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’étang 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, mutiexposure 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 populations 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 epidemiology* 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            | 0         | 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)

| Total number of studies |
|-------------------------|
| 27                     |

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
| 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 (3 km radius from the geographic centroid of any of the four petrochemical complexes) |
| Yu et al., 2006 [6]  | Taiwan     | Oil refinery                                                                           | Leukemia                         | Case control (171 cases and 410 controls) | Distance (0.5 miles, 1 mile, and 2 miles)                                             |
| Simonsen et al., 2010 [7] | United States | Petrochemical industries                                                               | Lung cancer (registry)           | Case control (455 cases and 437 controls) | Distance, guided by a validation study using data from historical records             |
| 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, based on measurements of sulfuric acid and the prevailing wind (6 km)     |
| 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                                                                            |
| 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 SO2 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 |
| Reference          | Country       | Industrial background | Health outcome                      | Epidemiological design | Exposure assessment                                                                 |
|--------------------|---------------|-----------------------|-------------------------------------|------------------------|--------------------------------------------------------------------------------------|
| Bhopal et al., 1994 [12] | United Kingdom | Coke ovens (66 from 1980) | Cancer (registry)                  | Standardised incidence ratio | Specified exposure (model not specified) 24-hour mean daily measures of SO₂ and smoke over 56 months (1987–91) |
| Bhopal et al., 1998 [13] |               |                       |                                     |                        |                                                                                      |
| Wilkinson et al., United Kingdom 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., Sweden 2010 [15] |           | Industrial complex including a large cracker producing ethylene and propene, Petroleum refineries, oil-fired power plant, and several large petrochemical, chemical, and agrochemical industries | 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., Israel 2010 [16] |              | Lung cancer, bladder cancer, and non-Hodgkin’s lymphoma | Standardised incidence ratio | | Spatial interpolation of SO₂ and PM10 routine monitoring data |
| Schechter et al., Canada 1989 [17] |             | Two natural gas refineries | Cancer (registry) | Standardised incidence ratio | | |
| Monge-Corella et al., 2008 [18] | Spain        | 18 EPER-registered paper, pulp, and board industries | Lung cancer (mortality) | Standardised incidence ratio | | |
| Pless-Mulloli et al., United Kingdom 1998 [19] |                     | Teeside | Lung cancer (mortality) | Standardised mortality ratio | Distance (0.1–2.7 km, 1.5–4 km, and farther) |
| García-Pérez et al., Spain 2010 [20] |               | 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., Spain 2009 [21] |               | 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., Spain 2010 [22] |               | 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 |
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\textsubscript{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 SO₂, 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 SO₂ and PM₁₀ [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 Stenlundet al. in Sweden, models (unspecified) of ethylene levels based on the emissions of year 2000 were used to classify a low level zone, which had operated and the degradation speed in soils provided a cumulative ground-level concentrations since the start of the activity [31].

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 [39]. 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. Cára 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; SO₂, O₃, 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  | 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 $O_3$               |
| Pascalet al., 2011 | 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 | Canada      | Industrial area in Montreal | Hospitalisations for cardiovascular and respiratory diseases | Standardised admissions rates | $O_3$, $NO_2$, $SO_2$, and PM measurements                                              |
| Bhopal et al., 1994 | United Kingdom | Coke ovens (66 from 1980) | Health status, pulmonary function tests (PFT), forced vital capacity (FVC) and forced expiratory volume during the first second (FEV1) | Questionnaires (ISAC (1998), ECRHS (2002), SIDRIA, MM040NA and MM080 standardized questionnaires, 3854 children) | Questionnaires (ATS and National Heart and Lung Institute) (1492 children)                        |
| Aylin et al., 2001  | United Kingdom | Coke works             | Hospitalisations for cardiovascular and respiratory diseases | Standardised admissions rates | Distance (7.5 km)                                                                     |
| Patel et al., 2008  | 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 | Italy         | Largest chipboard industrial park | Respiratory and skin diseases | Questionnaires (ISAC (1998), ECRHS (2002), SIDRIA, MM040NA and MM080 standardized questionnaires, 3854 children) | Questionnaires (ATS and National Heart and Lung Institute) (1492 children)                        |
| Dubnov et al., 2007 | 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) | Questionnaires (ATS and National Heart and Lung Institute) (1492 children)                        |
| Ginns and Gatrell, 1996 | 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 (180 children)                                                            | Annual mean NO₂ measurements                                                           |
| Rusconi et al., 2011 [45]  | Italy         | Petrochemical industries and oil refineries | Asthma, respiratory symptoms in children, FENO, and lung function measurements  | Questionnaires (ISAAC)                                                                   | Measurement of weekly concentrations of SO₂, benzene, NO₂, O₃                           |
| 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 Comparison of two periods before and after the closure of the factory (GP’s information for 874 children) | Dispersion of SO₂, NOₓ, and TSP                                                        |
| Căra et al., 2007 [49]     | Romania       | Iron, steel, and coke factory | Wheezing                                                                         | Distance (near the industry and 10 km away)                                             |                                                                                       |
| Pless-Mulloli et al., 2000 [50] | United Kingdom | Open cast coal mining sites | Respiratory illnesses                                                              | Questionnaires (3216 children) and GP’s records (2442 records)                           | Distance (5 cities near industries and 5 referent cities further away)                |
| Pless-Mulloli et al., 2001 [51] | United Kingdom | Open cast coal mining sites | Respiratory illnesses                                                              | Questionnaires (3216 children) and GP’s 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            | Weschler 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 NO$_x$ and SO$_2$ concentrations were high. For each episode, they computed an integrated concentration value (ICV) as NO$_x$ 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). Distance: 3 concentric zones of 5 km around the industries, dispersion model (CMPPM98) for SO2, O3, and SO2 measurements |
| Triolo et al., 2008 [64] | Italy         | Industrial settlement | Mortality (all causes, cancers, cardiovascular, respiratory, diabetes, injuries, etc.) | Standardised mortality ratio              | Distance (2 km, >2 km)               |
| 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 up to 20 km based on odors complaints |
| Sarov et al., 2008 [61]  | Israel        | 17 plants: chemical, pharmachemical, and heavy industry | Perinatal mortality                                   | Standardised mortality ratio              | Perceived exposure areas (criteria not specified), modeled exposure (model not specified) 24 hour mean daily measures of SO2 and smoke over 56 months (1987–91) |
| Bhopal et al., 1994 [12] | United Kingdom | Coke ovens (66 from 1980) | Mortality                                             | Age and sex standardised rates and ratios, Questionnaires (6399 adults, 1888 children) Time series |                                    |
| Bhopal et al., 1998 [13] | United Kingdom | Cookevens (66 from 1980) | Mortality                                             | Age and sex standardised rates and ratios, Questionnaires (6399 adults, 1888 children) Time series |                                    |

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 registred in the Toxic Release Inventory through questionnaires. In these studies, the main
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

| Reference | Country | Industry | Biomarkers | N cases |
|-----------|---------|----------|------------|---------|
| Barregard et al., 2006 [75] | Italy and Sweden | Chlor alkali plants, Biggest high complexity refinery in the Mediterranean Sea and largest European liquid fuel gasification plant | Urinary mercury | 193 |
| Rusconi et al., 2011 [45] | Italy | | MDA-dG adducts | 54 |
| Choi et al., 2000 [76] | Korea | Large-scale petrochemical industrial complex | Benzene in blood, metabolites of benzene in urine, Polychlorinated dibenzo-p-dioxins, furans, and polychlorinated biphenyls in blood | 115 |
| Pless-Mulloli et al., 2005 [77] | United Kingdom | Teesside | | 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 | Organochlorine 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 |
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 participant 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 Ginn 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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