

METHODS

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Our literature review was carried out in PubMed selecting English and Italian articles regarding human studies which were published between 2011 and 2016, maintaining the conceptual framework of SENTIERI methodology and continuing the evaluation of the epidemiological evidence performed by Pirastu et al.²⁷

The PubMed search term were:

■ **for environmental exposures:** [(residence OR municipality OR mines OR industry OR facilities OR estates OR landfill OR incinerator OR waste OR natural gas OR shale gas OR chemical OR harbor OR asbestos OR power plant) AND (“congenital anomalies” OR “congenital malformations” OR “birth defects” OR “birth outcomes”)];

■ **for individual exposure:** [(tobacco smoke pollution OR smoking OR alcohol drinking OR “alcohol consumption” OR occupational diseases OR occupations OR job OR workplace OR “work place” OR “work location” OR worksite OR “work site” OR jobsite OR “job site” OR socioeconomic factors OR “health status disparities” OR “standard of living” OR “living standard” OR inequality OR inequalities OR air pollution OR air pollutants OR “particulate matter” OR gases OR urban pollution) AND (“congenital malformation” OR “congenital malformations” OR “congenital anomaly” OR “congenital anomalies” OR “congenital defect” OR “congenital defects” OR “birth defect” OR “birth defects” OR “malformative syndrome” OR “malformative syndromes” OR congenital abnormalities OR deformity OR deformities) AND (birth OR parturition OR delivery OR pregnancy OR pregnancy outcome OR birth certificate OR prenatal OR perinatal OR “maternal exposure” OR “paternal exposure”)].

From our initial literature search, we selected 1,566 papers. The abstracts were screened by two researchers to identify potentially relevant articles to be included according to the objective of the present working paper. The identified full papers were reviewed by all the authors and only systematic reviews, meta-analyses, and observational epidemiological studies with cohort, case-control, cross-sectional, and ecological design, which reported estimates of association between the outcome (CAs) and at least one of

the risk factors of interest, were included in the present review. According to the SENTIERI methodology,²⁷ the environmental sources of exposure were divided into four macroclasses:

1. industries (refineries, petrochemicals, and metals);
2. mines;
3. landfills;
4. incinerators.

The considered individual exposures were:

- cigarette smoke (active and passive);
- alcohol consumption;
- socioeconomic status (SES);
- occupational exposure;
- air pollution.

To evaluate the evidence of the collected epidemiological literature, we applied the criteria developed by SENTIERI Working Group (WG),²⁷ which identified a hierarchy in the literature sources to classify each combination of outcome and exposure in terms of strength of association. According to the international consensus of the epidemiological community, SENTIERI WG classified the literature sources in **primary sources** (which express evaluations based on standardized criteria), and in **other sources**, such as quantitative meta-analyses, systematic reviews, multicentre studies, and singular studies. Therefore, for the evidence assessment, the SENTIERI WG criteria firstly favoured primary sources and quantitative meta-analysis and, secondly, consistency among sources. The evaluation of the epidemiological evidence for the association between outcome and exposure has been classified into three categories, as synthesized in table 1: • sufficient; • limited; • inadequate. The lack of an indication of the category implies the lack of epidemiological data on the association between outcome and risk factor both in primary sources and in quantitative meta-analyses, reviews, multicentre studies, or observational studies.

In our review, in the assessment of the epidemiological evidence, we took into account also the results of the evaluation performed by Pirastu et al. 2010.²⁷

TYPE OF EVIDENCE	CHARACTERISTICS
<p>SUFFICIENT sufficient to infer the presence of a causal association</p>	<p>One or more of the primary sources report the evaluation of sufficient evidence of a causal association or provide data for this evaluation</p> <p>OR</p> <p>metanalyses provide quantitative data for the evaluation of sufficient evidence of a causal association</p>
<p>LIMITED limited but not sufficient to infer the presence of a causal association</p>	<p>one or more primary sources / metaanalysis / reviews / multicentre studies / two or more studies report the existence of an association, but do not express the evaluation of sufficient evidence of a causal association or do not provide data for this evaluation</p>
<p>INADEQUATE inadequate to infer the presence or the absence of a causal association</p>	<p>several primary sources examine the association, but do not agree on the evaluation (conflicting evidence)</p> <p>OR</p> <p>quantitative metanalyses / reviews / multicentre studies / two or more studies examine the association, but do not agree on the evaluation (conflicting evidence)</p> <p>OR</p> <p>primary sources / quantitative metanalyses / reviews / multicentre studies / two or more studies examine the association, but none reports its existence</p> <p>OR</p> <p>several studies which do not agree on the evaluation are available (conflicting evidence)</p> <p>OR</p> <p>only one study investigating the association is available</p>

Table 1. Evaluation of the epidemiological evidence by Pirastu et al. 2010.²⁷

Tabella 1. Valutazione dell'evidenza epidemiologica dal lavoro di Pirastu et al. 2010.²⁷