Study of the incidence of cancers close to municipal solid waste incinerators

Summary

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Foreword
This document is a summary of the study report, presenting an exhaustive description of the materials and methods used in this work and all the results obtained. The complete report is available online from the InVS website: www.invs.sante.fr/publications
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ADEME</td>
<td>Agence de l’environnement et de la maîtrise de l’énergie / Agency for Environment and Control of Energy</td>
</tr>
<tr>
<td>ADMS</td>
<td>Atmospheric dispersion modelling system</td>
</tr>
<tr>
<td>AFSSET</td>
<td>Agence française de sécurité sanitaire de l’environnement et du travail / French Agency for Environmental and Occupational Safety</td>
</tr>
<tr>
<td>AhR</td>
<td>Aryl hydrocarbon receptor</td>
</tr>
<tr>
<td>CHU</td>
<td>Centre hospitalier universitaire / University hospital</td>
</tr>
<tr>
<td>ICD-O-2</td>
<td>Version 2 of the international classification of diseases for oncology</td>
</tr>
<tr>
<td>DRIRE</td>
<td>Direction régionale de l’industrie, de la recherche et de l’environnement / Regional Office of Industry, Research and Environment</td>
</tr>
<tr>
<td>FRANCIM</td>
<td>France-cancer-incidence et mortalité / French network of cancer registries</td>
</tr>
<tr>
<td>GAM</td>
<td>General additive models</td>
</tr>
<tr>
<td>PAH</td>
<td>Polycyclic aromatic hydrocarbon</td>
</tr>
<tr>
<td>IFEN</td>
<td>Institut français de l’environnement / French Institute for Environment</td>
</tr>
<tr>
<td>IGN</td>
<td>Institut géographique national / National Geographic Institute</td>
</tr>
<tr>
<td>IRIS</td>
<td>Îlots regroupés pour l’information statistique / Clusters for statistical information</td>
</tr>
<tr>
<td>INSEE</td>
<td>Institut national de la statistique et des études économiques / French Institute of Statistics and Economic Studies</td>
</tr>
<tr>
<td>INSERM</td>
<td>Institut national de la santé et de la recherche médicale / French Institute for Health and Medical Research</td>
</tr>
<tr>
<td>MNHL</td>
<td>Malignant non-Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>PCB</td>
<td>Polychlorobiphenyl</td>
</tr>
<tr>
<td>PM$_{10}$</td>
<td>Fine particles with a diameter of no more than 10 microns</td>
</tr>
<tr>
<td>TCDD</td>
<td>Tetrachlorodibenzo-p-dioxin</td>
</tr>
<tr>
<td>MSWI</td>
<td>Municipal solid waste incinerator</td>
</tr>
<tr>
<td>INRETS</td>
<td>Institut national de la recherche sur les transports et leur sécurité / French Institute for Research on Transportation and Safety</td>
</tr>
<tr>
<td>GIS</td>
<td>Geographic Information System</td>
</tr>
<tr>
<td>InVS</td>
<td>Institut de veille sanitaire / French Institute for Public Health Surveillance</td>
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<tr>
<td>RR</td>
<td>Relative Risk</td>
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1. Introduction

1.1 The incineration of household waste

France has been using incineration to eliminate household and similar waste since 1970. According to Ademe, French households produced more than 26 million tonnes of waste (household waste and large objects) in 2003, 35% of which was incinerated [1]. The number of municipal solid waste incinerators (MSWIs) has decreased in recent years, from 292 in 1985, to 213 in 2000 and 135 in 2004 [2].

However, the impact of the rejects discharge from MSWIs on human health remains a subject of concern for French populations living in the vicinity of these industrial installations.

The deleterious effects on health of the pollution generated by MSWIs result from the quantity and type of chemical agents emitted into the air from the incinerator stack. These emissions consist of complex mixtures containing, essentially, sulphur dioxide, nitrogen oxides, hydrochloric acid, heavy metals, dioxins, particles and polycyclic aromatic hydrocarbons (PAHs) [3-8]. Most of these compounds are toxic, and some have demonstrated or suspected carcinogenic properties in humans or animals [9-17].

1.2 Epidemiological justification of the study

Nowadays, all the 135 French MSWI meet the European norms of atmospheric emission [18-19]. Nevertheless, oldest incinerators have contributed to increase the past overall environmental load of dioxins and other persisting pollutants in soils and local food. The atmospheric emissions from incinerators contain various substances individually known or suspected to be toxic for human in chronic exposure situations [5;20-22]. The complex mixtures emitted from MSWI include numerous metals such as cadmium, thallium, lead, arsenic, antimony, chromium, cobalt, copper, manganese, nickel, zinc and mercury [12;23-26]. Information on effects of environmental exposure to metals is limited but some of them are classified as certain or potential carcinogens for humans by the International Agency for Research on Cancer (IARC) [27;28] Airborne particles, nitrogen dioxide, sulfur dioxide and carbon monoxide are also emitted by municipal incinerators [5]. Polycyclic aromatic hydrocarbons (PAHs), released during the incomplete combustion or pyrolysis of organic matter, are associated with cancer occurrence, in particular with lung [29;30], breast and bladder cancers [31;32] and also with non-Hodgkin’s lymphomas [17]. Moreover, poorly controlled combustion processes entail the production of dioxins, a class of compounds that includes two chemical families, polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzo-p-furans (PCDFs). In 1997, the IARC has classified the most toxic of these compounds, the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), as a known human carcinogen [10;11]. This statement was primarily based on animal experiments [33], and then has been essentially supported by numerous occupational studies. Becher, in highly dioxin and furan exposed workers, showed an excess risk of mortality by respiratory cancer (standardized mortality ratio (SMR)=1.54; 95% confidence interval (CI),1.15-2.02) [34]. Kogevinas in a historical cohort study showed a higher mortality rate from all malignant neoplasms (SMR=1.12; 95% CI,1.04-1.21) of 21,863 male and female workers in 36 cohorts exposed to phenoxy herbicides, chlorophenoins, and dioxin [35]. Hooeiveld in a retrospective cohort study of workers exposed to herbicides containing TCDD and other polychlorinated hydrocarbons showed increased relative risk (RR) for total mortality (RR=1.8; 95% CI,1.2-2.5), cancer mortality (RR=4.1; 95% CI,1.8-9.0), respiratory cancer mortality (RR=7.5; 95% CI,1.0-56.1) and non-Hodgkin’s lymphoma mortality (RR=1.7; 95% CI,0.2-16.5) in male workers [36]. Steenland, in a mortality cohort involving 5,132 TCDD exposed workers at 12 US plants observed a SMR of 1.60; 95% CI,1.15-1.82 for all cancers combined in the highest exposure group [30].

This IARC classification has also been supported by data issued from the follow-up of the cohort of the resident population accidentally exposed to nearly "pure" TCDD after the explosion of a plant in Seveso (Italy) which brought additional evidences after a sequential follow-up at 10, 15 and 20 years [37-40].

Fifteen years after the accident, mortality among men increased from all cancers (RR=1.3; 95% CI,1.0,1.7), rectal cancer (RR=2.4; 95% CI,1.2,4.6), and lung cancer (RR=1.3; 95% CI,1.0,1.7). An excess of non-Hodgkin’s lymphoma (RR=2.8; 95% CI,1.1,7.0) and myeloid leukemia (RR=3.8; 95% CI,1.2,12.5) were also observed. In women only, lymphohemopoietic neoplasms (RR=1.8; 95% CI,1.8,3.2) and multiple myeloma incidence (RR=3.2; 95% CI,1.2,8.8), were also increased. Twenty years after this industrial accident, an excess of lymphohemopoietic neoplasms was revealed in both genders (RR=1.7; 95% CI,1.2,2.5). The 30 year follow-up of this cohort revealed that the hazard ratio for breast cancer doubled with elevated TCDD serum levels [41].

However, in animal models, as well as in occupational or accidental settings in human, whatever the pollutant, the exposure is characterized by high doses during a relatively short period of time. The question of a potential effect remains open in environmental situation where the humans are daily exposed to extremely low concentrations of pollutants but for long periods of time, often several decades, as is the case for population residing in the vicinity of MSWI. Thus, it is not yet clear whether environmental exposure to MSWI atmospheric release affects the general population. Few studies have been carried out to evaluate the health impact of a long-term exposure of population living close to that type of facilities and some of them were controversial. For instance, Michelozzi in 1998 did not observe, in a suburb of Rome, overall excess or a gradient in risk for lung, liver, and lymphohaematopoietic cancers in either sex, with distance to a waste disposal site, a waste incinerator plant, and an oil refinery plant [42]. On the other hand, Elliott reported in 2000 an excess risk of liver cancer (between 0.53 and 0.78 excess cases per 10^4 per year) for people living within 1 km of 72 municipal solid waste incinerators in Great Britain [43;44]. Biggeri, also in 1996, showed in a case-control population-based study carried out in Italy a positive relationship between distance of homes from an incinerator and lung cancer incidence: p-value=0.0098 with an excess risk of 6.7 [45].

Viel, in 2000, identified clusters of non-Hodgkin’s lymphoma and soft tissue sarcoma (STS) from 1980 to 1995 around a MSWI in a French district by applying a spatial scan statistic to 26 electoral wards. The standardized incidence ratios were 1.44 (p-value=0.004)
and 1.27 (p-value=0.00003) for non-Hodgkin’s lymphoma and STS, respectively [46]. To complete these results, the authors found in a nested case-control study a 3 times higher risk of non-Hodgkin’s lymphomas (95% CI [1.4-3.8]) among individuals living in the area with the highest dioxin airborne concentration [47], but they didn’t find any significantly increased risk for STS [48]. Zambon, in a case-control population-based study in Italy with complete residential history, estimated in 2007 that the risk of developing a sarcoma was increased for subjects with the longest and highest exposure to emissions from incinerators and other industrial plants (Odd ratio (OR)=3.3; 95% CI,1.24-8.76) [49]. After complete reconstruction of the residential history of 37 population-based cases and 171 controls of STS, Comba, in Italy, showed a significant increase in risk of STS associated with residence within 2 km of an industrial waste incinerator (OR=31.4; 95% CI,5.6-176.1) [50].

Faced with public awareness and the growing number of epidemiological evidences of the health impact of the environmental pollution due to waste incineration, a working group was set up by the French Institute for Public Health Surveillance (InVS) in 2002, at the request of the Ministry of Health. The aim was to identify epidemiological studies that might help to increase our understanding of the environmental causes of cancer, focusing particularly on the effect of atmospheric emissions from MSWIs on the frequency of cancers in the neighbouring populations. This group recommended, in particular, the implementation of a multicentric study of cancer incidence to ensure a high level of statistical power and to increase the likelihood of observing a wide range of exposure levels.

This was the objective of the study described here, which was funded as part of the 2003-2007 Cancer Plan.
2. Study aims

2.1 Principal objective

The main objective of this study was to investigate the relationship between cancer incidence in the general population and exposure to atmospheric emissions from MSWIs.

2.2 Specific objectives

- To evaluate the exposure of populations to substances released into the atmosphere by MSWIs and to the main risk factors for cancer, during the period extending from 1970 to 1980.
- To estimate, in these populations, the incidence of cancers between 1990 and 1999, for all cancer types and for localisations for which a link has been established or suspected between cancer incidence and MSWs exposure.
- To quantify the risk of cancer as a function of exposure to the atmospheric emissions from MSWIs.
3. Methods

3.1 Type of study

This epidemiological work was a geographic, ecological study. It analysed, at a collective level, the incidence of cancers as a function of past exposure to the atmospheric discharge from MSWIs. We also tried to take into account other factors potentially contributing to the occurrence of cancers.

3.2 The statistical unit

We conducted this ecological study in four French “départements” (administrative district subdividing a Region): Haut-Rhin, Bas-Rhin, Isère, and Tarn, covered by a population-based cancer registry. These districts were chosen according to statistical power and feasibility criteria and to be roughly representative of the overall geographical and socio-economical French heterogeneity. All taken together they were large enough to permit a 10 year observation of 2.5 millions of adults. Given the a priori power calculation, this could allow us detecting a RR = 1.1 for leukemias with the power of 80%.

The four districts were divided into 2,270 sub-areas called “Îlot Regroupé pour l’Information Statistique” (IRIS). It was the statistical unit of this ecological study. This entity is a geographical unit defined by the French Institute of Statistics and Economic Studies (INSEE) by dividing up communities of more than 10,000 inhabitants into homogeneous groups of about 2,000 people. For each of these units, various types of information, including socio-demographic data, are available.

3.3 Study periods

This study included three successive periods: a phase in which the populations were exposed to emissions from MSWIs, followed by a latency period compatible with the onset of cancer and, finally, a period of observation in which the incidence of cancers was determined.

- The exposure period was defined as the time between the year in which each incinerator began activity (1972 for the oldest one) and the year at the start of the latency period, according to the year of calculation of the mean cancer incidence (1995), that is 1985 for solid cancers and 1990 for leukemias.
- The latency period is the minimum period between the start of exposure and the time of cancer diagnosis. Knowledge in this domain remains fragmented. However, based on the references consulted [40;51] the latency period applied for this study was five years for leukemias and 10 years for other kinds of general cancers.
- The cancer case collection period used for the observation of cancer incidence extended over ten years, from 01/01/1990 to 31/12/1999 inclusive.

3.4 Study population

The incidence of cancers was calculated for the adult population of both sexes aged over 14 years at the time of diagnosis.

3.4.1 Estimation of the required sample size

The population sample size required was estimated from cancer incidence rates for the French population during the study period, using leukemias as a reference, since these cancers had one of the lowest incidences among the types of cancer studied. We calculated that the observation of cancer incidence during 10 years of 446,700 exposed individuals would give a statistical power of 80%. A sample of this size could be attained by including two or three départements.

In practice, in view of data availability and the need to take into account adjustments for confounding factors, we decided to include the population of four départements, to maximise statistical power.

3.4.2 Selection of the study zone

In 1999, France had 21 cancer registries belonging to the FRANCIM (France-cancer-incidence and mortality). This network included 10 general cancer registries covering all tumours in 11 départements of mainland France: Bas-Rhin, Calvados, Doubs, Haut-Rhin, Hérault, Isère, Manche, Somme, Tarn, Loire-Atlantique and Vendée.

We developed a procedure for ranking départements on the basis of a score for each of the following feasibility criteria:

1) Existence of a general cancer registry with validated data for the period 1990-1999;
2) Number of cases of cancer observed during the study period 1990-1999;
3) Availability in digital format of the precise home address of the patients at the time of cancer diagnosis;
4) Number of communities split into IRIS units;
5) Minimal migration rates according to the 1990 census.

The four départements considered the most appropriate for study, based on this procedure, were Isère, Haut-Rhin, Bas-Rhin and Tarn (figure 1).

3.5 Types of cancer studied

Incidence rates were estimated for all cancers together and for pre selected subtypes for which a relationship with the exposure to pollutants emitted by MSWI was already suspected or demonstrated in the literature: lung, liver, breast, bladder cancers, soft-tissue sarcomas, myelomas, acute and chronic lymphoid leukemias. Non-Hodgkin’s lymphomas
The definition of cancer cases used in this study was that established by Remontet et al. [52;53]. Cancer sites were classified as in version two of the international classification of diseases for oncology (ICD-O-2). Only soft-tissue sarcomas were defined using a specific algorithm proposed by E. Desandes from the childhood solid tumours registry.1

In this study, we recorded only primary, strictly invasive cancers.

All cancers
The smoke released by MSWIs contains many chemical agents, several of which have been identified as carcinogenic in humans (2,3,7,8-TCDD, PAHs, heavy metals etc.) and are likely to affect various organs. The carcinogenic potential of one such group of agents, dioxins, has been well documented, but remains a matter of debate [11;54]. The biological mechanisms of action of dioxin is thought to involve the aryl hydrocarbon receptor (AhR), also known as the “dioxin receptor”, which is present in many of the cells in the body and plays a role in immune system function and the control of cell proliferation [55;56].

Liver cancers
Liver cancers were defined exclusively as hepatocellular carcinomas and carcinomas of the intrahepatic biliary canal. All other liver tumours were excluded for the purposes of this study. Together with the adipose tissue, the liver is one of the principal sites of storage of organochlorine compounds in the body. A relationship between the role of the AhR and oncogenic mutations in hepatic cells has been demonstrated in several experimental studies in animals [62-64]. P. Elliott showed, in a study of the general population in the United Kingdom, that there was a relationship between living near an incinerator and an excess risk of liver cancer [43;44].

Lung cancers
Lung cancers included malignant tumours of the trachea, bronchi and lung and contiguous sites to which cancers might extend via the bronchi or pulmonary tissues. Studies of various groups of workers have provided evidence of a relationship between exposure to 2,3,7,8-TCDD and the risk of lung cancer [35;36;65] General population studies and follow-up studies of the Seveso cohort [40] have also provided evidence in favour of a relationship between exposure to the pollutants released from incinerators and the risk of lung cancer [43;45].

Acute leukaemias
The term “acute leukaemia” encompasses the acute and subacute forms of leukaemia, aleukaemic forms, acute and subacute myeloid leukaemia, acute lymphoid leukaemia and acute lymphoblastic leukaemia, Burkitt cell leukaemia, erythroleukaemia, acute promyelo cytotic leukaemia, myelomonocytic leukaemia, acute and subacute monocytic leukaemia, megakaryocytic leukaemia and myeloid sarcomas.

1 The national registry of childhood solid tumours – Université Henri Poincaré Nancy 1, Faculté de Médecine 9, Avenue de la Forêt de Haye BP 184, 54505 Vandœuvre-lès-Nancy cedex, France.
Chronic lymphoid leukaemias

The hypothesis of a relationship between malignant haemopathies and industrial emissions has been raised by several studies: a case-control study in the general population living close to a source of industrial pollution in North America [66], a follow-up study by Elliott in the United Kingdom [43] and studies involving 15 to 20 years of follow-up of individuals accidentally exposed to 2,3,7,8-TCDD in the Seveso cohort [40].

ICD-O-2 characteristics: C00.0 à C80.9, M9823

Behavior/3

Bladder cancers

Several studies in occupational environments and in general populations have provided evidence for a link between the incidence of bladder cancers and exposure to various toxic compounds released by incinerators, including PAHs [67] and dioxins [68]. A similar link has also been reported for environmental exposure to dioxins [66] and for passive smoking [69].

ICD-O-2 characteristics: C67.0 à C67.9

All morphologies

Behavior/3

Breast cancers

Breast cancers were defined as tumours of the connective tissue of the breast, nipple, areole, central area and the four quadrants, axillary extensions and contiguous sites. In a literature review, the hypothesis of a relationship between breast cancer and dioxin exposure was initially rejected [6]. However, an analysis of the women of the Seveso cohort in autumn 2005 [41] revealed for the first time the existence of a highly significant relationship.

ICD-O-2 characteristics: C50.0 à C50.9

Toutes morphologies

Behavior/3

3.6 Collection and processing of data for the observed cancers

The data for cases of cancer diagnosed between 01/01/1990 and 31/12/1999, in patients of both sexes over the age of 14 years, were collected from general cancer registries in the four départements participating in the study. The data collected concerned:

- year of birth;
- age at diagnosis;
- gender;
- year of diagnosis;
- topography, morphology and behaviour of the cancer according to the second edition of the International Classification (ICD-O-2);
- postal code and town of residence at the time of diagnosis;
- precise home address at the time of diagnosis (including number, and the name and type of road).

The geographical coding of each cancer case to its IRIS of residence was based on the postal address of the patient at the time of diagnosis: more than 99% of cancer cases were successfully assigned to their IRIS of residence.

All cancer cases were then identified in accordance to their topography, morphology and behaviour ICD-O-2 characteristics. Then, cases of cancer were aggregated by IRIS to obtain the observed cancer incidence at the statistical unit level.

3.7 Estimate of exposure to atmospheric release from incinerators

Several steps were required to estimate retrospectively the level of exposure of statistical units to atmospheric discharge from incinerators.

3.7.1 Identification of sources of emission in the four départements studied

All incinerators operating between 1972 and 1990 in the four départements studied were considered. In total, 16 plants functioning during the study period were included (figure 1):

- 10 incinerators in Isère: the MSWIs of La Tronche, Pontcharra, Bourgoin-Jallieu, Sousville, Livet-Gavet, Saint-Marcelin, Pont-de-Beauvoisin, Saint-Laurent, Crolles and Vaulnaveys;
- 1 incinerator in Bas-Rhin: the MSWI of Strasbourg;
- 2 incinerators in Haut-Rhin: the MSWIs of Mulhouse and Colmar;
- 3 incinerators in Tarn: the MSWIs of Saint-Juéry, Lautrec and Aussson (also known as Mazamet).

3.7.2 Determination of the technical characteristics of the incinerators

Visits were made to all the incinerators. We asked the operators of the MSWIs and Regional Offices of Industry, Research and Environment (DRIRE) for technical and historical information concerning each of the MSWIs studied, from its opening to the end of the 1990s. The principal data collected were administrative and operating data, information on environmental characteristics and, where available, emission data.
Figure 1: The four départements included in the study and their municipal solid waste incinerators (MSWIs)

3.7.3 Retrospective evaluation of the flow of pollutants emitted from incinerator stacks

In the absence of direct measurements of pollutant emission during the exposure of the study period, it was necessary to quantify retrospectively, by an alternative method, the emissions of three main groups of pollutants from each incinerator: particles, heavy metals and dioxins.

This retrospective evaluation of stack emissions was based on the consensus of a group of experts, representing operators, public authorities and a research institution. We used a simplified version of the Delphi method [70], that is an iterative process towards consensus, and took into account the incinerators technical characteristics and their evolution over time: capacity, type of combustion, clearance and filtration processes. This task was performed in three subsequent steps:
- classification of incinerators into eight homogeneous groups according to their technical characteristics, including the nominal capacity of the incinerator, the volume of waste incinerated, the continuous/discontinuous nature of the process, energy recovery, the existence of discharge treatment systems and the age of the installation;
- estimate of the emission flow (in μg/Nm³) of pollutants released for each of the eight groups of MSWIs;
- the flow values estimated for each of the eight categories of incinerators were then multiplied by the annual tonnage of waste cremated by each incinerator: this gave the emission of each incinerator per μg/s.

The estimated emissions obtained for the three groups of pollutants were used as the input data for the model of atmospheric dispersion.

3.7.4 Modelling of atmospheric dispersion and surface deposition

A Gaussian model was used to model atmospheric dispersion and ground-level deposit within a square grid with unit cells of 200 m × 200 m, centred on the stack.

The extent of the modelling area was adapted to the plant characteristics and its environment, ranging from 20 km × 20 km to 40 km × 40 km. This work was done with the software ADMS version 3 (Numtech®) developed by CERC and UK Meteorological Office (www.cerc.co.uk). It is a second generation Gaussian model: it accounts for the changes in flow field and turbulence around complex terrain and uses them to compute concentrations. This was interesting as a few incinerasers in the Isère département are located in valleys next to mountains as it can be seen in figure 2. The parameters considered in the modelling process are: estimated flow obtained from the experts, pollutant characteristics, stack height, meteorological data (wind speed and direction, temperature, atmospheric stability) and environmental characteristics such as surface topography and soil roughness. Figure 2 shows an example of cartographic representation of the modelled ground-level deposit of dioxins around one of the incinerators included in the study.

3.7.5 Choice of the indicator pollutant for the substances emitted

Three types of pollutant were initially identified as indicators of emissions from incinerators: a mixture of heavy metals; a mixture of dioxins, furanes and polychlorobiphenyls (PCBs); and a mixture of particles (PMₙ). A comparison of emission flow showed a strong statistical correlation between the emission flow of particles and that of heavy metals. Furthermore, during the modelling of atmospheric dispersion, it became clear that there was a strong correlation between the deposition on the soil of particles and that of dioxin, and between atmospheric concentrations of dioxins and dioxin deposits.

We therefore retained, as exposure indicator of emissions and exposure, surface deposits of a mixture of dioxins, furanes and PCBs – expressed in μg I-TEQ (international toxic equivalents; WHO)/m²/year, which is referred to as "dioxins" hereafter.

3.7.6 Extent and route of exposure

Dioxins persist in the environment and bioaccumulate. Thus the index of exposure was calculated to account for the number of years the plant had operated and the degradation speed in soils. It was defined as the mean of the cumulated ground-level deposits of dioxins since the start of the plant activity (μg I-TEQ/m²/year). It corresponds to the annual average of the deposits accumulated on the ground surface over all the duration of the incinerators’ activity. It was obtained applying an exponential decreasing function with a half-life of 10 years for dioxins in the environment [71].

This exposure variable was considered suitable for representing long-term exposure, and including exposure through the consumption of local products – the principal route of human exposure to dioxins [72-74].

We calculated, for all the IRIS with more than one value from the modelling grid, the median value for all values lying within the contours of the IRIS, with a view to obtaining a single exposure value for each IRIS. For that purpose, a Geographic Information System (GIS) was developed with the ESRI ArcGIS® software. If the area of the IRIS was too small to contain a modelling point, we attributed to the IRIS concerned the value of the point on the modelling grid closest to that IRIS.

The exposure of IRIS located outside the modelling areas was defined, by default, as equal to the smallest median value obtained for all the IRIS located in the modelled areas in the four départements. This value (1.85 x 10⁻³ μg I-TEQ/m²/year) corresponds to the median value for an IRIS located in Isère.
3.8 POTENTIAL CONFOUNDING FACTORS

Our analysis took into account five factors known to affect the incidence of cancers that could be described at the level of the IRIS.

▶ Socio-economic level
The socio-economic status of individuals has been recognised as a confounding factor in studies on the effects of environmental exposure to a pollutant [75,76]. Using census information of 1990, the IRIS database (INSEE) and fiscal revenue data for 2001, a socio-economic indicator specific to the study was calculated for each IRIS by principal component analysis (PCA). The 6 socio-economic variables used to were selected according to several existing indices [76-78] and the composite poverty index defined for the Doubs [79,80]. This indicator was itself constructed using the following elements: the proportion of unemployed people, the proportion of low social class households, the proportion of households without a car, the proportion of households who are not owner-occupied, the proportion of public low-cost households and the mean number of people per room (for overcrowding).

▶ Population density
Several authors have suggested that this factor may be linked to the incidence of certain types of cancer [81-83]. The number of inhabitants per unit area of the IRIS was used to calculate population density (inhabitants/km²).

▶ The urban/rural status of the site of residence
Each town was classified into one of the categories of a complex indicator, established by Insee: urban centre, monopolarised perurban community, multipolarised community, largely rural area.
Pollution from road traffic

Many studies have addressed the possible carcinogenic effects of atmospheric pollutants from cars [84-86], justifying the consideration of this source of pollution as a putative confounding factor. However, the absence of precise and exhaustive measurements of road traffic pollution during the 1970s and 1980s, heterogeneity in vehicle counting data and the disparity of information concerning spatial changes in the road network in each département precluded the retrospective quantification of atmospheric pollution from road traffic at the scale of the IRIS. A proxy for exposure to road traffic pollution was defined by nitrogen dioxide (NO₂) concentrations (expressed in μg/m³) that were taken to be a marker of road traffic emitted carcinogenic pollutants. The data were obtained from the WHO study [87] supplied by The Agency for Environment and Control of Energy (ADEME): NO₂ concentrations were estimated on a grid of 4 km × 4 km unit cells covering the whole territory of France. These estimations were obtained by cokriging using observed NO₂ concentrations – year 2000 – and information about land use. These data were implemented in the GIS to be used and to define the variable at the IRIS level.

Industrial pollution

Exposure to carcinogenic agents released into the atmosphere from industries classified for the protection of the environment was taken into account (as a function of the type of cancer because it determined the latency time), for the period 1972-1985 (solid tumors), or for the period 1972-1990 (leukaemias). An exposure index to industrial pollution, expressed per industry-years, was defined as the number of existing industries every year in each IRIS. For communities broken down into IRIS, we divided the number of industry-years by the area of the IRIS.

3.9 Statistical analysis

Cancers at all the sites considered were analysed for both sexes together and for the two genders separately. However, cancers for which a difference in incidence between the sexes was expected (all cancers considered together, lung cancer and bladder cancer) were analysed only for the two sexes separately. Cancers at rare sites (soft-tissue sarcomas) were analysed only for both sexes together.

3.9.1 Statistical models

The association between the number of cases of cancer in a given IRIS and the indicator of exposure to incinerators was estimated by a regression analysis, taking the potential confounding factors into account.

Because the observed number of cases are small, Poisson regressions Generalized additive models (GAMs) were used to assess the associations between the risk of cancer and the index of exposure to MSWIs. The models were fitted with an offset as the expected number of cancers [88]. These models are appropriate for exploring forms of associations between the risk of cancer and the exposure to MSWIs or the confounders without presupposing the shape, for example, linear. We used GAMS with penalized cubic regression splines; the degree of smoothness of model terms is estimated as part of fitting [89;90]. The covariates were selected through the Akaike criterion [91]. We proceeded in several steps. At first, residual variation was taken into account by fitting a Poisson regression model allowing for overdispersion. After fitting standard Poisson regressions, we modelled the overdispersion in a hierarchical Bayesian framework which is well adapted to the analysis of disease risk on a small geographical scale [92-94]. It allows integrating, in the estimation of the unknown relative risks, local information consisting of the observed and expected number of cases in each area, the value of the variable of interest and of the potential confounding factors and prior information on the overall variability of the relative risks.

The approach we followed, suggested by Besag et al. [95], splits the extra-Poisson variation in two components. The first component of variation is the spatially unstructured extra-Poisson variation, called heterogeneity. Modelling the heterogeneity variation allows for unmeasured variables that vary between areas in an unstructured way. The second component of variation, called clustering, varies smoothly across areas. Modelling the clustering variation allows for those unmeasured risk factors that vary smoothly with location.

The significance threshold was fixed at 5%.

These analyses were carried out using the R package mgcv [100] and WinBUGS [99].

3.9.2 Variables introduced into statistical models

- Number of observed cases per IRIS.
- Number of expected cases per IRIS (offset).
- Effect of département. It was included in all models (the reference département was Isère).
- Index of exposure to incinerators: square root of the mean cumulative annual deposits of dioxins (µg I-TEQ/m²/year), estimated at the scale of the IRIS.
- Population density, calculated at the scale of the IRIS (number of inhabitants per km²).
- Socio-economic indicator, estimated at the scale of the IRIS.
- Urban/rural indicator, available for IRIS level (four classes).
- Indicator of exposure to road traffic estimated at the level of the IRIS: concentration of NO₂ in the air (μg/m³).
- Indicator of exposure to other industrial pollutants, calculated at the scale of the IRIS (number of industry-years).

The expected number of cases per IRIS was calculated in several steps:

1) population size per IRIS, per sex and per five-year age group was estimated for the year 1995 from data for the 1990 and 1999 censuses supplied by INSEE, by applying the “single diagonal” method to each age group; this estimate was used as denominator,

2) a reference incidence rate for each five-year age group and for each sex was then calculated from the cases of cancer recorded between 01/01/1990 and 31/12/1999 in the four cancer registries (Isère, Bas-Rhin, Haut-Rhin, Tarn), plus from those recorded in the registries of Doubs and Hérault. The 2 additional départements were taken to have more stable reference rates,

3) finally, the expected number of cases per IRIS was calculated from these reference incidence rates and population sizes per IRIS for 1995.
3.9.3 Expression of the results

The results of the study are expressed as relative risks (RR), comparing the risk of a cancer occurring in highly exposed zones with that for zones of low-level exposure.

High exposure is defined as the 90th percentile (P90) for the distribution of the 520 IRIS located within the modelled zones: only 4% of the total population of the four départements had a level of exposure equal or higher than this level.

Low-level exposure is defined as the 2.5th percentile (P2.5) for the distribution of IRIS within the modelled zones: 35% of the total study population was exposed to levels no higher than P2.5.

For each type of cancer, the coefficient of regression of the indicator of exposure to the MSWI obtained from the model was used to calculate the relative risk associated with an increase in the indicator of exposure from P2.5 to P90 for the distribution of the 520 IRIS located within the zones modelled.
4. Implementation of the study

4.1 Project team

This study was carried out by an interdisciplinary team composed of epidemiologists, risk assessors, a biostatistician specialized in spatial analysis, and modelling and geomatic engineers.

- Scientific coordination: Pascal Empereur-Bissonnet.
- Project leader: Adela Paez then Pascal Fabre.
- Retrospective quantification of exposure: Côme Daniau.
- Statistical analysis: Sarah Goria.
- Development of the GIS and mapping: Perrine de Crouy-Chanel and Lilias Louvet.
- Data collection: Jamel Daoudi and Béatrice Declercq.
- Secretary: Frédérique Suzanne and then Béatrice Jaillant.

4.2 Scientific Committee

This study had the support of a Scientific Committee. The principal missions of which were to evaluate the study protocol, to help resolve methodological difficulties encountered by the project team during the study, and to validate the results obtained. This committee consisted of the following individuals:

- Nathalie Bonvallot, followed by Sabrina Pontet and Cédric Duboudin, French Agency for Environmental and Occupational Safety (AFSSET);
- Pascal Brula, Polden-Insavalor;
- Marc Colonna, Isère cancer registry;
- Sylvaine Cordier, U625/French Institute for Health and Medical Research (INSERM);
- Hélène Desqueyroux, Agency for Environment and Control of Energy (ADEME);
- Pascal Empereur-Bissonnet, Department of Health and Environment/InVS;
- Pascal Fabre, Department of Environmental Health/InVS;
- Guy Launoy, French network of cancer registries (FRANCIM);
- Martine Ledrans, Department of Environmental Health/InVS;
- Sylvia Richardson, Imperial College of London, United Kingdom;
- Florence Suzan, Department of Chronic Diseases and Injuries/InVS;
- Jean-François Viel, Faculty of Medicine, Besançon, France.

4.3 Communication Committee

This committee met twice to advise the project team on aspects relating to the communication of the results of the study to the scientific community and to the population.

In addition to those in charge of the study, this committee included members from the Communication Department of the InVS, representatives of the Ministry of Health and ADEME and members of the Scientific Committee.

4.4 Partnerships

Scientific collaboration or service contracts were established between the InVS and:

- CHU of Besançon;
- The cancer registries of Bas-Rhin, Haut-Rhin, Tarn and Isère;
- The French Meteorological Bureau (Météo France);
- The French Institute for Environment (IFEN);
- INSEE;
- The National Geographic Institute (IGN);
- Géocible;
- Numtech;
- The Polden-Insavalor Group.
5. Results

5.1 Estimate of the intercensal population in 1995

The total population of individuals over the age of 14 years in the four départements studied was estimated to be 2,487,274 for 1995. The observation of this population over a ten-year period therefore corresponds to approximately 25,000,000 person-years.

Table 1 shows the estimated population for 1995, for each département. The four départements studied include a total of 2,270 IRIS. The atmospheric release from 13 incinerators for the study of solid cancers between 1972 and 1984 covered 23% of these IRIS, 520 in total, corresponding to 35% of the total estimated study population in 1995.

<table>
<thead>
<tr>
<th>département</th>
<th>Isère</th>
<th>Bas-Rhin</th>
<th>Haut-Rhin</th>
<th>Tarn</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of IRIS</td>
<td>682</td>
<td>711</td>
<td>488</td>
<td>389</td>
<td>2,270</td>
</tr>
<tr>
<td>Number of exposed IRIS (%)</td>
<td>255 (37)</td>
<td>129 (18)</td>
<td>82 (17)</td>
<td>54 (14)</td>
<td>520 (23)</td>
</tr>
<tr>
<td>Population</td>
<td>844,366</td>
<td>802,082</td>
<td>554,373</td>
<td>286,453</td>
<td>2,487,274</td>
</tr>
<tr>
<td>Exposed population (%)</td>
<td>413,739 (49)</td>
<td>248,645 (31)</td>
<td>155,224 (28)</td>
<td>60,55 (21)</td>
<td>877,763 (35)</td>
</tr>
</tbody>
</table>

We note that the four départements included in this study are quite heterogeneous: Isère is an urban department, it is the most populated (around 850,000 inhabitants), the most exposed to MSWIs (50% of the exposed IRIS are in Isère) and with the highest values of exposure.

On the contrary, Tarn is a rural department, it is the least populated (around 290,000 inhabitants), the least exposed (10% of the exposed IRIS are in Tarn) and with the lowest values of exposure.

5.2 Cancer cases observed during the study period

In total, just over 135,000 cases of cancer in adults were recorded in the four départements between 01/01/1990 and 31/12/1999.

Table 2 shows the number of observed cases for each type of cancer studied, for both sexes, with the exception of breast cancer, which affected only women.

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Isère</th>
<th>Bas-Rhin</th>
<th>Haut-Rhin</th>
<th>Tarn</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>41,809</td>
<td>45,343</td>
<td>30,868</td>
<td>17,103</td>
<td>135,123</td>
</tr>
<tr>
<td>Breast cancer (women)</td>
<td>6,187</td>
<td>6,267</td>
<td>4,293</td>
<td>2,077</td>
<td>18,824</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>4,169</td>
<td>4,694</td>
<td>2,918</td>
<td>1,565</td>
<td>13,346</td>
</tr>
<tr>
<td>MNHL</td>
<td>1,324</td>
<td>1,333</td>
<td>871</td>
<td>446</td>
<td>3,974</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>975</td>
<td>929</td>
<td>700</td>
<td>180</td>
<td>2,784</td>
</tr>
<tr>
<td>Soft-tissue sarcoma</td>
<td>221</td>
<td>208</td>
<td>132</td>
<td>94</td>
<td>655</td>
</tr>
<tr>
<td>Acute leukaemia</td>
<td>443</td>
<td>350</td>
<td>309</td>
<td>136</td>
<td>1,238</td>
</tr>
<tr>
<td>Chronic lymphoid leukaemia</td>
<td>376</td>
<td>356</td>
<td>369</td>
<td>161</td>
<td>1,262</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>578</td>
<td>454</td>
<td>435</td>
<td>233</td>
<td>1,700</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>1,456</td>
<td>1,744</td>
<td>1,141</td>
<td>770</td>
<td>5,111</td>
</tr>
</tbody>
</table>
5.3 IRIS Exposure

Table 3 shows the distribution of the exposure indicator "mean cumulative annual deposits" for dioxins (µg l-TEQ/m²/year) for the 1972-1984 period, for all the areas modelled.

### Table 3

<table>
<thead>
<tr>
<th>Exposure indicator (µg/m²/an)</th>
<th>No. of IRIS (%) with an exposure value ≥ the percentile</th>
<th>% of the population with exposure values ≥ the percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum</td>
<td>2.04 x 10⁻⁵</td>
<td>520 (22.9)</td>
</tr>
<tr>
<td>Percentile 2.5</td>
<td>1.25 x 10⁻⁴</td>
<td>507 (22.3)</td>
</tr>
<tr>
<td>Percentile 50</td>
<td>4.25 x 10⁻³</td>
<td>260 (11.4)</td>
</tr>
<tr>
<td>Percentile 75</td>
<td>8.93 x 10⁻³</td>
<td>130 (5.7)</td>
</tr>
<tr>
<td>Percentile 90</td>
<td>1.78 x 10⁻²</td>
<td>52 (2.3)</td>
</tr>
<tr>
<td>Maximum</td>
<td>9.18 x 10⁻²</td>
<td>1 (0.04)</td>
</tr>
<tr>
<td>Mean (standard deviation)</td>
<td>7.86 x 10⁻³ (1.09 x 10⁻²)</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 3 presents the distribution of mean cumulative annual dioxin deposits for the 520 IRIS for which exposure was modelled over the period 1972-1984. This distribution is highly asymmetric and shows that a large proportion of IRIS were subject to low levels of exposure. By contrast, only a few IRIS had high levels of exposure. We carried out a square root transformation of the exposure variable to prevent these few sites with high levels of exposure having too great a weighting in the statistical analysis.
5.4 RESULTS OF THE STATISTICAL ANALYSIS

Table 4 shows the results for all the types of cancer studied, the regression coefficient for the exposure indicator and its standard deviation, statistical significance (p-value), and the number of cancers observed, for each type of cancer and for each sex.

In women, a significant and positive association was demonstrated for "all cancers" (p=0.01) and for breast cancer (p=0.03) and MNHL (p=0.03).

In men, a significant, positive association was observed only for multiple myeloma (p=0.05).

Taking both sexes together, there was a significant positive relationship for MNHL (p=0.04) and non-significant (at the 5% level, but close to this threshold) positive relationships for three other types of cancer: soft-tissue sarcoma (p=0.07), liver cancer (p=0.07) and multiple myeloma (p=0.10).

Table 4: Results of regression modelling by cancer type and by sex

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Regression Coefficient</th>
<th>Standard Deviation</th>
<th>p-value</th>
<th>No. of cases observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers, women</td>
<td>0.502</td>
<td>0.223</td>
<td>0.01</td>
<td>59,076</td>
</tr>
<tr>
<td>All cancers, men</td>
<td>0.237</td>
<td>0.224</td>
<td>0.30</td>
<td>76,047</td>
</tr>
<tr>
<td>Breast cancer, women</td>
<td>0.680</td>
<td>0.320</td>
<td>0.03</td>
<td>18,824</td>
</tr>
<tr>
<td>Lung cancer, women</td>
<td>0.867</td>
<td>0.736</td>
<td>0.24</td>
<td>1,983</td>
</tr>
<tr>
<td>Lung cancer, men</td>
<td>0.430</td>
<td>0.445</td>
<td>0.34</td>
<td>11,363</td>
</tr>
<tr>
<td>MNHL, women + men</td>
<td>0.925</td>
<td>0.459</td>
<td>0.04</td>
<td>3,974</td>
</tr>
<tr>
<td>MNHL, women</td>
<td>1.340</td>
<td>0.628</td>
<td>0.03</td>
<td>1,827</td>
</tr>
<tr>
<td>MNHL, men</td>
<td>0.106</td>
<td>0.625</td>
<td>0.86</td>
<td>2,147</td>
</tr>
<tr>
<td>Liver cancer, women + men</td>
<td>1.204</td>
<td>0.662</td>
<td>0.07</td>
<td>2,784</td>
</tr>
<tr>
<td>Liver cancer, women</td>
<td>1.342</td>
<td>1.022</td>
<td>0.19</td>
<td>511</td>
</tr>
<tr>
<td>Liver cancer, men</td>
<td>1.020</td>
<td>0.700</td>
<td>0.14</td>
<td>2,273</td>
</tr>
<tr>
<td>Soft-tissue sarcoma, women + men</td>
<td>1.594</td>
<td>0.887</td>
<td>0.07</td>
<td>655</td>
</tr>
<tr>
<td>Multiple myeloma, women + men</td>
<td>1.161</td>
<td>0.709</td>
<td>0.10</td>
<td>1,700</td>
</tr>
<tr>
<td>Multiple myeloma, women</td>
<td>0.347</td>
<td>0.984</td>
<td>0.72</td>
<td>811</td>
</tr>
<tr>
<td>Multiple myeloma, men</td>
<td>1.597</td>
<td>0.823</td>
<td>0.05</td>
<td>889</td>
</tr>
<tr>
<td>Acute leukaemia, women + men</td>
<td>0.269</td>
<td>0.731</td>
<td>0.71</td>
<td>1,238</td>
</tr>
<tr>
<td>Acute leukaemia, women</td>
<td>0.767</td>
<td>1.007</td>
<td>0.45</td>
<td>592</td>
</tr>
<tr>
<td>Acute leukaemia, men</td>
<td>-0.324</td>
<td>1.023</td>
<td>0.75</td>
<td>646</td>
</tr>
<tr>
<td>Chronic lymphoid leukaemia, women + men</td>
<td>0.928</td>
<td>0.817</td>
<td>0.26</td>
<td>1,262</td>
</tr>
<tr>
<td>Chronic lymphoid leukaemia, women</td>
<td>1.275</td>
<td>1.192</td>
<td>0.28</td>
<td>541</td>
</tr>
<tr>
<td>Chronic lymphoid leukaemia, men</td>
<td>0.597</td>
<td>1.097</td>
<td>0.59</td>
<td>721</td>
</tr>
<tr>
<td>Bladder cancer, women</td>
<td>-1.631</td>
<td>0.854</td>
<td>0.06</td>
<td>997</td>
</tr>
<tr>
<td>Bladder cancer, men</td>
<td>-0.446</td>
<td>0.477</td>
<td>0.35</td>
<td>4,114</td>
</tr>
</tbody>
</table>

The figures in bold correspond to relationships significant at the 5% level (p<0.05).
5.5 Relative risks

The association between the risk of cancer and exposure to atmospheric emissions from incinerators is presented in table 5 in the form of relative risks of cancer for an increase in the exposure indicator from the 25th percentile to the 90th percentile in the distribution of exposed IRIS. For statistically significant relationships, these results correspond to an excess relative risk of between 6% for “all cancers” in women and 23% for multiple myeloma in men.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Relative risk (RR) of cancer (and 95% confidence intervals [95% CI]) for an increase in exposure from the 2.5th percentile to the 90th percentile, by type of cancer and by sex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
</tr>
<tr>
<td>All cancers, women</td>
<td>1.06</td>
</tr>
<tr>
<td>All cancers, men</td>
<td>1.03</td>
</tr>
<tr>
<td>Breast cancer, women</td>
<td>1.09</td>
</tr>
<tr>
<td>Lung cancer, women</td>
<td>1.11</td>
</tr>
<tr>
<td>Lung cancer, men</td>
<td>1.05</td>
</tr>
<tr>
<td>MNHL, women + men</td>
<td>1.12</td>
</tr>
<tr>
<td>MNHL, women</td>
<td>1.18</td>
</tr>
<tr>
<td>MNHL, men</td>
<td>1.01</td>
</tr>
<tr>
<td>Liver cancer, women + men</td>
<td>1.16</td>
</tr>
<tr>
<td>Liver cancer, women</td>
<td>1.18</td>
</tr>
<tr>
<td>Liver cancer, men</td>
<td>1.13</td>
</tr>
<tr>
<td>Soft-tissue sarcoma, women + men</td>
<td>1.22</td>
</tr>
<tr>
<td>Multiple myeloma, women + men</td>
<td>1.16</td>
</tr>
<tr>
<td>Multiple myeloma, women</td>
<td>1.05</td>
</tr>
<tr>
<td><strong>Multiple myeloma, men</strong></td>
<td><strong>1.23</strong></td>
</tr>
<tr>
<td>Acute leukaemia, women + men</td>
<td>1.04</td>
</tr>
<tr>
<td>Acute leukaemia, women</td>
<td>1.11</td>
</tr>
<tr>
<td>Acute leukaemia, men</td>
<td>0.96</td>
</tr>
<tr>
<td>Chronic lymphoid leukaemia, women + men</td>
<td>1.13</td>
</tr>
<tr>
<td>Chronic lymphoid leukaemia, women</td>
<td>1.18</td>
</tr>
<tr>
<td>Chronic lymphoid leukaemia, men</td>
<td>1.08</td>
</tr>
<tr>
<td>Bladder cancer, women</td>
<td>0.82</td>
</tr>
<tr>
<td>Bladder cancer, men</td>
<td>0.95</td>
</tr>
</tbody>
</table>

*The figures in bold indicate relationships statistically significant at the 5% level (p<0.05).*
6. Discussion

This ecological geographic study concerned about 135,000 cases of cancer occurring in four départements of mainland France between 1990 and 1999. It demonstrated the existence of a significant positive relationship between exposure to the atmospheric emissions from MSWIs and the incidence of breast cancers, MNHL and “all cancers” in women. A significant positive relationship was also found for multiple myeloma in men, and for MNHL in both sexes. The study also showed, for both sexes, that there is a link close to the limits of statistical significance between environmental exposure to the emissions from MSWIs and soft-tissue sarcoma, liver cancer and multiple myeloma.

6.1 INTERNAL VALIDITY OF THE RESULTS

6.1.1 Estimate of the incidence of cancers

The validity of the incidence rates for cancers calculated in this study is guaranteed by the quality and reliability of the data supplied by the registries. Grouped together into the Francim network, they apply the European guidelines for the standardisation and registering of cancers published in 2003 by the European Network of Cancer Registries [101]. The remarkable rate of geocoding of cancer cases to IRIS obtained, exceeding 99%, illustrates the high quality of the data provided by the registries, particularly as concerns home address.

The reference incidence rates for cancers used were calculated from the data from six registries, four of which corresponded to the four départements of the study. The populations in which these rates were measured included people exposed to emissions from incinerators. This may have decreased the difference between the numbers of expected and observed cases of cancer, leading to underestimate the exposure-risk relationships identified for cancer.

Scientific knowledge concerning latency times for cancers following environmental exposure remains limited. The values used here — five years for leukaemia and 10 years for solid cancers — were chosen on the basis of previous publications [51], as well as for operational reasons. However, the most recent publications providing information about latency times for cancers for environmental health, carried out in general populations exposed to urban traffic pollution [102], chronic industrial pollution [103] or accidental pollution [40], have reported lags of 15, or even 20 years. The latency periods used for the cancers considered in our study may therefore be too short. If this is the case, and if the MSWI exposure and cancer incidence relationship is thre, then all cancers induced by exposure to the pollutants emitted by incinerators would not have had the time to form or to reach a detectable level. This potential bias may lead to the underestimate of the observed relationships.

6.1.2 Estimate of exposure to atmospheric release from incinerators

The flux of emissions from MSWIs stacks was evaluated by consensus between experts, obtained with a modified version of the Delphi method. The retrospective evaluation of dioxin emissions led to the greatest discussion. We compared these estimates with flow values for eight incinerators for which real measurements were taken over the period 1994-2000 as part of another study [104]. The flow values estimated for the most polluting incinerators seem to have been underestimated by the experts, potentially decreasing the difference in emission levels between the MSWIs studied here. However, the gradients of emissions and deposits were largely similar between incinerators, so this underestimate should not affect the exposure-risk relationships observed. Indeed, the impact of this potential error on the numerical value of relative risks is probably low, the estimate of these risks being based on a comparison between two percentiles after square root transformation of the exposure variable. Conversely, this limitation indicates that the exposure-risk relationships calculated cannot be transposed to data for current emissions.

The median of all the points on the modelling grid corresponding to a given IRIS was used to describe the level of exposure to the pollutants discharged by MSWIs. Nonetheless, the relationships observed in this study between the incidence of cancers and exposure to emission from incinerators cannot be attributed either to these substances alone or to a particular route of exposure.

The median of all the points on the modelling grid corresponding to a given IRIS was used to describe the level of exposure to each statistical unit. However, we cannot rule out the possibility that this type of central indicator, by homogenising exposure over the whole IRIS, may have introduced a non-differential bias leading to underestimate of the observed relationships.

A default value for exposure was attributed to each IRIS located outside the zone modelled. This value corresponded to the lowest median deposition level obtained for the IRIS located in the zone modelled in the four départements. This arbitrary choice may have distorted the results obtained. It may have introduced a non-differential bias by diluting the observed effects.

6.1.3 Other factors taken into account

We used atmospheric NO2 concentrations for 2000 as a proxy of exposure to carcinogenic agents released into the air by motor vehicles [105]. The use of these data is nonetheless based on the
assumption that atmospheric NO$_2$ concentrations changed little, if at all, between the exposure period (1970s and 1980s) and the year 2000. Although the construction of stretches of motorway, bypasses and ring roads affect local air quality, it is reasonable to consider that generally, relative changes in the atmospheric concentration of NO$_2$ have been homogeneous over the entire study zone.

The indicator of industrial pollution used in this study imperfectly reflects the true exposure of an IRIS located at some distance from a polluting installation in the same département or, conversely, of an IRIS located close to an industrial installation in a neighbouring département. Nonetheless, it is the only indicator we could find to take into account exposure to past industrial pollution at the level of our statistical unit.

6.1.4 Statistical analysis

We used GAMs and hierarchical Bayesian models. GAMs make it possible to take into account possible non-linear effects of variables. Hierarchical Bayesian models, with their heterogeneity and spatial components, can be used to take into account unknown or unmeasured risk factors. In particular, the modelling of a spatially structured source of variation made it possible to take into account the effect of variations in risk factor clustering over the geographical area. This was important, given the high level of extra-Poisson variability.

Differences were found between the four départements studied. The much larger contribution of Isère than of the other three départements to the results obtained should be stressed. This département is the most populous (850,000 inhabitants), contains the largest number of Irises exposed to incinerator emissions (50% of all the exposed IRIS in this study) and had the highest exposure values. Conversely, Tarn, which is mostly rural, has the lowest population (290,000 inhabitants), the lowest level of exposure (10% of the IRIS exposed in this study) and the lowest exposure values. This heterogeneity is partly taken into account by covariables. An effect of département was introduced into all models. Regression coefficients for the exposure indicator were calculated for each département (interaction between the effect of département and the exposure indicator), but did not differ significantly (α=0.05) from that for Isère.

6.1.5 Conclusion concerning the internal validity of the results

6.1.5.1 Limitations

This is an ecologic study, that does not deal with individual subjects or individual level traits or exposures, but rather with the characteristics of block groups. Indeed, it was not possible to take into account individual risk factors known to be strongly associated with the incidence of certain cancers: alcohol and tobacco consumption, occupational exposure, exposure associated with housing and leisure activities, medical treatments, eating habits and the origin of food. Similarly, we had no information concerning the recent residential history of the people concerned.

However, there is no reason to expect the distribution of these individual risk factors to be associated with a particular level of exposure. Furthermore, it is unlikely that residential mobility differed between those with and without cancers.

The various biases that may affect our study would probably result in an overall underestimate of the exposure-risk relationships observed.

6.1.5.2 Strong points

First, this study used a population-based design. Cases were actively identified through multiple sources within defined geographic areas and benefited from a very high georeferencing rate. Compared to other ecological studies on populations living close to incinerators [41-43;46;49], the statistical power obtained from the follow-up of approximately 25 million person-years is one of the strong points of this ecological-type study. Such power made it possible to enhance the several statistical relationships found.

The analyses carried out identified the associations classically found between lung cancer and low socio-economic level, and inversely, between breast cancer in women and high socio-economic level, or between liver cancer and living in a rural environment (data not shown). This consistency with established knowledge suggests that the quality of the means of observation and analysis was high.

Finally, an analysis of sensitivity after excluding extreme values for exposure was conducted, and showed that the exposure-risk relationships observed were stable.

These findings provide solid evidence to support the validity of the results of this epidemiological study.

6.2 Consistency with the literature and interpretation of the relationships observed

The statistical relationship between exposure to emissions from MSWIs, and the incidence of all cancers in women has not previously been reported in a general population. This overall carcinogenic effect may reflect the large number of chemicals emitted from incinerators. However, it remains unclear why this increase in cancer incidence affected essentially women. It can be assumed that women, particularly in the 1970s and 1980s, were more sedentary than men, and less exposed to occupational risks or to certain other risk factors, such as smoking and alcohol consumption, that may have concealed the effect of exposure to incinerator emissions in men in this study. There may also be a hormonal explanation, as the toxicological relationships between oestrogens and the intranuclear receptor AhR in the control of cell proliferation and hormonal balance seem to be well established [55;56;106-108].

This study showed, for the first time in the general population, that exposure to the agents emitted by MSWIs may be an environmental risk factor for breast cancer in women. Studies in occupational settings in Russia [109;110] and Germany [110] had already shown an excess risk of breast cancer in female pesticide industry workers exposed to dioxin and furane residues. Nonetheless, conflicting results have been obtained concerning the effects of exposure to dioxin on breast cancer. A deficit of breast cancers was initially reported at Seveso [39], after a 10 year follow-up of the cohort, whereas other studies have suggested that long-term exposure to 2,3,7,8-TCDD may be associated with high breast cancer rates [111;112].
Finally, it should be noted that, in our study, the exposure-risk relationship for all cancers in women persisted, even if breast cancers were excluded from the analysis (data not shown).

The significant positive relationship between exposure to atmospheric emissions from incinerators and the incidence of MNHL is consistent with the results of cluster and case-control studies carried out in the general population living around the incinerator of Besançon [46;47]. These observations should be compared with those made during the follow-up of the Seveso cohort, in which MNHL in men seemed to be exclusively linked to accidental exposure to 2,3,7,8-TCDD [40]. In our analysis by sex, the association between the risk of MNHL and exposure to incinerator emissions was statistically significant in women, but not in men. Is there an environmental or hormonal explanation or are women particularly susceptible due to a specific gene-environment interaction [113]? This study cannot provide any explanation as to the female nature of the relationship observed in this study.

The non-significant positive association (p=0.07) observed for the risk of soft-tissue sarcomas is consistent with the results of case-control studies carried out in the area around a MSWI in France [46] in an area around an industrial waste incinerator in Italy [50] and around industrial sources of dioxins, including incinerators [49].

Similarly, the positive relationship, close to the significance threshold (p=0.07) observed between liver cancer and exposure to incinerator emissions is consistent with the results of a study of incidence based on data from registries in the United Kingdom, in a general population living close to incinerators [43;44].

The positive association observed for both sexes between the risk of multiple myeloma and exposure to incinerator emissions, which was not significant at the 5% level (p=0.10), reflects an excess relative risk of 16%. Our analysis by sex suggested that this association resulted from a significant relationship for men (p=0.05). Our observations are consistent with the results obtained after 15 years of follow-up in the Seveso cohort [38]. They are also similar to those obtained in studies carried out in Sweden on cohorts of fishermen consuming large quantities of fish contaminated with organochlorine compounds, including dioxins [114;115].

We obtained no evidence for a significant association with lung cancer in either of the sexes. Our analysis shows that the covariates included in the models (economic score, road traffic and population density) played a key role in determining the incidence of lung cancer.

We found no relationship between acute or chronic leukaemia and exposure to emissions from incinerators, whereas a relationship of this kind was reported for the Seveso cohort [38;40].

Finally, this study showed a negative relationship between the risk of bladder cancer and exposure to incinerator emissions in women but this relationship is difficult to explain.

6.3 IMPLICATIONS OF THE STUDY RESULTS

This ecological study provides new elements suggesting that past exposure to the pollutants emitted by incinerators has an effect on health, but it is not possible to presume a causal link from these observations. In addition, it should be noted that we used an exposure indicator identifying neither the substances involved, nor the route of exposure responsible for the relationships observed.

In terms of public health, excess risks observed should be interpreted depending on the number of people subject to the various situations of exposure.

Indeed, the relative risks for IRIS exposed to the 90th percentile (corresponding to 100 times background levels) concerned only 4% of the total population. The relative risks identified in IRIS exposed to the 50th percentile (4.25 x 10⁻³ μg I-TEQ of dioxins/m²/year) were lower (results not presented here), but concerned 20% of the total population studied.

Thus, the relative risk of breast cancer in women, for an increase in exposure from the 2.5th to the 90th percentile, was 1.09, whereas the relative risk for an increase in exposure from P2.5 to P50 was 1.04. In similar conditions and for all cancers in women, the risk decreases from 1.06 to 1.03. For MNHL in women, relative risk was 1.18 for an increase in exposure from P2.5 to P90 and 1.07 for an increase in exposure from P2.5 to P50. For multiple myeloma in men, the corresponding relative risks were 1.23 and 1.08.

Overall, for all the types of cancer for which we found significant relationships to past exposure to incinerator emissions, the excess relative risk of cancer for an increase in exposure from P2.5 to P50 was two to three times lower than that for an increase from P2.5 to P90. Nonetheless, this lower risk concerned a population five times larger. There is therefore a clear public health risk due to the number of people potentially affected, rather than an individual risk.

It would be difficult to transpose the exposure-risk relationships identified in this work outside our study zones. Indeed, the four départements studied do not adequately reflect the heterogeneity of the French population and the exposure-risk relationships demonstrated include multiple interactions with demographic, economic and cultural factors that are difficult to identify and to control.

Similarly, the level of exposure to incinerator emissions, which was quantified retrospectively in our study by an expert panel consensus, has only a relative value. The exposure-risk relationships calculated based on these estimates cannot be exploited with data generated by other quantification methods. In addition, the relationships identified refer to particular exposure and latency periods between 1972 and 1990, with characteristics (environmental and professional exposure, demographics, socio-economic, cultural and health context) different from those of today.
7. **Recommendations**

7.1 **Improvements in Epidemiological Knowledge**

Work towards three objectives could be valuable to improve knowledge concerning the relationship between incinerator emissions and cancer:

1) **Validation of the hypothesis generated by our study**, through an aetiological case-control study combined with the determination of biomarkers or other methods for determining individual exposure and including the collection of precise data on residential history and risk factors for each subject. Only this type of study would allow reliable confirmation that the relationships observed in our study persist after adjusting individual factors. It would also make it possible to obtain dose-response relationships and to develop predictive models. If positive, an analytical study could be used to confirm the excess risk of cancer associated with previous exposure. However, this would not provide information about the risk related to current emissions. The possible excess risk associated with current emissions could be evaluated only in 10 to 20 years, by carrying out another ecological study similar to this one;

2) **Testing of longer latency periods to estimate more completely the strength of the exposure-risk relationships**, by extending the observation of these populations. Indeed, given our lack of knowledge on the real duration of the latency period for cancers, it is possible that the observation period of our study extends only to the start of the period in which excess cancers are likely to occur. The extension of this study should also contributed to evaluate more precisely the latency period of cancers;

3) **Exploration of the relationship between cancers in women and exposure to incinerator emissions**, by completing the analysis of the study data, trying to find an explanation for the excess risk of "all cancers" in women. In particular, complementary studies of the incidence of uterine and ovarian cancers and particular aspects of breast cancer, such as age at diagnosis, comparing exposed and non-exposed women, would be informative.

7.2 **Implementation of Public Health Actions**

First and foremost, we recommend to widely disseminate the results obtained in an accessible form to the general public. The implementation of preventive measures against cancers induced by incinerator emissions is no longer possible for people who were exposed during the period considered (1970s and 1980s) and until the application of new regulations limiting atmospheric emissions from MSWIs in 1997.

Provided expert advice is not contradictory in this field, given the low excess relative risks observed, and in the absence of a demonstration of causality, we do not recommend the establishment of particular secondary preventive measures (early screening, medical follow-up) for this group of population.
8. Conclusion

This ecological study demonstrates the existence of a link between the exposure of adult populations to the atmospheric emissions from MSWIs in activity between 1972 and 1990, and the incidence of cancers in the 1990s.

It has highlighted the statistically significant relationships between the exposure of populations to incinerator emissions and the risks of:
- breast cancer and “all cancers” in women;
- MNHL, for both sexes analysed together and for women;
- multiple myeloma in men.

These results also suggest, for both sexes, a possible link with liver cancer, soft-tissue sarcoma and multiple myeloma.

This study provides new evidence relating to the health risks of long-term environmental exposure to the emissions from MSWIs. Our findings are consistent with other studies in this field.

The large size of the population included in the analysis, the quality of the data supplied by the registries and the procedures used for the retrospective quantification of past exposure of the population contribute to the quality of this study.

The exploitation of the results obtained is subject to certain limitations, particularly as concerns their transposition to other times and places. This study dealt with a period of exposure in the past, and its results cannot be transposed to the current situation. Given the particular characteristics of ecological studies, the causality of the statistical link observed between exposure to incinerator emissions and the incidence of certain cancers cannot be demonstrated. Nonetheless, there are several lines of evidence to support the causality of this relationship. An aetiological study, with measurements of exposure and control for individual risk factors, could be carried out to evaluate the causality of the exposure-risk relationships observed.

This study, by demonstrating the health impact of MSWIs, confirms the usefulness of measures for reducing the emissions of pollutants imposed on these industrial installations, in France, at the end of the 1990s. We may therefore expect to see a decrease in the risk of cancer in populations exposed to current emission levels. However, given the uncertainty concerning the duration of the latency period to cancer onset, we cannot rule out the possibility that past exposure, from the 1970s onwards, may continue to favour the occurrence of cancers today.


IARC. PAHs. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 2006;92.


Dere E, Boverhof DR, Burgoon LD, Zacharewski TR. In vivo-in vitro toxicogenomic comparison of TCDD-elicited gene expression in Hepa1c1c7 mouse hepatoma cells and C57BL/6 hepatic tissue. BMC Genomics 2006 Apr;12:7.


Kaupp H, McLachlan MS. Distribution of polychlorinated dibenzo-P-dioxins and dibenzofurans (PCDD/Fs) and polycyclic aromatic hydrocarbons (PAHs) within the full size range of atmospheric particles. Atmospheric Environment 34[1],73-83.2000. Ref Type: Journal (Full).


Wood SN, Augustin NH. GAMs with integrated model selection using penalized regression splines and applications to environmental modelling, Ecological Modelling. 2002.


Wood SN. The mgcv package: GAMs with GCV smoothness estimation and GAMMs by REML/PQL. Cran r-project org 2007 Available from: URL: cran.r-project.org/web/packages/mgcv/


[105] Correlation parameters of NO\textsubscript{2} to other traffic Pollutants near an Expressway Poster presentation, ISEE/ISEA International Conference Tucson 2006.


Study of the incidence of cancers close to municipal solid waste incinerators

Summary

This ecological spatial study was performed in the context of the French Cancer Plan 2003-2007. It aimed to assess the relationship between the incidence of cancers in adults and exposure to emissions from municipal solid waste incinerators. It was based on cancers diagnosed in the Haut-Rhin, Bas-Rhin, Isère and Tarn districts between 1990 and 1999. Around 135,000 cancer cases were reported over almost 25 million person-years. The exposure of each statistical unit to 16 incinerators during the 1970s and 1980s was quantified by modelling atmospheric dispersion and cumulative surface dioxin deposition. Results are expressed as relative risks, comparing the risks of cancer occurrence in areas with high and low levels of exposure.

A statistically significant relationship was found between exposure to incinerator emissions and the incidence, in women only, of all types of cancer considered together, breast cancer and non-Hodgkin’s lymphoma. A significant relationship was also found for malignant non-Hodgkin’s lymphoma in both men and women, and for multiple myeloma in men only.

Although this study does not establish the causality of the observed relationships, it provides additional epidemiological evidence for a health impact of incinerator emissions. However, these findings concern a past period and cannot be applied to current emissions. They do, however, justify the implementation of regulatory measures for reducing the emissions of such industrial plants introduced in France at the end of the 1990s.

Key words: epidemiology, ecological study, incidence of cancers, municipal solid waste incinerator, environmental exposure, spatial analysis, modelling of atmospheric dispersion