.2. Type of Studies and Exposure Assessment in the Studies Investigating Birth Outcome. The health outcomes and the study design were various. Exposure assessment was poorly described compared to papers dealing with cancer or morbidity. Distance was the method used by all the studies but one [12], although extensive measurements were available in some sites, like in Israel, for instance [67]. In that case, the measurements and the wind rose were used to validate the choice of the distance, resulting in a large exposed area, up to 20 km. By contrast, in the multicenter study in Texas, proximity to industrial sites was defined at 1 mile or less [69].

3.4. Mental Health. Three studies investigated mental health, psychological distress [72, 73], and one study investigated perceived pollution, perceived health and stigma [74]. All relied on postal questionnaires that may be complemented by a smaller number of semistructured face-to-face interviews [74]. For instance, the study by Bush et al. involved 5000 questionnaires and semi-structures in-depth interviews with 41 respondents. Participants were located in three areas distant to the site (1.5, 7, and 8 km) (Table 7).

3.4.1. Reasons for Performing Studies on Mental Health and Perceived Health. The local background and concerns of the population were not the main motivation in the two studies in the United States based on industrial registries [72, 73]. On the contrary, population concern was a major issue in the study on Teesside [74], as stated by Bush et al., "*a place stigmatized not only for its heavy industry (technological stigma) but also on the basis of air pollution and poor health*" [74].

3.4.2. Exposure Assessment for Performing Studies on Mental Health and Perceived Health. Two studies investigated the psychological distress of the population in relation to their proximity to industries registered in the Toxic Release Inventory through questionnaires. In these studies, the main

Table 5: Studies investigating birth outcome.

Reference	Country	Industries	Health outcome	Method	Exposure assessment
Bhopal et al., 1994 [12]	United Kingdom	Teeside	Sex ratio, birthweights, and stillbirths	Sex ratio	Perceived exposure areas (criteria not specified), modeled exposure (model not specified)
Bentov et al., 2006 [67]	Israel	17 chemical facilities	Major congenital malformations of the central nervous system	Standardized incidence ratio	Distance (exposed < 20 km), wind direction
Brender et al., 2006 [68]	United States	113 industries in the Texas National Priority Listing (NPL) sites	Oral clefts	Logistic regression	Distances (proximity ≤ 1 mile)
Brender et al., 2008 [70]	United States	113 industries in the Texas National Priority Listing (NPL) sites	Chromosomal anomalies	Case control (2099 cases, 4368 controls)	Distances (proximity ≤ 1 mile)
Yang et al., 2000 [28]	Taiwan	Kaohsiung oil refineries	Sex ratios	Standardized sex ratio	Distance (all municipalities in the area)
Yang et al., 2002 [71]	Taiwan	Kaohsiung oil refineries	Preterm delivery	Logistic regression model	Distance (at least 50% population or 50% area falling within a distance of 3 km from any one of the three complexes)
Yang et al., 2004 [65]	Taiwan	Kaohsiung oil refineries	Preterm delivery	Logistic regression model	Distance (at least 50% population or 50% area falling within a distance of 3 km from any one of the three complexes)

Table 6: Biomonitoring studies.

Reference	Country	Industry	Biomarkers	*N* cases
Barregard et al., 2006 [75]	Italy and Sweden	Chlor alkali plants	Urinary mercury	193
Rusconi et al., 2011 [45]	Italy	Biggest high complexity refinery in the Mediterranean Sea and largest European liquid fuel gasification plant	MDA-dG adducts	54
Choi et al., 2000 [76]	Korea	Large-scale petrochemical industrial complex	Benzene in blood, metabolites of benzene in urine	115
Pless-Mulloli et al., 2005 [77]	United Kingdom	Teesside	Polychlorinated dibenzo-p-dioxins, furans, and polychlorinated biphenyls in blood	40
Thomas et al., 2009 [78]	United Kingdom	Large smelter lead/zinc smelter	Cadmium in urine	180
Sala et al., 1999 [79]	Spain	Organochlorine compound factory	Organochloring in blood	608
Stroh et al., 2009 [80]	Sweden	Lead smelters	Lead in blood	3879
Williamson et al., 2006 [81]	United States	Six superfund sites	Serum Immunoglobulins	3916
Thomas et al., 2009 [78]	United Kingdom	Large smelter lead/zinc smelter	Cadmium in urine	180

assumption is not that an over-exposure to air pollutants can create adverse psychological effects, but that *"proximity to industrial activity is psychologically harmful because many individuals perceive industrial activity negatively, as a potential health threat or a sign of neighborhood disorder"* [73]. Therefore, exposure was defined based on distance, taking into account the volumes of the emissions as a proxy for facility size and visibility. The authors made the assumption that *"industrial facilities are not likely to impact residents' mental health if residents are unaware of them"* [72]. They propose a method to compute a potential visual exposure to industrial activity for each resident [72, 73].

3.5. Biomonitoring. Nine biomonitoring studies were reviewed. In none, even the one based in Teesside [77], concern of the population was mentioned as a motivation for the

Table 7: Studies investigating mental health.

Reference	Country	Industries	Health Outcome	Method	Exposure assessment
Bush et al., 2001 [74]	United Kingdom	Teeside	Stigma	5000 questionnaires + 41 interviews	Distance (three areas at 1.5, 7, and 8 km)
Downey and Van Willigen, 2005 [73]	United States	Industries in the Toxic Release Inventory	Psychological distress (depression), perceived disorders	1210 questionnaires	Distance, visual exposure
Boardman et al., 2008 [72]	United States	Industries in the Toxic Release Inventory	psychological distress (K6 scale)	1139 questionnaires	Distance, visual exposure

study. Participants were always recruited based on their residency in a city close to the industry. Additional data were usually collected to refine the exposure assessment of each participants for instance, near chlor alkali plant in Sweden and Italy, measurements of total gaseous mercury and a dispersion model (Transport Air Pollution Model (TAPM)) were used to assess the exposure at residence (Table 6) [75].

3.6. Results Described in the Studies. Discussing the results of the studies was not the objective of this literature review. However, it was interesting to note that when studying cancer, very few results were statistically significant, although several studies concluded on a gradient of risk following the exposure gradient [4, 19–21]. The risks estimated by the multicenter studies were also statistically nonsignificant, although significant risks may be found when a subanalysis of the study focuses on a single industry [18] or a subgroup of industries [23, 24].

Morbidity, and especially less severe outcomes such as respiratory symptoms, eyes symptoms or consultations to the general practitioners tended to increase with exposure [35, 39, 40, 42–45, 53–56, 62]. Similar results were found for hospitalizations for respiratory and cardiovascular causes [1, 34, 36, 52].

In the studies of declared health, complaints about odors or dust were correlated with the discomfort, in some cases positively [58] but also negatively [46]. The populations declaring a bad health status were not always the more exposed [13]. All studies on mental health underlined the influence of living near major industrial sites on psychological distress [72–74].

4. Discussion

4.1. Limits of the Literature Review. Epidemiological studies investigating the impacts of air pollution produced by major industrial sources are scarce, as only 77 papers were found in this review. They correspond to a wide range of industrial activities. However, our search is likely to be incomplete, and the limits of this search are probably the largest on the biomonitoring studies and the mental health studies, as we did not included these as explicit key words in the search.

However, given that the papers we included in the review were written by different teams, in different areas and at different periods, we are still confident that it can give a good overview of the practices in the field. Yet, it has to be noted that several papers were produced by the same team and/or part larger initiatives on industrial pollution, which may limit the diversity of practices reported. We also included two reports from the grey literature in the review [1, 36], but there are probably many unpublished work on the health status around industrial areas. For instance, Bentov et al. performed a study on the congenital malformation of a large industrial estate in Israel, explaining that their study was "*initiated by the Israel Ministry of Health, following complaints of residents of surrounding localities who blame the IP emissions for the odor nuisance and suspect that possible long- or short-term health disorders could be attributed to this exposure*" [67]. It is likely that other health outcomes have been investigated given the context, yet no paper was found on that area. Similarly, Rusconi et al. mentioned that an excess of respiratory symptoms in children was observed in the Sarroch region, near a major petrochemical area, referring to *"unpublished data"* [45].

Several reasons may explain the low number of publications; few epidemiological studies may be performed because of the complexity of collecting health and exposure data or because quantitative risk assessment is extensively used to study industrial pollution. There may also be a publication bias, with studies showing no link between exposure and health not being published.

4.2. Site Selection and Studies Justification. In many of the cases, the studies are justified by a concern from the population; that is, epidemiology is used to test the hypothesis made by the population that the industries impair their health. It is also used to investigate areas where an overincidence of a health outcome had been previously observed. There are few initiatives to identify the health effects of a given industry independently of the local context, and these initiatives are mostly multicenter studies based on industrial registries indeed, whatever the topic (cancer, mental health, etc).

In summary, the multicenter studies based on industrial registries are not taking into account the local context to select the areas under investigation, while mostly all others studies do. Therefore, there is likely to be a bias in site selection where to perform epidemiological studies, based on the existence of a local social mobilization. It would be interesting to understand why in some areas industries raised high concerns and lead to epidemiological studies, while in others there is such social mobilization, and if these reasons may result in biases in the result of the studies. On

the other hand, it is essential to answer the population concerns, and, as stated by Ginns et al., *"the kind of epidemiological study we have conducted regards local concerns and beliefs as a 'nuisance', the effect of an already sensitized population and an 'obstacle to scientific enquiry' that seeks to uncover 'real' health effects. A more socially informed epidemiology, however, would wish to give lay beliefs some prominence, to regard local concerns as data that are as valid as those derived from more formal questionnaires such as that used in the present study"*. A similar conclusion was reached by Phillimore on Teesside , showing that concern is an obstacle for epidemiology, especially when using questionnaires, as it introduces a bias in the population answer. But concern is also seen as an important issue by social scientists, including its possible health consequences [82, 83]. It is also interesting to note that several authors of the papers on mental health in these reviews are affiliated to social sciences department and that the papers were not published in epidemiological journals [72–74]. This calls for a broadening of the competency when answering the populations concerns near major industrial sites, that is, including a social sciences dimension in the analysis and not underestimating the influences of the industry and of its designation as a possible danger on the stress and well-being of the population.

4.3. Multicenter Studies. Multicentric design is believed to be a solution to the local biases, as the influence of the confounding factors may decrease as the number of sites increases [84]. However, it is difficult to identify relevant sites that could be included in the same studies. In the literature, the choices to aggregate industries based on large classes may hide differences linked to the industrial processes used, the size of the plant, its operating time, and so forth. Yet, multicenter studies may not fully answer the local concerns, and as Ramis stated, "*each industrial source has its own characteristics, and subsequent studies will therefore have to address these on a case-by-case basis*" [23].

4.4. Exposure Assessment. Independently of the health outcome and the statistical design used, the lack of information on the environmental and industrial background of the sites is striking in many papers. A major issue is raised by the exposure assessment. As industrial sites emit a complex mixture of pollutants, with plumes varying in composition and over time and space, epidemiologists have to rely on measurements and modeling of a subset of pollutants to assess an integrated exposure. Modeling is seen as the most efficient tool to avoid exposure misclassification. In Teesside, environmental data, land-use data, historical data, and data on the perception of air pollution and odors were analyzed to check that the distance to the site was an interesting proxy. Globally, measurements did not show large differences between exposed and nonexposed areas, but the dispersion models confirmed a gradient of pollution with distance [50]. However, environmental data and modeling are not easily accessed, especially when investigating past exposures. Indeed, several authors mentioned that emissions data were not available to perform a dispersion modeling or that they could not afford the cost of such modeling. Some authors underline that some environmental data collected for regulatory purposes are not usable for epidemiological studies [16].

This lack of environmental data is a major obstacle. It is striking to see that in many areas the population is highly concerned by the environmental pollution and its consequences, and that these concerns are answered through complex epidemiological studies, relying on poor environmental data. In short, there is a discrepancy between the expectancies of the population, the investment in collecting and analyzing health data, and the poor accessibility to key emissions and concentrations data.

When distance is the only possible choice, Hodgson et al. advised to integrate knowledge of the factors that drive exposure, for example relative emissions, and wind direction [85]. Interestingly, odors are mentioned by several authors as an issue, but data are used to define the exposure area (e.g. [61]) and not to investigate a possible health impact.

The bias in exposure assessment and the ecological bias are likely to limit the possibility of ecological studies to reveal low relative risks with statistically significant results, especially when studying cancer with a latency of several decades. Leukemia may be the only cancer for which the latency is a priori short enough to allow a good reconstruction of exposure based on present data.

4.5. Ways Forward. A combination of multicentric studies and local studies could be efficient ways to increase knowledge on the health effects of industrial areas and answer the concerns from the population. As stated below, multicenter studies would limit local biases, and sites would not be selected based on an a priori population concern or over incidence. However, criteria to decide that sites are similar enough to be included in a multicenter study need to be defined. A focus on sites where the population requests more information could then be performed, with the support of social scientists.

These studies could be performed on several health issues and with several designs. An investigation of the mental health impacts would be highly relevant, as this issue seems to have been poorly taken into account by epidemiologists so far.

For the multicenter and the local studies, a better characterization of exposure would be an asset to improve our capacity to investigate the impacts of industrial pollution. It requires improving the availability of emission data and of monitoring data.

Finally, intervention studies documenting the possible improvements of the health status of the population after the closure of a plant, or a change in the industrial processes, would be highly informative to improve the knowledge and to help for management (a change in the industrial processes that have been shown to have positive effect in the environment and the health status could be reproduced elsewhere).

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