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Simona Catalani: data curation; original draft writing, review and editing; visualization.

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Eva Negri: data curation; methodology; original draft writing, review and editing; supervision

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Health effects of living near an incinerator: a systematic review of epidemiological studies, with focus on last generation plants.

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Abstract

Huge reductions in incinerators' emissions occurred over time, and results of older studies cannot be directly generalized to modern plants. We conducted a systematic review of the epidemiologic evidence of the health effects of incinerators, classifying plants in three generations, according to emissions.

A systematic search identified 63 epidemiologic studies, published in English, investigating health effects of incinerators on humans. We focused on cancer, cardio- cerebrovascular diseases (CVD) and respiratory diseases, pregnancy outcomes and congenital anomalies. Only six studies in the general population were on third generation incinerators providing data on pregnancy outcomes and congenital anomalies. Given the heterogeneity of methods, the abundance of ecological/semi-ecological studies and the lack of reliable quantitative measures of exposure in several studies we did not perform any meta-analysis.

No excesses emerged concerning all cancers and lung cancer. An excess of non-Hodgkin lymphoma was reported in some earlier studies, but not for second generation plants. Possible excesses of soft tissue sarcomas were confined to earlier incinerators and the areas closer to the plants. No clear association emerged for CVD and diseases of the respiratory system. Several different pregnancy outcomes were considered, and no consistent association emerged, in spite of a few positive results. Studies were negative for congenital anomalies as a whole. Sporadic excesses were reported in a few studies for specific types of anomalies, but no consistent pattern emerged. Evaluation of the evidence was hindered by heterogeneity in reporting and classification of outcomes across studies.

Direct evidence from third generation plants is scarce. Methodological issues in study design (mainly related to exposure assessment, confounding and ecological design) and analysis make interpretation of results complex. In spite of this, the overall evidence suggests that, if there were any excesses at all for older incinerators, they were modest at most. Additional monitoring of third generation plants needs to overcome methodological weaknesses.

KEYWORDS: Waste incineration, cancer, cardiovascular diseases, diseases of the respiratory system, reproduction.

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Contribution:

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Francesca Bravi: data curation; original draft writing, review and editing; visualization.

Valentina Guercio: data curation; methodology; draft review and editing; visualization.

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Introduction

Waste management is currently tightly regulated in high income countries and includes the generation, collection, processing, transport and disposal of waste. Incineration, defined as the controlled burning of waste at high temperatures, is widely used to reduce the volume of municipal solid waste, the potential infectious properties and volume of medical waste, and the potential toxicity and volume of hazardous chemical and biological waste (Crowley et al., 2003; Rushton, 2003).

The formation of polluting substances, emitted in solid and gaseous form from an incinerator, depends on several factors such as the type of waste treated (chemical composition), the conditions of combustion, and the pollutant abatement systems. Inorganic emissions include water (vapour), carbon oxide (CO), carbon dioxide (CO_2), sulphur oxides (SOX), nitrogen oxides (NOX), and products of incomplete combustion such as silicates, inorganic ash, soot, metal elements and their oxides and salts (for example, mercury and other metals with high vapour pressure). Organic emissions include volatile organic compounds (VOCs), hydrocarbons (HC), dioxins (polychlorinated dibenzo-p-dioxin (PCDDs) and polychlorinated dibenzofuran (PCDFs)), polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs). Particles (including particulate matter (PM) with an aerodynamic diameter smaller than 10 µm (PM_{10}) and 2.5 µm ($PM_{2.5}$)) are emitted too.

Further emissions, not related to the stack, can be summarized by ash, bottom ash, fly ash, noise, odour, pests, transport–related emissions, dusts and spores (Crowley et al., 2003; WHO, 2007). Populations living near incinerators are potentially exposed by inhalation of contaminated air, consumption of contaminated foods, water, or dermal contact with contaminated soil. In addition to the emissions of the incinerator, they are also generally exposed to increased traffic, particularly from heavy good vehicles, transporting waste to the incinerator.

In recent years several epidemiologic studies investigated the health effects of urban waste and other types of incinerators. Several different health effects have been investigated, including cancer, respiratory diseases, CVD, and pregnancy outcomes; sometimes also blood levels of chemicals have been measured (Enviros Consulting Ltd, 2004; Mattiello et al., 2013; Staines and Crowley, 2007). It is difficult to interpret the overall evidence, given the large number of health effects considered, and the heterogeneity of results. Causal inference is further complicated by design issues (most of the studies are ecological or semi-ecological), and by difficulties in the definition of exposure. Previous reviews indicate that results are inconsistent, also due to limitations in the available literature (Ashworth et al., 2014; Giusti, 2009; Mattiello et al., 2013; Ncube et al., 2017; Porta et al., 2009). The main limitations include poor exposure assessment, aggregate level of analysis, and lack of information on relevant confounders.

In previous reviews, the generation of incinerator, technological process or regulatory reference limits were not considered. New plants (thereafter used as synonymous of incinerator) are often bigger, and the

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volumes emitted are consequently higher. Over recent decades, however, substantial technological changes in incineration plants occurred, with consequent massive reductions in emissions. (Forastiere et al., 2011; World Health Organization, 2015).

Studies on the association between exposure to incinerators and health effects mostly refer to older incinerators with less stringent emission standards, and their results cannot therefore be directly generalized to modern incinerators (World Health Organization, 2015). Supplemental file S1 provides details on the historic evolution of daily average emissions limits, according to EU Waste Incineration Directives, as well as technical characteristics of incineration plants.

The aim of this study is to analyse and critically evaluate the results in the available epidemiologic literature on the relation between incinerators and health effects in the general population, with particular attention to the generation of incinerator, considering the different regulations on emission limits and continuous technological adaptations.

For this purpose, we conducted a systematic review of the epidemiologic literature, classifying incinerators in three generations, according to emissions.

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Methods

This report follows the PRISMA guidelines for reporting systematic reviews. The PRISMA flow diagram and checklist are given in supplementary file S2.

Search strategy: We conducted a systematic search of epidemiological studies published up to October 2019, in PubMed and Embase, using the following search terms: "(incinerator OR waste management) AND (human health OR health effect)", without any restriction. Two authors independently assessed all the articles and performed the study selection according to predefined inclusion/exclusion criteria. In addition, the reference lists of the selected articles and of previous reviews were manually searched to identify any other relevant publication.

Inclusion/exclusion criteria: Publications included reported original data based on epidemiological studies on the association between exposure to waste incinerators emissions and effects on human health. In particular, studies were considered if they had a cohort, case-control, cross-sectional or ecological design, and were published in English.

The following studies were excluded: animal or *in vitro* studies; studies concerning waste management preceding the incineration process (e.g. waste collection, or waste recycling); studies estimating only exposure to incinerator emissions, without assessment of any health effect; studies concerning risk perception in the population, without assessment of any health effect; studies concerning body burden, haematological or biochemical measures (such as hepatic enzymes, or oestrogen levels), or urinary mutagenicity analyses.

Data extraction. From each publication we extracted data on location and period of exposure/observation; type of incinerator (including starting year, any structural renovations, type of waste, capacity, emissions, if reported); study design; exposure assessment and exposure levels; study population (including exposed and comparison populations); outcome description and assessment; risk indicator, risk estimates, and the confounding factors considered. One person (EN, SC or FB) extracted the data, and another one checked them.

Classification of incinerators: Incinerators were classified according to 3 generations: first generations, plants active until 1989, (first European directive on waste incineration, 89/429/EEC); second generations, plants active between 1989 and 2006 (transition period: revamping or closing of old plants and building of new plants); third generation, plants active after 2006 (publication of BAT REF Waste incineration). Details on changes in European emissions regulations are provided in Supplementary File S1. Our distinction of generation stems from the fact that the concentration of released substances is specific to the period of investigation. The ratios of concentrations of relevant substances between the 1990s and the 2000s ranges from one order of magnitude for selected metals and particulate matter and four orders for dioxins, as stated in the WHO Europe 2015 meeting report (World Health Organization, 2015). For plants outside the EU, they were attributed a generation according to their characteristics. In particular, studies outside the EU were conducted in the USA, Japan, Taiwan and Australia. Legislations in these high income countries have paralleled or closely followed in the wake of the EU legislation. Thus, in several cases we were able to define the generation for these incinerators as well. Studies including plants for which a "generation" could not be attributed or multiple plants of different generations were classified as "undefined" generation.

Classification of outcomes: The following health effects were considered as outcomes: all-cause mortality/hospitalization; cancer incidence/mortality; respiratory system diseases; cardio- and cerebrovascular diseases; pregnancy outcomes; genetic or congenital malformations; other (including e.g. metabolic diseases, immunological diseases).

Study design classification: We defined studies as ecological if all variables (exposure, outcome, confounders) were measured at population level, semi-ecological if some variables were measured on an individual level (generally outcome) and some at the population level (mostly exposure and/or confounders), and individual if all variables were measured at the individual level.

Risk of bias (RoB) evaluation: For each individual study in the general population, RoB was assessed using the tool proposed by (Johnson et al., 2014), which evaluates 8 different domains: recruitment strategy (selection bias), blinding, exposure assessment, confounding, incomplete outcome data, selective outcome reporting, conflict of interest and other bias. For each domain, RoB is defined either low or high, according to a low risk of bias designation. RoB was defined "probably low" or "probably high" when information was not complete. Whenever possible, we used design features to define RoB. For example, when exposure was based on

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residence, or in general, exposure was derived from existing databases, blinding RoB was considered low/probably low, even in studies with a case-control design. For exposure assessment, we considered RoB low when an exposure was assesses using a dispersion model in combination with geocoding or a small area (e.g. census block or full postcode), while exposure RoB was defined high when exposure was defined by area of residence or distance alone. For adult cancer, exposure RoB was considered high when latency was not considered or was less than 10 years. For confounding, RoB was considered high when only a few individual confounders were available (e.g. age and sex). Besides age and sex, important individual confounders were considered an indicator of individual socioeconomic status and smoking, the latter particularly for cancer, CVD and respiratory conditions in adults. The category "other bias" was used to consider other important sources of bias not considered in other domains, like an ecologic design, the presence of other pollution sources not distinguishable from the incinerator, or a weak statistical analysis. In Supplementary file S3 a designation of low risk of bias and the predetermined rules for RoB evaluation are provided.

Statistical analysis: Given the great heterogeneity of methods used in various studies, the abundance of ecological/semi-ecological studies, and the fact that in most studies a reliable quantitative measure of exposure was lacking, we did not perform any meta-analysis of study results. A large number of different risk estimates were presented in various studies, including standardized mortality or incidence ratios (SMR, SIR), modelled estimates of SIRs or SMRs, rates and rate ratios, odds ratios (ORs) and hazard ratios (HRs).

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Results

The PubMed search yielded 8,924 articles, while the search on Embase 18,855. Combining the articles from the two databases and eliminating duplicates, a total of 24,033 articles were examined. The fist sift using title and abstract (when available) resulted in the examination of the full text of 944 articles. After exclusion of articles which did not satisfy the inclusion/exclusion criteria, we selected 63 studies for the present review (Ancona et al., 2015; Baccarelli et al., 2005; Biggeri et al., 1996; Candela et al., 2015; Candela et al., 2013; Castello et al., 2013; Charbotel et al., 2005; Chen et al., 2006; Comba et al., 2003; Coppeta et al., 2019; Cordier et al., 2004; Cordier et al., 2010; Cresswell et al., 2003; Dummer et al., 2003; Elliott et al., 1992; Elliott et al., 1996; Federico et al., 2010; Floret et al., 2003; Freni-Sterrantino et al., 2019; Fukuda et al., 2003; Garcia-Perez et al., 2013; Ghosh et al., 2019; Goria et al., 2009; Gray et al., 1994; Gustavsson, 1989; Hazucha et al., 2002; Hours et al., 2003; Hsiue et al., 1991; Hu et al., 2001; Jansson and Voog, 1989; Knox, 2000; Lee and Shy, 1999; Lin et al., 2006; Lloyd et al., 1988; López-Abente et al., 2012; Lung et al., 2013; Michelozzi et al., 1998; Miyake et al., 2005; Mohan et al., 2000; Nakayama and Ohkuma, 2006; Obi-Osius et al., 2004; Ortega-Garcia et al., 2017; Parkes et al., 2019; Parodi et al., 2004; Pronk et al., 2013; Ranzi et al., 2011; Rapiti et al., 1997; Reeve et al., 2013; Romanelli et al., 2019; Rydhstroem, 1998; Santoro et al., 2016; Shy et al., 1995; Tango et al., 2004; ten Tusscher et al., 2000; Viel et al., 2000; Viel et al., 2008a; Viel et al., 2008b; Vinceti et al., 2009; Vinceti et al., 2008; Vinceti et al., 2018; Williams et al., 1992; Yamamoto et al., 2015; Zambon et al., 2007).

Organization of tables: Given the large number of characteristics considered, and the fact that several studies presented many different outcomes, we did not present all information for each study in a single table. Supplementary Table S4 (summarized in Table 1) provides detailed information on location and period of the study, type of incinerator, study design, exposure assessment, study population, and shows the outcomes considered only in broad categories.

Main results for each study are provided in brief in Tables 2-6 for the following outcomes: all cancers, non-Hodgkin lymphoma (NHL), soft tissue sarcomas (STS), pregnancy outcomes, and congenital anomalies. Supplementary tables S5-S12 provide results in more detail for the above mentioned outcomes, as well as for other haematopoietic cancers, lung and laryngeal cancer, cardiovascular diseases (CVD), and respiratory diseases. These outcomes have been selected since they have been related with specific substances (i.e., dioxin for all cancers, STS and lymphoid neoplasms, and/or particulate matter and nitrogen dioxide for lung cancer and other outcomes).

In all tables, studies are grouped according to i) population considered (general population/workers); ii) generation of incinerator (first/second/third/undefined) and iii) country (European countries in alphabetic order/ North American/Asian countries).

Supplementary Table S4 provides detailed characteristics of included studies, summarized in Table 1. Table 1 shows the number of identified studies according to incinerator generation and selected characteristics. Out of 63 studies, only 7 concerned third generation plants, while 32 were based on second generation plants, 19 first generation plants, and 5 plants of undefined generation. The majority of the studies (47) were form Europe, while 10 were from Australasia, and 6 from the USA. Twenty studies considered only 1 incinerator, 16 included 2 to 9 plants, 20 were based on 10 or more incinerators, while 7 did not report the number of plants in the area under investigation. As for the type of waste, in 42 studies the plants managed municipal solid waste, in 2 other types of waste, in 15 mixed types of waste, while 4 studies did not provide information on the type of waste. As for the year of publication, 14 were published before 2000, 28 in 2000-2009, 21 from 2010 onward. Concerning the population, 31 studies involved the residents in the area under investigation, 23 studies concerned other types of subjects including children and newborns from mothers residing in the area, 8 studies concerned workers in incinerator plants, and 1 study included both persons residing and working i to the incinerator. Out of the 7 studies on third generation plants, 5 concerned other type of participants (such as newborns delivered by mothers residing near an incinerator). With regard to the exposure assessment, in 14 studies it was based on area (mostly municipality) of residence, in 20 on distance of the residence from the incinerator, in 19 on concentration levels of some pollutant emitted from

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the incinerator at the residence as estimated by a dispersion model, in 8 on occupation, in 3 on another type of assessment (including distance of the birth clinic from the incinerator, serum concentration of dioxin, or dioxin per population). Out of the 7 studies based on third generation plants, 5 used a dispersion model. Twenty-eight studies had an ecological design, 26 a semi-ecological design, and 9 were based on individual data. As for the health outcomes, 10 studies considered total mortality/morbidity, 27 all cancers and/or different cancer sites, 10 CVD, 16 non-malignant respiratory diseases, 15 pregnancy outcomes, 11 congenital malformations, and 9 various other outcomes.

In the following sections we present results for selected health effects: All cancers, Lung and laryngeal cancers, Lymphoid cancers, STS, CVD, Respiratory diseases, Pregnancy outcomes and Congenital anomalies.

Supplementary file S3 provides risk of bias (RoB) evaluation for studies on the general population by generation and by outcome, as well as justification of RoB evaluation for each individual study. Apart from a few studies, no RoB emerged for the domains "recruitment strategy" (selection bias), "blinding", "incomplete outcome data", "selective outcome reporting" or "conflicts of interest". On the contrary the major RoB emerged from potential for exposure misclassification, incomplete control of confounding, and other bias, mainly due to the presence of several ecologic studies. In the six studies concerning third generation incinerators, the major source of RoB was due to lack of individual confounders, while dispersion models were used in 5 out of 6 studies, thus improving exposure estimation, as compared to previous studies.

Of the 24 studies reporting some results on cancer, only two (Biggeri 1996, Pronk 2013) had information on several individual confounders, and other two (Ancona 2015 and Ranzi 2011) had low RoB in the exposure assessment domain, since they used a dispersion model to estimate exposure and considered an appropriate latency period (Supplementary file S3). Fifteen studies had a high RoB from "other sources", mainly because of ecological design. Details on how latency was considered in studies on cancer are also given in Supplementary file S3.

All cancers

Results on all cancers are presented in Table 2 and Supplementary Table S5.

Three studies were available on first generation plants. In an ecological study from France (1972-1990), mostly focusing on methodology, there was a significant excess in women and a non-significant one in men (Goria et al., 2009). An ecological study from Italy (Michelozzi et al., 1998) conducted in 1987-1993 found no association between mortality from all cancers separately for males and females in bands of increasing distance from the plants, up to a radius of 10 km, nor for residents within <10 km from the plant. An ecological study conducted in England, in 1974-1986 in people living near 72 municipal solid waste incinerators showed a modest excess risk for the populations close to the plants, which was however present even in the period before the incinerator started to operate (Elliott et al., 1996).

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Six studies were available for second generation plants. Of these, three were conducted in Italy, two in Spain and one in Japan. Only one of the Spanish studies showed some borderline significant excess risk for proximity (Garcia-Perez et al., 2013), while no consistent association was apparent in the other five reports. In an Italian record linkage cohort study conducted in 2001-2010 (Ancona et al., 2015), the hazard ratios (HR) for all cancers mortality and hospital admission were not associated with annual mean concentration of PM_{10} from the incinerator (HRs ranging between 0.95 and 1.04). In an ecological study conducted in Modena (Italy) in 1991-2005 (Federico et al., 2010), the standardized incidence ratios (SIR) for all cancers was not elevated in the area closest to the plant (SIR=1.00). A semi-ecological historical cohort conducted on two incinerators located near Forlì (Italy) (1990-2003) used modelled concentration of heavy metals (annual average) from the plant to estimate exposure. High exposure was associated with a significantly higher mortality rate ratio in women (1.47, 95% confidence interval, CI 1.09-1.99), while rate ratios for mortality in men (1.02) and incidence in both sexes (0.96 and 0.95) were below unity (Ranzi et al., 2011). A Spanish ecological study (Garcia-Perez et al., 2013) investigated whether there was an excess cancer mortality in towns situated in the vicinity of Spanish-based incinerators and installations for the recovery or disposal of hazardous waste, according to the different categories of industrial activity. It found a borderline significant excess risk (Bayesian modelled SMR=1.09, 95% CI 1.01-.18)) for residence <5 km from the plant(Garcia-Perez et al., 2013). Another ecological study from Spain on pediatric cancers (<15 years) investigated proximity of residence to industrial areas of various type. No association between cancer incidence and residing in the vicinity of incinerators emerged (Ortega-Garcia et al., 2017). An ecological Japanese study (Fukuda et al., 2003) showed no significant relation between mortality from all cancer and the existence of incineration plants and dioxins from the plants at the municipal level.

No study on third generation plants was available.

Two historical cohort studies on workers of first generation plants from Italy (Rapiti et al., 1997) and Sweden (Gustavsson, 1989) found no excess risk in workers (SMRs=0.95 and 1.07 respectively)..

Lung and laryngeal cancers (Supplementary Table S6)

Five studies, from the UK and Italy, considered earlier plants. The first British study involved 10 incinerators (Elliott et al., 1992), and the second one 62 plants (Elliott et al., 1996). Both considered distance of the residence from the plant, and computed observed/expected case ratios (Elliott et al., 1992). While in the first study no excess emerged for either lung (SMR=1.08) or laryngeal cancer (SMR=0.94), in the second one significant excesses were reported for both (SMR=1.14 and 1.12, respectively). In an Italian case-control study (Biggeri et al., 1996), a complex model estimated a significant odds ratio (OR=6.7) in the source, with a rapid risk decay with increasing distance. In an ecological study from Italy (Michelozzi et al., 1998) conducted in 1987-1993, no overall excess in risk of mortality from lung cancer with distance was found (SMR=101 in men and 104 in women). For male laryngeal cancer, an increased but not significant risk was found at 0–3 km (SMR=236.95%CI 27-800) and 3–8 km (SMR=133, 95%CI 80-206), with a borderline trend in risk (p=0.06). An ecological study conducted in Liguria, Italy (1988-1996) in two areas exposed to environmental pollution emitted by a coal-fired power station and other industrial sources, including a waste incinerator, found and excess risk for lung cancer in women but not men, but the excess risk could not be attributed to a specific emission (Parodi et al., 2004).

Seven studies, from England, Italy, Spain and Japan considered second generation plants. Only the Spanish and the Japanese study showed some borderline excess lung cancer risk (Ancona et al., 2015; Federico et al., 2010; Fukuda et al., 2003; Garcia-Perez et al., 2013; Ranzi et al., 2011; Reeve et al., 2013; Romanelli et al., 2019). The results of all other studies were scattered, with some risk estimate above, and some below unity, but no consistent pattern of trends.

An Italian record linkage cohort study conducted in 2001-2010 (Ancona et al., 2015) found no excess risk for lung cancer mortality (SMR=1.04 in men and 1.24 in women) and hospital admission (SMR=1.01 in men and 0.98 in women). In women only, the HR for laryngeal cancer mortality (SMR=1.92, 6 cases) and hospital admission (SMR=1.83, 9 cases) were significantly above unity. Another ecological study conducted in Italy (Modena) in 1991-2005, did not show any excess of SIR for lung (SIR=1.00, 95% CI 0.79-1.25) and laryngeal (SIR=0.81, 95% CI 0.33-1.68) cancers in the area closest to the plant (Federico et al., 2010). In a semi-ecological historical cohort conducted in two incinerators located near Forlì (Italy) (1990-2003), modelled concentration of heavy metals (annual average) from the plant were considered as indicators of exposure (Ranzi et al., 2011). No increased risk of mortality and morbidity for lung (mortality: rate ratio=1.17 in men and 0.95 in women) and larynx cancer emerged in more exposed groups (Ranzi et al., 2011). The Spanish ecological study (Garcia-Perez et al., 2013), found some borderline excess risk for proximity in population residing in the vicinity of incinerators (modelled SMR=1.17, 95% CI 1.01-1.34). An ecological study conducted in circular regions of radius 10 km around five industrial incinerators in England and five matched control regions in 1998–2008 (Reeve et al., 2013) showed no elevated risk of lung cancer incidence or mortality in the vicinity of plants. An ecological Japanese study (Fukuda et al., 2003) found that in men the mean of age-standardized rates of municipalities with incinerators was significantly lower than the mean of rates in municipalities without incinerators. No study on third generation plants was available.

With reference to workers, two historical cohort studies, one Italian (Rapiti et al., 1997) and one Swedish (Gustavsson, 1989), considered earlier plants. The SMRs were below unity in the Italian study (SMR=0.55, 95% CI 0.15-1.42), and not significantly above unity in the Swedish one, when comparison was made with local population rates (SMR=197, 95%CI 90-347).

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Lymphoid cancers

Results for "Lymphoid cancers" are presented in Table 3 for NHL, and Supplementary Table S7 for all lymphoid cancer types.

With reference to older incinerators there are four studies, from France, the UK and Italy. The two French studies (Floret et al., 2003; Viel et al., 2000) are from Besançon on the same period of observation (1980-1995). One of these, based on an ecological design, found significant clusters around the incinerator for NHL, but not Hodgkin lymphomas, while the other, based on dioxin exposure estimates, found an excess risk of NHL for very high exposures (OR=2.3, 95% confidence interval, CI: 1.4-3.8). A national cross-sectional study from Great Britain on people living near 72 municipal solid waste incinerators (Elliott et al., 1996) found an excess risk, of borderline significance, for NHL (SIR=1.04, 95%CI 1.01-1.08), but not for other hematopoietic cancers. In an ecological study from Italy (Malagrotta, Rome, Italy) (Michelozzi et al., 1998) conducted in 1987-1993, no overall excess in risk of mortality for all lymphohematopoietic cancers, NHL (SMR=100 (95% CI 77-127) in men and 116 (95%CI 90-149) in women), Hodgkin disease, multiple myeloma, and leukaemia with distance was found (Michelozzi et al., 1998).

At least 9 studies were available for second generation plants, 8 on NHL. One report from France showed some borderline excess risk of NHL incidence (Viel et al., 2008b). The remaining 8 studies from the UK, Italy, Spain and the USA, were negative for various outcomes considered both for mortality and incidence. An ecological study conducted in five circular regions of radius 10 km near industrial incinerators in England and five matched control regions, 1998–2008 (Reeve et al., 2013) showed no evidence of elevated incidence for childhood leukaemia and NHL (modelled SIR=0.99, 95% CI 0.95-1.03) and a weak excess risk of incidence for leukaemia (Reeve et al., 2013). An Italian semi-ecological cohort study conducted in 2001-2010 (Malagrotta, Rome, Italy) (Ancona et al., 2015), found no excess risk for lymphohematopoietic mortality and hospital admission. In another ecological study conducted in Italy (Modena) in 1991-2005 (Federico et al., 2010), the SIR for NHL (SIR=0.94, 95%CI 0.68-1.27) and leukemia in the area closest to the plant was not increased. In a semi-ecological historical cohort conducted on two incinerators located near Forlì (Italy) in 1990-2003, modelled concentration maps of heavy metals (annual average) were considered the indicators of exposure to atmospheric pollution from the incinerators. No increased incidence and mortality for lymphohematopoietic cancers, NHL (mortality rate ratio 2.03 in women and 0.52 in men, incidence 1.06 in women and 0.59 in men), multiple myeloma, leukemia was found in men and women in the entire area divided in four exposure categories (Ranzi et al., 2011). Another Italian semi-ecologic study estimated NO_x emissions through a dispersion model and showed no association with hospital admissions or mortality for lymphatic and hematopoietic tumors, leukemia, and not significantly elevated HRs for NHL (HR ranging between 1.37 and 2.31 (Romanelli et al., 2019). A Spanish ecological study (Garcia-Perez et al., 2013), found no excess risk of leukaemia and NHL (SMR=1.02) in populations residing in the vicinity of incinerators.

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Another Spanish ecological study analyzed the spatial distribution of cases of pediatric cancers (<15 yr) in relation to industrial areas and showed no significant association between incidence of childhood leukemia, Hodgkin disease, NHL (SIR=1.65, 95% CI 0.61-3.60) and residence in the vicinity of incinerators (Ortega-Garcia et al., 2017). An American semi-ecological case-control study showed that the proximity (5-10 km) to any dioxin-emitting facility was not associated with NHL risk (OR=0.5, 95% CI=0.3-0.9) (Pronk et al., 2013). No study on third generation plants was available.

Two reports of limited power were available on workers in older plants in Italy and Sweden (Gustavsson, 1989; Rapiti et al., 1997). None of these showed a significant association with hematopoietic cancers as a whole (SMR=0.95 and 1.07 respectively).

Soft Tissue Sarcomas (STS)

Results on STS are presented in Table 4. Details are provided in Supplementary Table S8.

Four studies refer to first generation plants (Comba et al., 2003; Elliott et al., 1996; Viel et al., 2000; Zambon et al., 2007). A study from France (Viel et al., 2000) found a significant spatial cluster around the incinerator, a small Italian semi-ecological case-control study (Comba et al., 2003) found a strong increase in risk (OR=31.4, 95% CI: 5.6-176.1) restricted to those residing less than 2 km from the industrial incinerator, as compared to 5 km or more. Another Italian semi-ecological case-control study (Zambon et al., 2007) reported an excess risk with estimated exposure to PCDD/PCDFs (OR=3.3 95%CI (1.4-7.9) for the highest vs the lowest exposure category. These two Italian studies were conducted in highly industrialized areas, without any differentiation between the sources. An ecological study from the UK (Elliott et al., 1996) found no excess for residing within 7.5 km from the incinerator (SMR=1.16, 95% CI=0.96-1.41).

Three studies from Italy and Spain considered STS risk for second generation plants. (Federico et al., 2010; Garcia-Perez et al., 2013; Ranzi et al., 2011). Neither studies found excesses (SIR=1.15 (95%CI 0.24-3.37), SMR=0.84 95%CI (0.09-8.06), and modelled SMR=1.04 95%CI (0.74-1.41)) for the highest vs the lowest exposure category).

There are no studies on third-generation plants or on workers.

Cardio- and cerebrovascular diseases (CVD)

For the six CVD studies on the general population major sources of potential bias (Supplemetary file S3) derived from lack of control of confounding (4 out of 6) and misclassification of exposure (4 out of 6).

Results on CVD are provided in Supplementary Table S9. No study on first generation plants in the general population was found. Six studies were available on second generation plants, three from Italy and one each from the USA, Japan and Taiwan. These examined various outcomes (incidence, mortality, or CVD risk indicators such as hypertension or arrhythmia), and no consistent pattern of risk emerged. In an Italian record linkage census cohort carried out between 2001 and 2010 no association was evident between exposure estimated through a dispersion model and CVD mortality (HR were 1.02 and 1.03 in men and women for CVD mortality, and 0.99 and 1.00 for CVD hospital admissions) (Ancona et al., 2015). In a semi-ecological historical cohort conducted on two Italian incinerators in 1990-2003, modelled concentration maps of heavy metals were considered as indicators of exposure to atmospheric pollution from the incinerators. Mortality was not significantly increased for ischemic heart diseases (rate ratio=0.79 in men and 1.14 in women in the highest exposure category) and hospitalization for acute myocardial infarction (rate ratio=0.81 in men and 1.40 in women) and chronic heart failure (rate ratio=0.78 in men and 1.48 in women) in men and woman in subsequent categories of heavy metal exposure, compared to the lowest one, except CVD mortality in women but not men (rate ratio=0.98 in men and 1.32 in women) (Ranzi et al., 2011). Another Italian semi-ecological historical cohort reported no consistent association between the exposure to NO_X - assessed with a dispersion model - and mortality and hospital admission for cardiovascular diseases (HR=1.21 in men and 1.02 in women), acute myocardial infarction, ischemic heart disease, and cerebrovascular diseases (Romanelli et al., 2019). In a semi-ecologic longitudinal study from southwestern North Carolina, USA, conducted in 1992-1994, there was no association with a generic "heart trouble" (possibly self-reported) according to $PM_{2.5}$ from the incinerator (Shy et al., 1995). An ecological Japanese study conducted in 1996-1997 found no difference in mean age-adjusted mortality rates from stroke and ischemic heart disease in municipalities with and without incinerators (Fukuda et al., 2003). In the cross-sectional study conducted in Taiwan in 2000-2001 there was no association between the serum PCDD/Fs levels and hypertension (OR=0.91 95%CI (0.23-3.73) per 1 unit increase in serum dioxin toxic equivalent levels) and arrhythmia (OR=1.75, 95%CI (0.16-20.48) (Chen et al., 2006). No study was reported on newer generation plants.

With reference to studies on workers, reports were available from Italy (Rapiti et al., 1997), Sweden (Gustavsson, 1989) (first generation plant) and Japan (Yamamoto et al., 2015) (second generation plant). Some of the risk estimates for various outcomes were above, and some below unity, but there was no consistent indication of excess risk.

Respiratory diseases

While for all other outcomes studies mostly relied on record linkage between administrative and healthcare databases, for respiratory diseases there were also studies where individual participants were contacted and interviewed (Miyake 2005, Mohan 2000,Hazucha 2002, Hsiue 1991, Gray 1994). However, few individual confounders were used in the analyses and thus RoB from lack of control of confounding remained, together with exposure misclassification (Supplementary file S3).

Results concerning respiratory diseases are given in Supplementary Table S9. No study was available on first generation plants. Seven studies considered various respiratory measures, symptoms or diseases in the general population with reference to second generation plants.

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In a record linkage cohort study from Italy (Ancona et al., 2015), there was no significant association with respiratory disease mortality (HR 1.12 in men and 0.86 in women) or hospital admissions (1.05 in men and 0.98 in women), all risk estimates being close to unity. In another study from Italy (Ranzi et al., 2011), which considered mortality from respiratory diseases and chronic pulmonary disease, and incidence of chronic and acute lung diseases, no consistent pattern of risk with increasing exposure was observed for any of the outcomes, some of the risk estimates being above and some below unity (rate ratios ranging between 0.27 and 1.43 in the highest exposure category), in the absence of any clear trend in risk. Another Italian semi-ecological historical cohort study reported no consistent pattern of increased mortality or risk of hospitalization with increasing exposure to NO_X for different acute and chronic respiratory diseases (Romanelli et al., 2019). The only significantly increased HR was for acute respiratory disease mortality in women (HR=2.52 95%CI 1.31-4.83), but not in men (HR=0.53 95%CI 0.26-1.04) An ecological cohort study from southwestern North Carolina, USA (Shy et al., 1995), conducted in 1992-1994, and considering a large number of measures, complaints and diseases, found some associations with a number of minor, poorly defined conditions, including sinus troubles, wheeze in the past 3 years (but not in the past year), runny nose and sore throat, reported only in figures. However, there were no consistent associations with asthma, phlegm or cough in the morning, cough in the past month, or measures of peak expiratory flow rate (PEFR). Some of the apparently positive associations may be due to recall bias, and/or multiple testing. Another publication of the same study (Lee and Shy, 1999), conducted in 1992-1993, reported no significant association for measures of PEFR. A further publication of the same cohort based on data from 1992-1994 (Hu et al., 2001) considered various measures of lung function assessed by spirometry. All findings were non-significant, in the absence of a consistent pattern of risk. A semi-ecological cross-sectional study conducted in Japan in 1997 on children of public elementary schools found an association, of borderline significance, with wheeze (OR=1.08, 95% CI 1.01-1.15 in the closest residents), but not with allergic rhinitis (Miyake et al., 2005).

Four studies were based on plants for which we were not able to determine the generation. A semi-ecological cross-sectional study conducted in North and South Carolina, USA, in 1994-1995 (Mohan et al., 2000) found inconsistent associations with wheeze, and a large number of short duration conditions, including eye irritation, sore throat, runny nose and nasal irritation, for some exposed communities but not others, in the absence of a consistent pattern, and in the presence of likely recall bias, since data collection was based on telephone interviews. Another ecological cross-sectional study conducted in North Carolina, USA, in 1992-1994 (Hazucha et al., 2002) found no consistent association over space and time with repeated measures of lung function. A semi-ecological cross-sectional study from Taiwan (Hsiue et al., 1991) found some positive association with forced vital capacity (FVC) and forced expiratory volume in the 1st second (FEV_1), but not with the ratio FVC/FEV_1, nor with forced expiratory flow between the 25% and 75% of the

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$FEF_{25-75\%}$. A semi ecological cross-sectional study from Australia (Gray et al., 1994) found no consistent association with various asthma symptoms and various measures of lung function.

With reference to workers, two studies on first generation plants were available. A historical cohort study from Italy, with a follow-up between 1965 and 1992 (Rapiti et al., 1997), found no association with respiratory disease mortality, with no observed deaths, and a limited number of expected deaths. Another historical cohort study conducted in Sweden, over the period 1951-1985 (Gustavsson, 1989) found no association with mortality from all respiratory diseases, nor separately from asthma, bronchitis and emphysema.

A cross-sectional study, conducted in 1996 in France, considered workers in a second generation plant (Hours et al., 2003). There was some association with measures of FEV_1, peak flow (PF), and FEV_1/FVC, in the absence, however, of any consistent pattern. In an historical cohort of workers from Italy, a non-significant decline in lung function was reported over a 5-years period (Coppeta et al., 2019).

Another cross-sectional study from workers from France, concerning an incinerator of unclassified type, considered a large number of lung function measures. Most of the results were null or not significant, but there was a positive association with FEV_{50}/PV% and FEF_{25-75}/FVC. Some of these apparent association may be due to multiple testing.

Pregnancy outcomes

Confounding and other sources were the main domain with high RoB for studies on pregnancy outcomes. Exposure misclassification affected studies on earlier generation incinerators, but only 1 out of 5 studies on third generation plants (Supplementary file S3).

Results on pregnancy outcomes are presented in Table 5. Details are provided in Supplementary Table S11.

Several different pregnancy outcomes were considered in 15 studies. Of these, dispersion models to estimate exposure were used in 7 studies (Candela et al., 2015; Candela et al., 2013; Ghosh et al., 2019; Lin et al., 2006; Santoro et al., 2016; Vinceti et al., 2008; Vinceti et al., 2018), while the others relied on distance/area of residence only. Five studies (Candela et al., 2013; Freni-Sterrantino et al., 2019; Ghosh et al., 2019; Santoro et al., 2016; Vinceti et al., 2018), referred to third generation incinerators.

Of the five studies reporting on multiple births, two small studies, one on a UK first generation (rates of 16 and 20 in two primary risk areas, as compared to rates between 3.3 to 12.5 in 10 control areas) (Lloyd et al., 1988) and one on a German second generation plan (OR between 1.69 and 2.03 in four exposed areas, compared to a control one) (Obi-Osius et al., 2004) found an excess of twins, while a study on a second generation plant from Sweden (SIR between 0.46 and 1.72 in 14 exposed municipalities) (Rydhstroem, 1998), a study on a third generation plant from Italy (OR=0.87 (0.57-1.33) for high PM_{10} exposure) (Candela et al., 2013) and a large study on third generation plants from the UK (OR=0.99 per doubling of PM_{10}) (Ghosh et al., 2019) did not report any association.

Concerning sex ratios, one study (first generation) found a possible excess of female births (Williams et al., 1992), but other four (second and third generation) did not find any significant association (Candela et al., 2013; Freni-Sterrantino et al., 2019; Lin et al., 2006; Santoro et al., 2016).

Candela and colleagues found an excess of miscarriages (OR=1.29, (0.97-1.72), significant only in women without previous miscarriages (Candela et al., 2015), while Vinceti and colleagues found little evidence of any association either in women residing (SIR=1.00 and 0.98) or in women working (SIR=1.04 and 0.91) in the high/intermediate exposure area around the Modena incinerator, in two studies conducted in different time periods (Vinceti et al., 2008; Vinceti et al., 2018).

Five studies reported on preterm birth (PTB). Three studies found some positive association, significant in one only: one study from Taiwan (OR=1.22, 95% CI: 0.97-1.52 for the highest exposure category) on a second generation plant (Lin et al., 2006), and two Italian studies (Candela et al., 2013; Santoro et al., 2016) on third generation plants reporting ORs of 1.30 (1.08-1.57) and 1.61 (0.88-2.94) respectively, while a study from Spain (Castello et al., 2013) (second generation, SIR=0.99 (0.92-1.07)) and the large one from the UK (Ghosh et al., 2019) (third generation, SIR=0.99 (0.97-1.01) per doubling of PM_{10}) found no association.

A positive significant weak association with low birth weight (LBW) was reported in one study (Castello et al., 2013) (second generation, SIR=1.06 (1.01-1.11)), but no significant results were reported in other four (SIR=1.00; OR=1.06; OR=0.85; mean birthweight difference 12g per doubling of PM_{10}) (Ghosh et al., 2019; Lin et al., 2006; Santoro et al., 2016; Tango et al., 2004).

Concerning Small for Gestational Age (SGA), three studies found no significant associations (OR ranging between 0.99 sand 1.30) (Candela et al., 2013; Ghosh et al., 2019; Santoro et al., 2016), while one reported a weak significant positive association (second generation plant, SIR=1.06 (1.02-1.11) (Castello et al., 2013).

Results were negative in the four studies investigating fetal/neonatal deaths (Dummer et al., 2003; Freni-Sterrantino et al., 2019; Ghosh et al., 2019; Tango et al., 2004).

No study on workers was available on pregnancy outcomes.

Congenital anomalies

Again, exposure assessment (not in the two third generation studies), confounding and other sources were the main determinants of RoB.

Results of “Congenital anomalies” are presented in Table 6 and in Supplementary Table S12.

Of the 11 studies reporting on any congenital anomalies, three, six and two respectively were on first, second and third generation plants, including two studies from Modena, Italy on the period before (second generation) and after (third generation) renovation of the same plant (Vinceti et al., 2008; Vinceti et al., 2018). Six studies (Cordier et al., 2004; Cordier et al., 2010; Parkes et al., 2019; Vinceti et al., 2009; Vinceti et al., 2008; Vinceti et al., 2018) used a dispersion model to estimate exposure at the area of residence, five relied on distance/area of residence (Cresswell et al., 2003; Dummer et al., 2003; Jansson and Voog, 1989;

Parkes et al., 2019; Tango et al., 2004), and one considered the births clinic as proxy of the area of residence (ten Tusscher et al., 2000).

There is substantial heterogeneity concerning the type of anomalies considered. Of the studies that presented results for the category of "all congenital malformations" six (Cordier et al., 2004; Cresswell et al., 2003; Parkes et al., 2019; Vinceti et al., 2009; Vinceti et al., 2008; Vinceti et al., 2018) reported no association with congenital malformations in offspring or aborted fetuses, while one (first generation plant) study found a positive association for lethal anomalies (Dummer et al., 2003) with proximity to the incinerator (OR=1.10, (1.03-1.19), not confirmed by another study (SIR=1.06; 95% CI 0.91-1.22) (Tango et al., 2004).

Concerning cranio-facial anomalies, positive results were reported for facial cleft (SIR=1.30 (1.06-1.59)) (Cordier et al., 2004) and cleft lip/soft palate 2.4/1000 births in the clinic near the incinerator and 1.2 in the one 12 km away) (ten Tusscher et al., 2000), but other three studies did not find an association (rate ratio period post over period pre=1.02 (0.71-1.47); OR=1.0 (0.94-1.07) for oro-facial clefts; 0 cases vs 22 controls), (Jansson and Voog, 1989; Parkes et al., 2019; Vinceti et al., 2009).

Concerning various other anomalies, one study (Cordier et al., 2004) found a positive association with renal dysplasia (modelled SIR=1.55 (1.10-2.20)), and with renal birth defects and obstructive uropathy (OR=1.99 (1.17-3.40) in an analysis on a later time period of the same area (Cordier et al., 2010). The excesses of heart defects (OR=1.12 (1.03-1.22)) and neural tube defects (OR=1.13 (1.04-1.23)) reported by Dummer and colleagues (Dummer et al., 2003) were not confirmed in other studies (Cordier et al., 2004; Parkes et al., 2019; Vinceti et al., 2009).

No study on workers investigated congenital anomalies.

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Discussion

This comprehensive review of epidemiological evidence of the health effects of incinerators on the general population indicates that the data on newer generation incinerators are scant, limited to selected outcomes, and methodological weaknesses hamper interpretation of results.

In fact, most studies investigating the association between exposure to incinerators and health are ecological or semi-ecological, i.e. all or some among outcomes, exposures and confounders are measured at group, rather than at individual, level. The loss of information due to aggregation prevents the identification of parameters of interest of the underlying individual level model. This leads to potential "ecological fallacy", i.e. the association at the individual and grouped level can differ in quantitative terms, and even go in qualitative ones (Wakefiled and Lyons, 2010).

Several of the studies considered are semi-ecological, i.e. some aspects (mostly outcome) are measured at the individual levels while other (exposure and/or confounders) are measures at the aggregate level. This design does not fully solve the problem of the ecological fallacy, since the variance within groups of the aggregated factors remains unknown. If some conditions regarding this variance are not met, they also can provide biased estimates of the association when referred to the individual level.

Thus, the results from ecologic and semi-ecological studies should be interpreted with caution, even more than individual level observational studies.

In addition, in almost all studies, exposure has been evaluated at the place of residence, thus ignoring variations arising from individuals who spent a substantial portion of time away from the residence (e.g., at work, commuting, in leisure time activities, traveling etc.). Even exposures at the place of residence estimates are generally less than optimal, since only some studies applied dispersion models to provide quantitative estimates, while several others simply relied on distance from the plant, often evaluated at an aggregate area level. All studies ignored characteristics of the residence and lifestyle habits that can affect exposure.

Apart from a few exceptions, mainly related to studies on respiratory outcomes, most studies relied solely on available databases collected for other purposes (e.g. disease registries, hospital discharge or mortality records, etc.) to evaluate outcome and potential confounders, and no data collection at the individual level occurred from the subjects in the study. Thus, information on some potentially important confounding factors (e.g., smoking and other lifestyle habits, and individual level social class) is lacking in most studies.

Several studies evaluated different outcomes without applying corrections for multiple testing, thus the possibility of chance findings (false positives) in a single study is high. Even some of the studies presenting results on one outcome only may have done so only after noting an excess of one particular health effect among several others, thus not avoiding the multiple testing problem. The possibility of high type two error rates (false negatives) in underpowered studies should also be considered, particularly for the studies based on only one or a small number of incinerators, and thus on a small exposed population. Therefore, the available literature should be evaluated in its entirety, and for each outcome the consistency of results across studies must be considered.

We evaluated risk of bias (RoB) using a tool proposed by the Navigation Guide systematic review methodology, developed for observational human studies on environmental health (Johnson et al., 2014). The limitations mentioned above are reflected in the high RoB in the domains "exposure misclassification", "control of confounding", and "other bias" (set high for ecologic studies). On the contrary, apart from a few exceptions, RoB was low for the domains "recruitment strategy/selection bias", "incomplete outcome data", "selective outcome reporting" and "conflicts of interest".

Our RoB analysis showed improvements in the quality of epidemiologic studies, since newer studies relied more on dispersion models to evaluate exposure, and more information on potential confounders was available in the databases utilized (Cordioli et al., 2013; World Health Organization, 2015).

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The exposure of interest in this review was living in the proximity of an incinerator, regardless of the specific pollutants that may cause health effects. Most studies used area of residence or distance from the incinerator as indicator of exposure, and thus they did not focus on any specific pollutant. Also for studies using dispersion models, it is a reasonable assumption that the pollutant used reflects exposure patterns to other pollutants as well (Douglas et al., 2017). Thus the pollutant model can be considered a tracer of "exposure to incinerator emissions" and dispersion models offer a more accurate fingerprint of the exposure area.

Concerning the classification of incinerators, the European Union has been at the forefront in the development of both technologies and legislations concerning incinerators' emissions. After the finding of relevant dioxin emissions from first generation incinerators, the EU developed the first regulation of emissions in 1989, which has been implemented in the various member states in subsequent years. Concerns about emissions prompted substantial technologic developments, reflected in the 2000 EEC legislation and then in the 2006 BATs. Our classification of incinerators aims at separating exposures occurred (mostly) in a period without any specific emission legislation (first generation before 1989), from exposures occurring in an intermediate period during which huge technological improvements were gradually implemented, resulting in the closure of some plants, substantial renovations of others, and construction of new ones (second generation 1990 to 2006), and a more recent period when a stricter legislation was in place (after 2006). Thus, incinerators in the third generation follow at least the directives of 2000. This does not exclude that some incinerators classified in previous generations had relatively low emissions, also considering the different times at which the EU directives were implemented in various member states. Still, selected technological advancements were not available before a certain date.

With specific reference to cancer risk, a weakness in several studies was the fact that latency was not considered or only marginally considered, which is a crucial issue for cancer. In some studies, many different cancer sites were investigated. We concentrated on four outcomes, namely all cancers, laryngeal and lung cancer, lymphohematopoietic cancers and STSs. The latter two are the ones that have been more specifically suggested to be associated with incineration/dioxins exposure, while lung cancer has been related with exposure to particulate matter and air pollution in general.

With reference to all cancers combined, most studies did not find an association, including two studies on workers. No overall excess emerged from the several studies investigating the association with laryngeal and lung cancers. Lymphoid neoplasms, particularly NHL, and STS are of specific interest because of their alleged association with exposure to dioxins. For lymphoid cancer, an excess of NHL was reported in some earlier studies, while studies on second generation plants did not find a consistent association. For STS as well, associations were reported in older studies on first generation plants, where assessment of exposure was based solely on distance. These excesses were confined to the area within 2-3 km from the plant, and

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studies on plants of second generation were negative. Thus, this possible association was confined to the highest exposure categories, and declined when exposure decreased either by increasing distance from the plant or by decreased emissions in newer plants. No study on third generation plants was available, also because latency consideration does not allow any meaningful inference. However, the aforementioned lack of consideration of an appropriate latency period hampers a clear conclusion. Due to time considerations, studies assessing only exposure to new generation plants and with an appropriate latency period were not feasible at the time of this review.

With reference to CVD and respiratory diseases, these have been associated with exposure to particulate matter and air pollution in general. Most studies considered second generation plants. No clear association emerged for any group of diseases, as expected, given that incinerators are a minor source of PM, as compared to other sources, and background concentrations (Douglas et al., 2017). This was confirmed by the only study (Ancona et al., 2015) using PM_{10} concentrations estimated from dispersion model as indicator of exposure. That study did not find any association with CVD or respiratory diseases; if anything, some inverse associations were reported. Also of note, is the very low PM_{10} estimated exposure levels, with a mean annual concentration below 0.17 ng/m^3 (Ancona et al., 2015).

Given the short time-lag between exposure and outcome, five studies on third generation plants (i.e. incinerators) were available concerning pregnancy outcomes. Several different outcomes have been considered. Despite scattered evidence of positive findings in some third generation studies on PTB (Candela et al., 2013; Santoro et al., 2016) the recent larger UK study found no association (Ghosh et al., 2019). No consistent associations emerged for SGA or LBW, suggesting that exposure does not influence foetal growth. Also, no clear association emerged for multiple births, sex ratio, miscarriages and neonatal deaths.

Studies are consistently negative for congenital anomalies as a whole. Concerning specific types of anomalies, the literature is more difficult to interpret, since studies reported on different types of anomalies and adopted different classifications. Thus, the evidence on individual types of anomalies is scarce, and no consistent excess emerged. Early reports of increased cranio-facial anomalies (Cordier et al., 2004; ten Tusscher et al., 2000) were not confirmed in a recent much larger study (Parkes et al., 2019) that used a PM_{10} dispersion model to estimate exposure. Weak associations were found when distance was considered as exposure metric, in particular with congenital heart defects and genital anomalies.

Although the focus of this review was on the general population, we also included studies on occupational exposure. Although no adequate quantitative measure of exposure was available, studies on occupationally exposed populations are of interest because workers are typically more exposed than the general population. However, those studies investigated mostly adult chronic diseases, and thus provide no information on pregnancy outcome and malformations. Another issue is their small sample size. These

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problems notwithstanding, it is of interest that studies on occupational exposures were broadly consistent with those on the general population and essentially did not find major risk excesses.

Some limitations of this systematic review are inherent to the available material, i.e. the fact that most data were based on ecological or semi-ecological studies, the difficulties in exposure measurement and the different latency of various diseases that have been considered. In addition, we restricted our search to papers published in English, resulting in the loss of some studies. However, it has been shown that positive findings tend to be published more often in the international literature. Thus, it is likely that more negative rather than positive studies were excluded. Given that our aim was to consider all health effects, we used the general search terms "human health" and "health effects". Our search strategy may again have resulted in the loss of some articles. However, we considered two different databases, and our search provided an extensive number of hits (over 24,000). Moreover, we also hand-searched the references of previous reviews and of the articles included.

Among the strengths of this work, there are the extensive coverage of a large number of incinerators and populations at risk, as well as different outcomes considered.

In conclusion, the available evidence on a large number of health effects in the general population living near incinerators, and the few available data on workers, showed no consistent excess risk. Data on older plants show that, if there were any excesses at all, these were at most modest. Direct evidence from third generation plants is scarce, and only related to selected short term outcomes. Thus, their effect on chronic diseases, and particularly cancer, remains an open issue, also because of possible latency bias. On the one hand, the methodological limitations of the available data do not allow to firmly conclude for an absence of any health effect of modern incinerators. On the other hand, no strong and consistent signal emerged from the available literature. Should additional monitoring of health effects be carried out, there is a need to overcome the design weaknesses of previous studies. In fact, more recent studies tended to provide more precise measures of exposure, including the use of dispersion models and geocoding of addresses. Also, newer health databases tend to incorporate more information on potential confounding factors. In addition, biomonitoring of exposed populations or workers (Campo et al., 2019) and health impact assessments based on quantitative estimates of pollutants (de Titto and Savino, 2019) may provide further information.

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Table 1. Number of studies by incinerators' generation and selected characteristics

	Total	Generation			
		1st	2nd	3rd	undefined
Total	63	19	32	7	5
Geographical area					
France	9	3	5	/	1
Italy	17	6	7	4	/
UK	11	6	2	3	/
Other European countries	10	4	6	/	/
USA	6	/	4	/	2
Japan	5	/	5	/	/
Taiwan	4	/	3	/	1
Australia	1	/	/	/	1
Number of incinerators					
1	20	8	9	3	/
2-9	16	4	7	2	3
10+	20	7	11	2	/
NR	7	/	5	/	2
Type of waste					
Municipal Solid Waste	42	11	22	7	2
Other	2	1	1	/	/
Mixed	15	6	7	/	2
NR	4	1	2	/	1
Year of publication					
Before 2000	14	10	2	/	2
2000-2009	28	9	16	/	3
2010 onward	21	/	14	7	/
Population					
General					
Residents	31	10	18	1	2
Other	23	7	9	5	2
Occupational					
Incinerators' workers	8	2	4	1	1
Mixed (residents and workers)	1	/	1	/	/
Exposure assessment[1]					
Area	14	6	4	1	3
Distance	20	7	11	1	1
Dispersion model	19	3	11	5	/
Occupation	8	2	4	1	1
Other	3	1	2	/	/
Design					
Ecological	27	12	12	2	1
Semi ecological	27	5	15	4	3
Individual	9	2	5	1	1
Health outcome[2]					
Total mortality/morbidity	10	3	6	1	/
Cancer	27	13	14	/	/

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Cardio- and cerebrovascular diseases	10	2	8	/	/
Respiratory diseases	16	2	8	1	5
Pregnancy outcomes	15	4	6	5	/
Malformations	11	3	5	3	/
Other	9	2	6	/	1

[1] The sum does not add up to the total because one study used both distance and dispersion model. [2] The sum does not add up to the total because some studies included more than one outcome.

NR: not reported.

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Table 2 – Studies investigating the association between exposure to incinerators and all cancers.

First author, year	Location, Period	Incinerator generation	Design	Exposure assessment	Number of events/ Risk indicator	Exposure category; Risk estimates
General population						
Goria, 2009	France, 1972-1990	1	ECO	DM	N=Inc 2941 (W) & 3367 (M)/ Poisson regression coeff of incidence for an index of exposure based on the square root of dioxin	Continuous; W 0.671 (0.370-0.971) M 0.214 (-0.092-0.520)
Michelozzi, 1998	Italy, 1987-1993	1	ECO	DIST	N= Mort 2165 (W) & 2838 (M) / O/E Ref: Rome municipality	0-10 km, W 1.01 (0.96-1.05), M 0.97 (0.94-1.01)
Elliott, 1996	UK, 1974-1987	1	ECO	DIST	N=Inc 354831/ O/E ratio Ref: UK	0-7.5km; 1.02 (1.02-1.02); stone's p-value 0.001
Ancona, 2015	Italy, 2001-2010	2	record linkage CO	DM	N= Mort 893 (W) & 1303 (M); HAdm N=2796 (W) & 3258 (M)/ , HR, for a 0.03 ng/m^3 difference in annual mean concentration of PM_{10}	Continuous; Mort: W 1.04 (0.92-1.17), M 1.02 (0.92-1.12) HAdm: W 0.96 (0.89-1.03), M 0.95 (0.89-1.02)
Federico, 2010	Italy, 1991-2005	2	ECO	DIST	N Inc 10,450/ SIR ref: City of Modena	0-5km; 1.00 (0.98-1.02)
Ranzi, 2011	Italy, 1990-2003	2	semi ECO Hist CO	DM	N= Mort 524 (W) & 669 (M); Inc N=1146 (W) & 1218 (M)/ Rate ratios estimated by Poisson Regression. Ref: <0.5 ng/m^3 heavy metals	>2 ng/m^3; Mort: W 1.47 (1.09-1.99), M 0.85 (0.64-1.12) Inc: W 0.90 (0.73-1.11), M 0.87 (0.72-1.06)
Garcia-Perez, 2013	Spain, 1997-2006	2	ECO	DIST	N=Mort 13,051/ RR from Bayesian modelling of O/E Ref: Spain	≤5 km; 1.09 (1.01-1.18)
Ortega Garcia, 2017	Spain, 1998-2015	2	ECO	DIST	N= Inc 41 (age<15 years)/ O/E Ref Murcia Region in 2011	<4 km; 0.75 (0.51-1.02)
Fukuda, 2003	Japan, 1996-1997	2	ECO	AREA	Mean (± SD) age-adjusted mortality rate per 100,000 in 426 municipalities with vs 164 without incinerators	W 118.0 ± 13.0 vs 118.5 ± 13.2, p=0.68 M 187.4 ± 22.5 vs 191.6 ± 22.2, p=0.048
Workers						
Rapiti, 1997	Italy, 1962-1992	1	Hist CO	Employment rec	N= Mort 15/ O/E Ref: Lazio Region	0.95 (0.58-1.46) (90%CI)
Gustavvson, 1989	Sweden, 1951-1985	1	Hist CO	Employment rec	N=Mort 22, O/E Ref: national and local rates	National 1.35 (0.85-2.05) Local 1.07 (0.67-1.62)

Abbreviations: CO=Cohort; DIST=Distance; DM=Dispersion Model; E=Expected; ECO=Ecological; HAdm=Hospital admissions; Hist=Historical; HR=Hazard ratio; Inc=Incidence; M=Men; Mort=Mortality; N=number; O=Observed; rec=records; Ref=Reference; RR=Relative risk; SD=Standard Deviation; SIR= Standardized Incidence Ratio; W=Women.

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Table 3 – Studies investigating the association between exposure to incinerators and Non-Hodgkin Lymphoma (NHL).

First author, year	Location, Period	Incinerator generation	Design	Exposure assessment	Number of events, Risk indicator	Exposure category; Risk estimates
				General population		
Viel, 2000	France, 1980-1995	1	ECO	DIST	N= Inc 286, Spatial scan statistic to identify O/E clusters, Ref. Doubs department	3 Spatial cluster, 1.27, p-value 0.00003
Floret, 2003	France, 1980-1995	1	semi ECO CC	DM	N= Inc 31/ OR, Ref. <0.0001 pg/m^3 dioxin conc.	0.0004-0.0016 pg/m^3 dioxin: 2.3 (1.4-3.8)
Michelozzi, 1998	Italy, 1987-1993	1	ECO	DIST	N= Mort 63 (W) & 64 (M)/ SMR*100 Ref: Rome municipality	0-10 Km; W 116 (90-149) p trend 0.18 M 100 (77-127) p-trend 0.48
Elliott, 1996	UK, 1974-1987	1	ECO	DIST	N=Inc 2689/SIR; Ref UK	0-7.5Km; 1.04 (1.01-1.08), Stone's p value 0.015
Viel, 2008b	France, 1990-1999	2	ECO	DM	N= Inc 3974, RR derived from Poisson modelled O/E Ref: <2.5th percentile of dioxin exposure	>90th percentile; 1.120 (1.002-1.251)
Federico, 2010	Italy, 1991-2005	2	ECO	DIST	N= Inc 420/ SIR Ref: Modena municipality	0-5Km; 0.97 (0.88-1.06)
Ranzi, 2011	Italy, 1990-2003	2	semi ECO Hist CO	DM	N= Mort 12 (W) & 14 (M); Inc N=27 (W) & 28 (M)/ Rate ratios estimated by Poisson Regression. Ref: <0.5 ng/m^3 heavy metals	>2 ng/m^3 ; Mort: W 2.03(0.48-8.67) M 0.52(0.11-2.45); Inc: W 1.06(0.39-2.93) M 0.59 (0.23-1.57)
Romanelli, 2019	Italy, 2001-2012 (mortality) 2001-2014 (hospital admissions)	2	semi ECO Hist CO	DM	Mort N= 20 (M) & 13 (W); Inc N= 35 (M) & 28 (W) HR estimated by Cox regression. Ref: NO$_x$ ≤0.013 µg/m^3	NO$_x$ >0.031 µg/m^3 Mort M 2.31 (0.80-6.68), p=0.08 Mort W 1.37 (0.55-3.41), p=0.61 Inc M 1.85 (0.88-3.89), p=0.06 Inc W 1.54 (0.76-3.12), p=0.25
Garcia-Perez, 2013	Spain, 1997-2006	2	ECO	DIST	N= Mort 2396/ RR from Bayesian modelling of O/E Ref: Spain	≤5 km; 1.02(0.94-1.11)
Ortega Garcia, 2017	Spain, 1998-2015	2	ECO	DIST	N= Inc 6 (age<15 years)/ SIR Ref Murcia Region in 2011	<4 km; 1.65 (0.61-3.60) p value 0.15
Reeve, 2013	UK, 1998-2008	2	ECO	DIST	N= Inc 820/ RR derived from Poisson modelled O/E Ref: Control areas (without incinerators)	Areas with incinerator; 0.986 (0.945-1.028)
Pronk, 2013	USA, 1998-2000	2	semi ECO CC	DIST	N= 969 cases & 749 Controls/ OR Ref: never lived within 5 km from MSWI	Ever lived within 5 km; 0.5 (0.3-0.9)

Abbreviations: CC=Case-control; CO=Cohort; DIST=Distance; DM=Dispersion Model; E=Expected; ECO=Ecological; HAdm=Hospital admissions; Hist=Historical; Inc=Incidence; M=Men; Mort=Mortality; N=number; O=Observed; OR=odds ratio; Ref=Reference; RR=Relative risk; SIR= Standardized Incidence Ratio; SMR=Standardized mortality ratio; W=Women.

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Table 4 – Studies investigating the association between exposure to incinerators and Soft Tissue Sarcoma (STS)

First author, year	Location, Period	Incinerator generation	Design	Exposure assessment	Number of events/Risk indicator	Exposure category; Risk estimates
General population						
Viel, 2000	France, 1980-1995	1	ECO	DIST	N=Inc 45/ Spatial scan statistic to identify O/E clusters, Ref. Doubs department	Spatial cluster around the plant; 1.44 (p=0.004)
Zambon, 2007	Italy, 1990-1996	1	semi ECO CC	DM	N=Inc 81 cases & 190 controls/ OR Ref: <4 fg/m^3 TEQ PCDD/PCDFs (time weighted average)	≥ 6 fg/m^3 3.27 (1.35-7.93), p trend 0.0152
Comba, 2003	Italy, 1989-1998	1	semi ECO CC	DIST	N=Inc 37 cases & 171 controls/ OR Ref: >5 Km	≤ 2 Km; 31.4 (5.6-176.1)
Elliott, 1996	UK, 1974-1987	1	ECO	DIST	N=Inc 334/ SIR, Ref: Whole UK	0-7.5 Km; 1.03 (0.93-1.15), Stone's p value 0.490
Federico, 2010	Italy, 1991-2005	2	ECO	DIST	N=Inc 42/ SIR Ref: Modena	0-5 Km; 0.94 (0.68-1.27)
Ranzi, 2011	Italy, 1990-2003	2	semi ECO Hist CO	DM	N= Inc 5 (W) & 7 (M)/ Rate ratios estimated by Poisson Regression. Ref: <0.5 ng/m^3 heavy metals	>2 ng/m$^{3;}$; W 0.00, M 0.84 (0.09-8.06)
Garcia-Perez, 2013	Spain, 1997-2006	2	ECO	DIST	N= Mort 57/ RR from Bayesian modelling of O/E Ref: Spain	≤5 km; 1.04 (0.74-1.41)

Abbreviations: CC=Case-control; CO=Cohort; DIST=Distance; DM=Dispersion Model; E=Expected; ECO=Ecological; Hist=Historical; Inc=Incidence; M=Men; Mort=Mortality; N=number; O=Observed; OR=odds ratio; Ref=Reference; RR=Relative risk; SIR= Standardized Incidence Ratio; W=Women.

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Table 5 – Studies investigating the association between exposure to incinerators and pregnancy outcomes

First author, year	Location, Period	Incinerator generation	Design	Exposure assessment	Number of events/ Risk indicator	Exposure category; Risk estimates
Multiple births						
Rydhstroem, 1998	Sweden, 1973-1990	1	ECO	AREA	N range: before 25-234; after 16-269 RR as ratio of O/E ratios after and before start. Ref: Sweden	Range: 0.46 (0.29-0.73) to 1.72 (1.22-2.43) in 14 municipalities with incinerators
Lloyd, 1988	UK, 1975-1983	1	ECO	AREA	N= primary risk areas 10 & 16, secondary risk areas 25 & 4; control areas from 3-16/ Twinning rates/1000, in 1980-83	2 primary risk areas: 16.0 and 19.9 2 secondary risk areas: 12.1 and 5.6 Other 10 control areas: from 3.3-12.5
Obi-Osius 2004	Germany, 1994-1997	2	semi ECO CC	AREA	N= 275 mothers of twins and 20425 mothers/ OR Ref living in a non-exposed area	Living in 4 exposed areas: 1.89 (1.21-2.95); 2.03 (1.28-3.22); 1.77. (1.14-2.74); 1.69 (0.90-3.16)
Candela, 2013	Italy, 2003-2010	3	semi ECO CS	DM	N=260/ ORs by quintile of exposure Ref: <0.07 ng/m^3; of PM$_{10}$	PM$_{10}$ >0.81: OR= 0.87 (0.57-1.33) ; p-trend 0.923
Ghosh, 2019	UK, 2003-2010	3	semi ECO CS	DM	N=30,910/ OR per doubling of PM$_{10}$	Continuous; 0.99 (0.99-1.00).
Sex Ratio (SR)						
Williams, 1992	UK, 1975-1983	1	ECO	AREA	Total births =3577/ SR=(M/F)*100	3 risk areas; 87 (p<0.05), 105, 110 4 Comparison areas; range: 88-105
Lin, 2006	Taiwan, 1997	2	semi ECO CS	DM	Total births=6282/ OR of F Reference <0.03 pg TEQ/m^3 PCDD/F	>0.05 pg TEQ/m^3; 0.90 (0.78–1.05).
Candela, 2013	Italy, 2003-2010	3	semi ECO CS	DM	N of girls=10227/ ORs of F by quintile of exposure Ref <0.07 ng/m^3 PM$_{10}$	>0.81 ng/m^3; OR=0.91 (0.83-0.99) (p-trend=0.249)
Santoro, 2016	Italy, 2001-2010	3	semi ECO CO	DM	Total births =3069/OR of M. Ref ≤0.126 ng/m^3 PM$_{10}$	>0.196 ng/m^3 ; OR=1.17 (0.89-1.52) (p-trend=0.250)
Freni-Sterrantino, 2019	UK, 1996-2012	3	ECO	AREA	Total births=113,411 SR(F/M)=4.8 (IQR:9.6) MSWI area before MSWI opening Total births=157,317 SR(F/M)=3.9 (IQR:7.9) MSWI area after MSWI opening Total births=107,844 SR(F/M)=5.0 (IQR:9.4) comparator area before MSWI opening Total births=148,070 SR(F/M)=4.6 (IQR:9.0) comparator area after MSWI opening	summary index of difference (95% CrI) -0.004 (-0.02;0.01)
Miscarriage						
Vinceti, 2008	Italy, 2003-2006	2	ECO	DM	N=23 (residents) & 5 (workers)/ O/E ratio Ref: Modena municipality	all exposed residents; 1.00 (0.65-1.18); all exposed workers; 1.04 (0.38-2.30);

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First author, year	Location, Period	Incinerator generation	Design	Exposure assessment	Number of events/ Risk indicator	Exposure category; Risk estimates
Candela, 2015	Italy, 2002-2006	2	semi ECO CC	DM	N=1375/ OR ; Ref PM_{10}=0	PM_{10} >1.33; 1.29 (0.97-1.72); p- trend= 0.042
Vinceti, 2018	Italy, 2003-2013	3	ECO	DM	N=21 (residents) & 7 (workers)/ O/E period 2010-2013 Ref: Modena municipality	all exposed residents; 0.98 (0.63-1.48); all exposed workers; 0.91 (0.10-1.80);
Preterm birth						
Castello, 2013	Spain, 2004-2008	2	ECO	DIST	N=3933/ O/E ratios from Bayesian model; Ref: Spanish municipalities with no industries	<3.5 km; 0.99 (0.92-1.07)
Lin, 2006	Taiwan, 1997	2	semi ECO CS	DM	N=753/ OR; Ref <0.03 pg TEQ/m^3 PCDD/F	>0.05 pg TEQ/m^3; 1.22 (0.97-1.52);
Candela, 2013	Italy, 2003-2010	3	semi ECO CS	DM	N=1316/ ORs by quintile Ref <0.07 ng/m^3 PM_{10}	>0.81 ng/m^3 ; 1.30 (1.08-1.57); p-trend<0.001
Santoro, 2016	Italy, 2001-2010	3	semi ECO CO	DM	N=164/ OR Ref ≤0.126 ng/m^3 PM_{10}	>0.196 ng/m^3; 1.61 (0.88-2.94); p-trend=0.098
Ghosh, 2019	UK, 2003-2010	3	semi ECO CS	DM	N=42,224/ OR, per doubling of PM_{10}	Continuous; 0.99 (0.97, 1.01)
Low birth weight						
Castello, 2013	Spain, 2004-2008	2	ECO	DIST	N=4160/ O/E ratios from Bayesian model; Ref: Spanish municipalities with no industries	<3.5 km; 1.06 (1.01-1.11)
Tango, 2004	Japan, 1997-1998	2	ECO	DIST	N= 18167/ Cumulative O/E <10km	1.00 (0.98-1.01); p=0.786
Lin, 2006	Taiwan, 1997	2	semi ECO CS	DM	N=237/ OR Ref <0.03 pg TEQ/m^3 PCDD/F	>0.05 pg TEQ/m^3: 1.06 (0.71-1.57)
Santoro, 2016	Italy, 2001-2010	3	semi ECO CO	DM	N=74/ OR Ref ≤0.126 ng/m^3 PM_{10}	>0.196 ng/m^3 : 0.85 (0.34-2.08); p-trend=0.751
Ghosh, 2019	UK, 2003-2010	3	semi ECO CS	DM	N=634,347/ Mean difference in term birth weight per doubling of PM_{10}	Continuous; 0.12 g (-1.51-1.75)
Small for gestational age (SGA)						
Castello, 2013	Spain, 2004-2008	2	ECO	DIST	N=6633/ O/E ratios from Bayesian model; Ref: Spanish municipalities with no industries	<3.5 km; 1.06 (1.02-1.11)
Candela, 2013	Italy, 2003-2010	3	semi ECO CS	DM	N=2278/ ORs by quintile Ref <0.07 ng/m^3 PM_{10}	>0.81; 3 1.11 (0.96-1.28); p-trend =0.129
Santoro, 2016	Italy, 2001-2010	3	semi ECO CO	DM	N=456/ OR Ref ≤0.126 ng/m^3 PM_{10}	>0.196 ng/m^3: 1.30 (0.90-1.88); p-trend=0.155
Ghosh, 2019	UK, 2003-2010	3	semi ECO CS	DM	N=64,088/ OR per doubling of PM_{10}	Continuous; 0.99 (0.98, 1.00)
Neonatal death						
Dummer, 2003	UK, 1977-1993	1	semi ECO CO	DIST	N=570/OR per unit increase in distance function.	Continuous; 1.02 (0.90-1.14)
Tango, 2004	Japan, 1997-1998	2	ECO	DIST	N=471/ Cumulative O/E <10km	1.03 (0.94-1.13) p (Stone's unconditional)=0.523

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First author, year	Location, Period	Incinerator generation	Design	Exposure assessment	Number of events/ Risk indicator	Exposure category; Risk estimates
Freni-Sterrantino, 2019	UK, 1996-2012	3	ECO	AREA	Infant deaths/liver births mean rate (IQR) X 1000 MSWI exposed before opening 562/113,411 4.8 (9.6) MSWI exposed after opening 650/157,317, 3.9 (7.9) comparator area before opening 551/107,844 5.0 (9.4) comparator area after opening 699/148,070 4.6 (9.0)	summary index of difference (95% CrI) -8 (-62;40)
Ghosh, 2019	UK, 2003-2010	3	semi ECO CS	DM	N=3260/ OR per doubling of PM_{10}	Continuous; 0.99 (0.96-1.01)

Abbreviations: CC=Case-control; CO=Cohort; CS=cross-sectional; DIST=Distance; DM=Dispersion Model; E=Expected; ECO=Ecological; F=female; IQR=interquartile range; M=Male; MSWI=municipal solid waste incinerator; N=number; O=Observed; OR=odds ratio; Ref=Reference; RR=Relative risk; SR=sex ratio.

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Table 6. Studies investigating the association between exposure to incinerators and congenital anomalies

First author, year	Location, Period	Incinerator generation	Design	Exposure assessment	Number of events/Risk indicator/reference category	Exposure category; Risk estimates
Cardiovascular anomalies						
Dummer, 2003	UK, 1977-1993	1	semi ECO CO	DIST	N=417/ OR per unit increase in the (inverse) distance function $1/(d+0.1)^2$	Continuous; 1.12 (1.03-1.22)
Cordier, 2004	France, 1988-1997	2	ECO	DM	Conotruncal cardiopathies: N=670. Other cardiac anomalies: N=1288/ RR from Poisson modelled O/E Ref:2678 not exposed communities	194 exposed communities; Conotruncal cardiopathies: 1.12 (0.90-1.40). Other cardiac anomalies: 1.02 (0.87-1.20)
Vinceti, 2009	Italy, 1998-2006	2	semi ECO CC	DM	N=96 cases & 228 controls/ OR Ref< $<0.50*10^{-9}$ µg/m^3 PCDD/F	>0.50; 0.86 (0.40–1.86); P trend 0.666
Parkes, 2019	UK, 2003-2010	3	semi ECO	DM DIST	OR (95% CI); DM: risk per doubling in modeled PM$_{10}$; DIST: risk per km closer to the nearest MSWI (continuous) congenital heart defects: N=1232 severe congenital heart defect: N=436	congenital heart defects: N at risk=216,644; 0.99 (0.93-1.05) for DM; 1.04 (1.01-1.08) for DIST severe congenital heart defect: N at risk=215,954; 1.03 (0.97-1.10) from DM; 1.02 (0.97-1.07) for DIST
Chromosomal anomalies						
Cordier, 2004	France, 1988-1997	2	ECO	DM	N=1094/ RR from Poisson modelled O/E Ref:2678 not exposed communities	194 exposed communities; 1.01 (0.86-1.20)
Vinceti, 2009	Italy, 1998-2006	2	semi ECO CC	DM	N=41 cases& 228 controls/OR Ref $<0.50*10^{-9}$ µg/m^3 PCDD/F	>0.50; 1.82 (0.70–4.72); P trend 0.486
Congenital malformations (CM)						
Dummer, 2003	UK, 1977-1993	1	semi ECO CO	DIST	CM as cause of death: N=417/ OR per one unit increase in the (inverse) distance function $1/(d+0.1)^2$	Continuous; 1.10 (1.03-1.19).
Cordier, 2004	France, 1988-1997	2	ECO	DM	CM in offspring or aborted fetuses n=8211/ RR from Poisson modelled O/E Ref:2678 not exposed communities	194 exposed communities; 1.04 (0.97-1.11)
Vinceti, 2008	Italy, 2003-2006	2	ECO	DM on area	CM in offspring or aborted fetuses N=4 (residents) & 3 (workers) / O/E Ref: Modena municipality	all exposed residents 0.64 (0.20-1.55); all exposed workers 2.26 (0.57-6.14);
Vinceti, 2009	Italy, 1998-2006	2	semi ECO CC	DM	CM. in offspring or in aborted fetuses n=228 cases; n=228 controls/ OR Ref $<0.50*10^{-9}$ µg/m^3 PCDD/F	>0.50; 1.11 (0.60–2.04); P trend 0.881
Cresswell, 2003	UK, 1985-1999	2	ECO	DIST	CM in offspring or aborted fetuses N=1188/Rate ratios Ref: 3-7 km	<3 km; 1.11 (0.96-1.28)

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First author, year	Location, Period	Incinerator generation	Design	Exposure assessment	Number of events/Risk indicator/reference category	Exposure category; Risk estimates
Tango, 2004	Japan, 1997-1998	2	ECO	DIST	CM as cause of neonatal death: n=186/ Cumulative O/E Ref: Japan	<10km ; 1.06 (0.91-1.22); p (Stone's unconditional) 0.629
Vinceti, 2018	Italy, 2003-2013 (2010-2013)	3	ECO	DM	CM. in offspring or aborted fetuses / N=1 (residents) & 2 (workers). O/E period 2010-13 Ref: Modena municipality	all residents: 0.44 (0.02-2.19) all workers: 2.99 (0.60-9.57);
Parkes, 2019	UK, 2003-2010	3	semi ECO CS	DM DIST	OR (95% CI); DM: risk per doubling in modeled PM_{10}; DIST: risk per km closer to the nearest MSWI (continuous) all congenital anomalies: N=5154	all congenital anomalies: N at risk=219,486; 1.00 (0.98-1.02) from DM; 1.02 (1.00-1.04) for DIST
cranio-facial anomalies						
Jansson, 1989	Sweden, 1973-1986	1	ECO	mother's residence	Pre incinerator: n=130. Post incinerator: N=38/rate ratio Ref: pre incinerator	1.02 (0.71-1.47)
ten Tusscher, 2000	The Netherlands, 1960-1969	1	ECO	birth clinic	N=59/incidence (n/1000 births) Ref: Wilhelmina hospital	1960-1969 2.4 Zeeburg (close to incinerator) 1960-1969 1.2 Wilhelmina (12 km away)
Cordier, 2004	France, 1988-1997	2	ECO	DM	Craniostenosis n=224. Facial clefts n=738 / RR from Poisson modelled O/E Ref:2678 not exposed communities	Craniostenosis: 1.10 (0.68-1.77). Facial clefts: 1.30 (1.06-1.59)
Vinceti, 2009	Italy, 1998-2006	2	semi ECO CC	DM	N=0 cases & 22 controls/ OR Ref <0.50* 10^{-9} $\mu g/m^3$ PCDD/F	>50; not estimated
Parkes, 2019	UK, 2003-2010	3	semi ECO CS	DM DIST	OR (95% CI); DM: risk per doubling in modeled PM_{10}; DIST: risk per km closer to the nearest MSWI (continuous) oro-facial clefts: N=339 cleft palate: N=124 cleft lip with or without cleft palate: N=217	oro-facial clefts: N at risk=215,931; 1.00 (0.94-1.07) from DM; 0.99 (0.94-1.05) for DIST cleft palate: N at risk=215,749; 1.02 (0.92-1.13) from DM; 0.98 (0.90-1.06) for DIST cleft lip with or without cleft palate: N at risk=215,822; 1.00 (0.93-1.08) from DM; 1.00 (0.94-1.07) for DIST
nervous system anomalies						
Dummer, 2003	UK, 1977-1993	1	semi ECO CO	DIST	N=132/ OR per one unit increase in the (inverse) distance function $1/(d+0.1)^2$	Continuous; 1.13 (1.04-1.23)
Cordier, 2004	France, 1988-1997	2	ECO	DM	Eye anomalies N=136. Neural tube defects N=402 Other cerebral anomalies N=476// RR from Poisson modelled O/E Ref:2678 not exposed communities	194 exposed communities; Eye anomalies 1.09 (0.67-1.77). Neural tube defects 0.86 (0.63-1.20). Other cerebral anomalies 0.99 (0.77-1.28)

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First author, year	Location, Period	Incinerator generation	Design	Exposure assessment	Number of events/Risk indicator/reference category	Exposure category; Risk estimates
Parkes, 2019	UK, 2003-2010	3	semi ECO CS	DM DIST	OR (95% CI); DM: risk per doubling in modeled PM$_{10}$; DIST: risk per km closer to the nearest MSWI (continuous) nervous system: N= 543 neural tube defect: N=264	nervous system: N at risk=215,863; 0.97 (0.92-1.02) from DM; 0.97 (0.93-1.02) for DIST neural tube defect: N at risk=215,695; 1.00 (0.92-1.07) from DM; 0.97 (0.91-1.03) for DIST
					other anomalies	
Dummer, 2003	UK, 1977-1993	1	semi ECO CO	DIST	N=181/ OR per unit increase in the (inverse) distance function $1/(d+0.1)^2$	Continuous; 0.90 (0.67-1.22).
Cordier, 2004	France, 1988-1997	2	ECO	DM	Unknown or multifactorial aetiology N=5202. Minor anomalies N=3009. Major anomalies N=761/ RR from Poisson modelled O/E Ref:2678 not exposed communities	194 exposed communities; Unknown or multifactorial aetiology: 1.07 (0.98-1.16). Minor anomalies: 0.94 (0.84-1.06). Major anomalies: 1.00 (0.81-1.23)
Vinceti, 2009	Italy, 1998-2006	2	semi ECO CC	DM	N=16 cases & 228 controls/ OR Ref< $<0.50*10^{-9}$ µg/m^3 PCDD/F	>0.50; 1.11 (0.24–5.10)
Parkes, 2019	UK, 2003-2010	3	semi ECO CS	DM DIST	OR (95% CI); DM: risk per doubling in modeled PM$_{10}$; DIST: risk per km closer to the nearest MSWI (continuous) abdominal wall defects: N=222 gastroschisis: N=133 digestive system: N=355 oesophageal atresia: N=51	abdominal wall defects: N at risk=215,788; 1.00 (0.92-1.08) for DM; 1.00 (0.94-1.07) for DIST gastroschisis: N at risk=215,753; 1.04 (0.94-1.15) from DM; 0.97 (0.89-1.05) for DIST digestive system: N at risk=215,928; 1.00 (0.92-1.09) from DM; 1.00 (0.95-1.06) for DIST oesophageal atresia: N at risk=215,681; 1.04 (0.88-1.22) from DM; 0.92 (0.80-1.05) for DIST
					renal anomalies	
Cordier, 2004	France, 1988-1997	2	ECO	DM	Obstructive uropathies N=429. Other renal anomalies N=79. Renal agenesis N=107. Renal dysplasia N=254/ RR from Poisson modelled O/E Ref:2678 not exposed communities	194 exposed communities; Obstructive uropathies 1.22 (0.90-1.65) Other renal anomalies 0.44 (0.20-0.97) Renal agenesis 1.11 (0.64-1.93) Renal dysplasia 1.55 (1.10-2.20)
Cordier, 2010	France, 2001-2003	2	semi ECO CC	DM	N=304 cases & 226 controls/OR Ref: "not exposed" to atmospheric dioxin	renal birth defects and obstructive uropathy: exposed; 1.99 (1.17-3.40)

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First author, year	Location, Period	Incinerator generation	Design	Exposure assessment	Number of events/Risk indicator/reference category	Exposure category; Risk estimates
Parkes, 2019	UK, 2003-2010	3	semi ECO CS	DM DIST	OR (95% CI); DM: risk per doubling in modeled PM_{10}; DIST: risk per km closer to the nearest MSWI (continuous) anomalies of the renal system: N=241 obstructive defects of renal pelvis: N=255	anomalies of the renal system: N at risk=215,803; 1.02 (0.95-1.10) from DM; 1.00 (0.93-1.07) for DIST obstructive defects of renal pelvis: N at risk=215,840; 0.97 (0.90-1.04) from DM; 1.03 (0.97-1.10) for DIST
skeletal anomalies						
Cordier, 2004	France, 1988-1997	2	ECO	DM	Limb reduction defects N=251. Preaxial limb deformities N=95. Vertebral anomalies N=119/ RR from Poisson modelled O/E Ref:2678 not exposed communities	194 exposed communities; Limb reduction defects 0.78 (0.51-1.20). Preaxial limb deformities 0.72 (0.33-1.60). Vertebral anomalies 1.20 (0.65-2.10)
Vinceti, 2009	Italy, 1998-2006	2	semi ECO CC	DM	N=139 cases & 228 controls/ OR Ref< $<0.50*10^{-9}$ $\mu g/m^3$ PCDD/F	>0.50; 1.13 (0.41–3.10) P trend 0.928
Parkes, 2019	UK, 2003-2010	3	semi ECO CS	DM DIST	OR (95% CI); DM: risk per doubling in modeled PM_{10}; DIST: risk per km closer to the nearest MSWI (continuous) limb defects: N=746 limb reduction defect: N=122	limb defects: N at risk=216,252; 1.01 (0.94-1.08) from DM; 1.02 (0.97-1.08) for DIST limb reduction defect: N at risk=215,725; 1.02 (0.91-1.14) from DM; 0.98 (0.90-1.08) for DIST
urogenital anomalies						
Cordier, 2004	France, 1988-1997	2	ECO	DM	N=442/ RR from Poisson modelled O/E Ref:2678 not exposed communities	194 exposed communities; 0.88 (0.66-1.19)
Vinceti, 2009	Italy, 1998-2006	2	semi ECO CC	DM	congenital malf. in offspring or in aborted fetuses N=23 cases & 228 controls/ OR Ref< $<0.50*10^{-9}$ $\mu g/m^3$ PCDD/F	>0.50; 0.41 (0.05–3.17) P trend 0.344
Parkes, 2019	UK, 2003-2010	3	semi ECO CS	DM DIST	OR (95% CI); DM: risk per doubling in modeled PM_{10}; DIST: risk per km closer to the nearest MSWI (continuous) urinary system: N=534 genital system: N=472 hypospadias: N=407	urinary system: N at risk=216,037; 1.00 (0.94-1.07) from DM; 1.02 (0.97-1.06) for DIST genital system: N at risk=216,053; 1.03 (0.95-1.13) from DM; 1.07 (1.02-1.12) for DIST hypospadias: N at risk=216,004; 1.00 (0.90-1.12) from DM; 1.07 (1.01-1.12) for DIST

Abbreviations: CC=Case-control; CM=congenital malformations; CO=Cohort; DIST=Distance; DM=Dispersion Model; E=Expected; ECO=Ecological; N=number; O=Observed; OR=Odds ratio; Ref=Reference; RR=relative risk.

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- Emissions declined over time, and older studies do not apply to new incinerators.
- This systematic review of health effect in the population considered the generation.
- Evidence on effects of modern incinerators is scarce and limited to pregnancy.
- Increases in lymphomas and sarcomas in older plants were not found in newer ones.
- Methodological improvements are warranted in further research.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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