CROhn disease and Pollution of Soils

Summary table of persons involved in the project:

Partner	Name	First name	Current position	Role & responsibilities in the project (4 lines max)	Involvement (person.month) throughout the project's total duration
INFINITE	*GOWER*	*Corinne*	*Clinical Lecturer*	*Coordinator Scientific leader WP1 Tasks WP1*	*8p.month Research time**
INFINITE	*Unknown to date*		*Research Ingeneer*	*Project Manager Tasks WP1*	*17 p.month Part- time*
INFINITE	*SARTER*	*Hélène*	*Research Ingeneer*	*Other member Task 4.2*	*4 p.month Full- time*
INFINITE	*VIGNAL*	*Cécile*	*Assistant Professor*	*Scientific leader WP5 Task 1.1, WP5*	*2 p.month Research time*
LGCgE	*DERAM*	*Annabelle*	*Professor*	*Scientific leader WP2 Task 1.1, WP2, 3.4, 4.2*	*8 p.month Research time*
LGCgE	*OCCELLI*	*Florent*	*Assistant Professor*	*Scientific leader WP3 Task 1.1, 1.3, 2. , WP3, WP4*	*16 p.month Research time*
LGCgE	*CUNY*	*Damien*	*Professor*	*Other member Task 1.1, 2.1, 3.4, 4.2*	*6 p.month Research time*
LGCgE	*LANIER*	*Caroline*	*Assistant Professor*	*Other member Task 1.1, 2.1, WP3, 4.2*	*6 p.month Research time*
LGCgE	*Unknown to date*		*Technician*	*Other member Tasks WP2 et WP3*	*17p.month Full- time*
LGCgE	*PAUMELLE*	*Martin*	*PhD student*	*Other member Tasks WP2, WP3*	*24 p.month** Full- time***
LGCgE	*WAKIM*	*Lara-Maria*	*PhD student*	*Other member Task 2.1*	*12 p.month*** Full-tim*
METRICS	*GENIN*	*Michaël*	*Assistant Professor*	*Scientific leader WP4 Tasks 1.1, WP4*	*10 p.month Research time*
METRICS	*AHMED*	*Mohamed -Salem*	*Research Ingeneer*	*Other member Task 4.1*	*12 p.month Full- time*
IRHIS	*TOUCHELAY*	*Béatrice*	*Professor*	*Other member Task 2.2*	*3 p.month Research time*
IRHIS	*HEUGUEBART*	*Léo*	*PhD student*	*Other member Task 2.2*	*6 p.montt**** Full- time*
IRHIS	*Unknown to date*		*Research Ingeneer*	*Other member Task 2.2*	*7 p.month Full- time*

*As lecturers spend 50% time for research (24 months on a 48 months period), 12 p.month is equivalent to 50% of the research time devoted to the CROPS project.

** The PhD corresponds to a 36 months thesis (2020-2023; funding: Lille University – I-SITE) in relation to the CROPS project. The PhD student will be 2/3 devoted to CROPS.

*** The PhD corresponds to a 36 months thesis (2020-2023; funding: Programme for EArly-stage Researchers in Lille (PEARL)) in relation to the CROPS project. The PhD student will be 1/3 devoted to CROPS.

**** The PhD corresponds to a 36 months thesis (2019-2023; funding: Lille University – I-SITE) in relation to the CROPS project. The PhD student will be 1/6 devoted to CROPS.

Any changes that have been made in the full proposal compared to the pre-proposal

The name of two partners changed due to the 2020-2025 contractualization: LIRIC is now named INFINITE, and CERIM is now named METRICS.

I. Proposal's context, positioning and objective(s)

a. Objectives and research hypothesis

Crohn's disease (CD) is a relapsing-remitting, chronic, inflammatory bowel disease (IBD) characterized by uncontrolled over-activation of the intestinal immune system. CD is not a rare disease; it affects over 3 million people worldwide (1.5 million in North America and 1.5 million in Europe, including 250,000 in France) and thus constitutes a major public health concern. In this context, we intend to determine whether the presence of pollutants in the outdoor environment is a risk factor for CD.

Aim. To analyze environmental and social determinants associated with CD and their interactions.
Hypothesis. There is a link between the quality of the outdoor environment and the spatial variability in the incidence of CD. Here, the term "environment" refers to air, water and soil contamination that might contribute to the pathogenesis of CD.
Scientific questions. Is there a difference in environmental contamination (*i.e*. environmental inequalities) between clusters with a high incidence of CD and clusters with a low incidence of CD? Is the environment more degraded in high-incidence areas? If so, which pollutants cause these differences? The influence of social inequalities will be included in our analysis.
Issue. To facilitate the diagnosis of CD and to guide the search for the disease's causes. To identify and prioritize new environmental factors (including socio-environmental factors) that might influence the risk of developing CD.

More than 30 years ago, the world's largest population-based study of the incidence of CD (the EPIMAD registry) was launched in the Hauts-de-France region of northern France. By building on this asset, we propose a new transdisciplinary approach that will specifically (**i**) take advantage of the known geographic and temporal variability in the incidence of CD, (**ii**) rely on powerful spatial analysis methodologies, and (**iii**) be driven by population- and geography-based approaches.
This project will build a multiscale spatial database - mainly from open-access sources - and enable ecological regressions. Given that (**i**) the link between environmental quality and socio-economic factors is widely acknowledged, and (**ii**) the relationship between CD and environmental hazards must be statistically robust, the project will necessarily require a transdisciplinary team of epidemiologists, environmentalists, historians, toxicologists, and statisticians. This transdisciplinary approach will ensure the timely delivery of (**i**) a comprehensive territorial diagnosis by our historians and environmentalists, (**ii**) a statistical analysis of past and current environmental contamination and the population-level risk of developing CD by our statisticians and epidemiologists, and (**iii**) the ranking of the identified hypotheses by our toxicologists.

b. Position of the project as it relates to the state of the art

Over the past 30 years, the incidence of chronic inflammatory diseases has risen worldwide, and especially in Western societies (Lerner et al., 2015). A systematic review of the worldwide incidence of CD found an average annual percentage change of 1.2% to 23.3%, depending on the study and the time period considered (Molodecky et al., 2012). The frequency of CD peaks at around the age of 30, and is higher among females (Malik, 2015; Panes et al., 2007). However, these patterns are changing: the incidence of CD is rising adolescents and young adults, and childhood-onset CD now accounts for around 10% of new cases (Ghione et al., 2018; Gower-Rousseau et al., 2013). Despite this disturbing progression, the cause of IBDs is not known, and there is no cure. Given that genetic determinants alone cannot fully explain the development of CD, there is growing interest in environmental determinants. This interest is also emphasized by the observation of 50% concordance in homozygous twins, and the significant increase in CD observed when migrant populations move from low-incidence to high-incidence areas. In this context, we intend to determine whether the presence of pollutants in the outdoor environment is a risk factor for CD.

In a literature review performed by our groups (Tenailleau et al., 2020), only 39 publications dealt with the outdoor environment as a risk factor for CD, and only 16 of these were field studies. Most of these publications were conducted by pioneering medical scientists. A joint analysis with environmental specialists would drastically increase the robustness of the interpretation. Despite the fact that laboratory studies have highlighted a number of interesting leads, only 12 environmental stressors have been studied in the field. The few associations observed to date are not strong enough and not coherent enough to allow the development of a scientific consensus on the potential impacts of environmental stressors on CD. In other words, no one hypothesis on how CD might be influenced by environmental stressors appears to be more reliable than the others. Epidemiologists find it impossible to test millions of environmental hazards (alone or in combination) in order to isolate hypotheses to then be tested at the individual level. We need to find a new approach to hypothesis generation, based on a population-scale territorial diagnosis.

In an analysis of the EPIMAD Registry and the French hospital discharge database (an ecological regression analysis of 5610 spatial units), we recently discovered that an elevated risk of CD was significantly associated with areas with a high level of social deprivation (relative risk [95% confidence interval] = 1.05 [1.02-1.08]) and areas with a high proportion of artificialized land (1.09 [1.04-1.14]). These results suggested that urban pollutants (such as metals) have a potential role in CD (Genin et al., 2019).

The EPIMAD Registry is accredited by the French Ministry of Health, the National Institute for Health and Medical Research (INSERM), the National Public Health Institute, and the National Cancer Agency, and is currently the world's largest prospective study of CD. It is an exceptional tool that "monitors" new cases of CD among the region's 6 million inhabitants via a unique, exhaustive network of private-practice and hospital-based gastroenterologists and pediatricians (n=264). Nearly 15,000 cases of CD are currently recorded in the EPIMAD's register - giving us significant statistical power and augmenting the likelihood of finding one or more environmental causes of CD.

In our pre-proposal, we presented the spatial heterogeneity of CD incidence in the EPIMAD area at the canton scale (the canton is the geographical unit within which the electors elect a country councilor; there are currently 2 059 cantons in France). Thanks to funding obtained from the DigestScience Foundation, we recently refined our results for the spatial heterogeneity of CD incidence by working at the municipality scale and mapping the corresponding standardized incidence ratios. We also used isotonic spatial scan statistics methods to identify statistically significant clusters of CD incidence (Figure 1). These methods enable the objective detection of significant spatial clusters of events in which the risk of being affect by CD is higher (or lower) than the rest of the studied area, and is modeled by a function that decrease from the center of the cluster to its border. We highlighted 4 "epidemic" clusters (red zones), with an average excess of risk of CD from 25% to 52% compared to the average for the region (white zones). The relative risks varied from 1.90 to 4.24 in the cluster centers. We also identified 5 clusters with a low risk of developing CD (blue areas), with an average reduction of risk of CD from 33% to 24% compared to the average for the region. The relative risks ranged from 0.74 to less than 0.01 in the cluster centers. In view of our exclusion of known genetic and familial cases from this analysis, we hypothesize that the spatial heterogeneity of the CD risk is due to environmental exposure. Hence, we now want to establish the socio-environmental profile of each high- or low-incidence cluster.

From a methodological viewpoint, our project is highly innovative because it is based on both geographic and historical data. Historical analysis and its results for environmental quality are more consistent for chronic diseases. Spatiotemporal analysis of the incidence of a disease and the quality of the environment will make it possible to understand the latency between exposure to environmental risk factors and an increase in the incidence. Furthermore, the population of northern France is known to be relatively immobile (i.e. a low migration rate). It is therefore an ideal area for the assessment of spatiotemporal patterns. The combination of environmental, social and historical approaches is also innovative in the field of epidemiology.

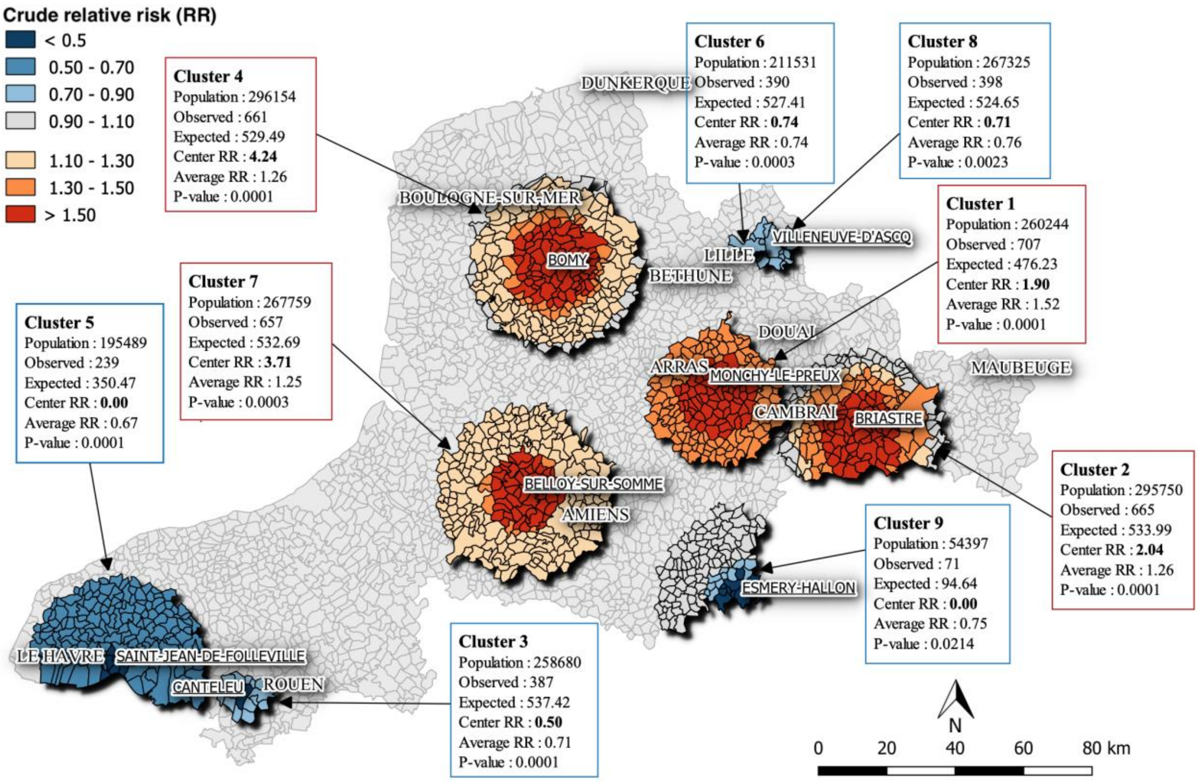

Figure 1: Spatial clusters detected by isotonic spatial scan statistics, including all incident CD cases from 1990 to 2014 (n=10420). High-incidence areas are represented in warm colors, and low-incidence clusters are represented in blue. The grey part corresponds to the mean CD incidence in the area

The Highlighting EnviROnmental features In epidemic areas of CD (HEROIC) transdisciplinary consortium was created in 2018 after two years of informal collaboration; it involves clinicians, toxicologists, epidemiologists, environmentalists, statisticians, historians, and sociologists. The consortium's goal is to identify new ecological and socio-environmental factors that might have a role in the risk of developing CD through an integrated, interdisciplinary epidemiological analysis - first at the municipality level (i.e. on the ecological scale – the subject of the present application), and then at the individual scale (the subject of future applications).
The ecological study consists in an environmental, sociological and historical review of epidemic and non-epidemic CD areas. Thus, scientific partners from different disciplines will work together and synthesize cognitive approaches.

c. Methodology and risk management

Our project will be divided into 5 WPs (Figure 2) and will involve 4 partners:

- **INFINITE**: Institute of Translational Research in Inflammation (U1286 INSERM, Univ. Lille) – epidemiology and functional analysis of CD;
- **LGCgE**: Civil engineering and Geo-environmental Laboratory (URL 4515, Univ. Lille) - environmental analysis and biomonitoring, exposure evaluation using geographic information systems (GIS);
- **IRHiS**: Northern Historical Research Institute (UMR-CNRS 8529, Univ. Lille) - contemporary economic and social history;
- **METRICS**: Assessment of health technologies and medical practices (ULR 2694, Univ. Lille) - statistical and spatial analyses.

Overall, the WP's organization is logical; an initial data acquisition phase will feed into two databases. The first will be supplemented by local field investigations at the cluster scale (WP3), and the second will be supplemented with re-used open-source data at the municipality scale for the whole EPIMAD area (WP3). The latter database constitutes the basis for the creation of a composite index and for spatial analysis more generally. These statistically processed environmental and historical data will then be interpreted by our toxicology and physiopathology experts.

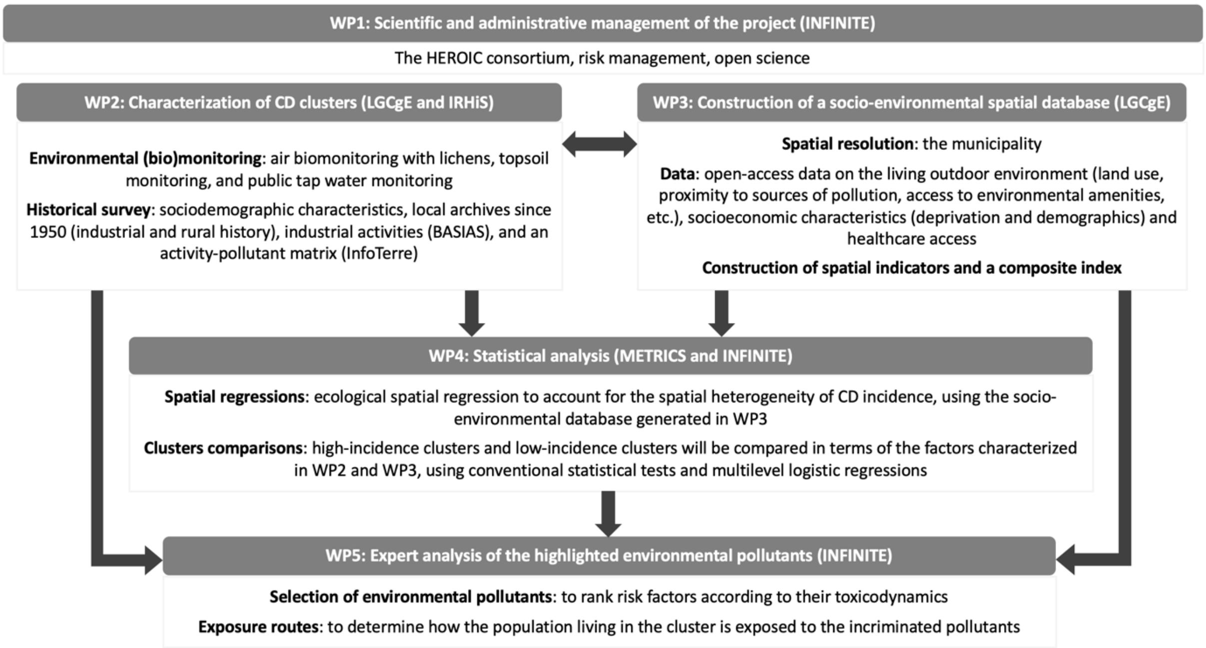

Figure 2: Architecture of the project

WP1: Scientific and administrative management of the project (led by INFINITE).

For each WP, a designated group will lead the work - even though all groups are involved in all WPs.

Task 1.1. Scientific management. Half-yearly meetings will be attended by all the members of the HEROIC consortium.

⇒ Task led by the future project manager (to be recruited)

Task 1.2. Risk management.

Since efficient risk management is a crucial success factor, the consortium has adopted a relevant risk-driven approach for the whole project (Figure 3), including an executive committee, a scientific advisory board, and a monitoring committee.

⇒ Task led by the future project manager

Task 1.3. Open science. Creation of a hosting server for sharing scientific data between the HEROIC consortium partners. The project will benefit from a strong support from the University Library whose Open Science dedicated service will help us to build the data management plan and will ensure open access to all the project's peer-reviewed publications on HAL, the French national repository. As required by the French National Research Agency (ANR), we will provide a data management plan after six months and at the end of the project, plus an intermediate plan during the second year of the project.

⇒ Task led by the future project manager and the scientific leaders of each WP.

Deliverables. (i) data management plan, (ii) dissemination plan, and (iii) intermediate and final reports.

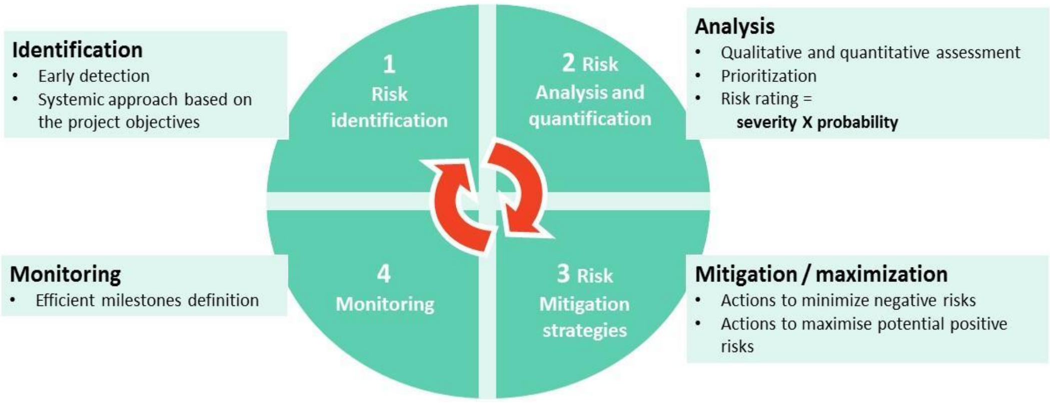

Figure 3: The continuous approach set up by the consortium members

WP2: Characterization of CD clusters (led by the IRHis and the LGCgE).

The clusters with a high or low incidence of CD will be characterized via an interdisciplinary approach. They will be compared in terms of environmental contamination and past industrial activities. As Clusters 6 and 8 are close together (Figure 1); potentially, they could be considered as a single area with a low risk of developing CD. In this WP, we will focus on 4 high-risk clusters and 4 low-risk clusters.

Task 2.1. Environmental monitoring and biomonitoring. A field-based environmental approach (including monitoring and environmental biomonitoring) will be used to assess the outdoor environment's quality and to generate proxy markers of the long-term exposure of populations living in the identified areas. A sampling plan will be adapted for each cluster as a function of its surface area and population density, with a maximum of 250 samples in the whole area. The use of GISs will ensure spatial coverage by systematic, stratified sampling by land use (urban, agricultural and industrial areas). Air, soil and water contaminations will be then characterized for each point location.

As we breathe more than 15,000 L of air each day, the air constitutes one of the most direct routes of exposure to anthropic contamination. Air quality biomonitoring – based on the analysis of plants and fungi, mainly epiphytic lichens – is a validated approach to evaluating long-term air contamination. Lichens are exclusively dependent on the atmosphere for their nourishment, and absorb pollutants such as metals in the same way as they do essential elements. Indeed, lichens are acknowledged to be highly useful bioaccumulators of metal contaminants in the outdoor environment, and monitors of spatial and temporal patterns of metal deposition (Occelli et al., 2016). Moreover, we recently demonstrated that lichens can be used in environmental epidemiology (Occelli et al., 2020).

According to the French standard NF X43-904, the multimetal burden will be evaluated by measuring the bioaccumulated levels 14 metals in the thalli of the foliose lichen *Xanthoria parietina* (aluminum, antimony, arsenic, cadmium, chromium, copper, lead, manganese, mercury, nickel, palladium, titanium, vanadium, zinc). With an annual growth rate of approximately 1 cm, the harvesting of thalli with a diameter of 6 cm thus corresponds to approximately 6 years of exposure. Briefly, at each point location, 9 small thalli will be sampled on tree trunks (1.5 m above the soil) and pooled. In the laboratory, the lichen samples will be air-dried and sorted manually (using a ceramic forceps) to remove adhering particles of bark, moss or soil.

Topsoil quality also reflects long-term environmental quality, since pollutants in soil mainly come from dry and wet atmospheric depositions, and can accumulate in the uppermost layers. Ingestion of soil particles is not considered in many health studies. However, health risk assessments have estimated the daily intake of soil to be 100 mg for adults and 200 mg for children (U.S. EPA, 2011). As with the lichen samples, soil samples will be collected in public areas. The sampling method will be consistent with the NF X 31-620 standard ("Provision of services relating to polluted sites and soils"). The samples will be collected with a manual auger.

For agricultural and urban soils, samples will be taken from the 0-25 cm section after removing plant cover. The boreholes will be described, in order to differentiate the materials brought in (backfill) from natural terrain, as well as any organoleptic pollution anomalies (color, odor, or impregnation of the soil) if needed. The soils will be packaged in bottles supplied by the analytical laboratory. Agronomic, physical and chemical characteristics (moisture, pH, %clay, %silts, %sand, organic matter, N total, nitric, ammonium, C/N, CEC, CaCo3) and concentrations of a hundred chemical species will be measured by an accredited soil analysis laboratory: total metals (14), monoaromatic hydrocarbons (11), halogenated hydrocarbons (24), polycyclic aromatic hydrocarbons (PAHs) (16), phthalates (8), polychlorinated biphenyls (PCBs) (9) and pesticides (12). Our soil database will also be fed with historical data from the sampling campaigns carried out by the LGCgE in the north of France since 1996. The topsoil characterization will be led by the PhD student recruited via the Programme for EArly-stage Researchers in Lille (PEARL).

Public water quality will also be assessed. To this end, water samples will be collected from cemetery taps and/or public fountains. The samples will be collected after 30 seconds of purging and then packaged in bottles supplied by the analytical laboratory. The studied analytes in tap water are as follows: 8 metals, total hydrocarbons (THC), PAH (16), Benzene, Toluene, Ethylbenzene, and Xylenes (BTEX), Highly Volatile Organic Compounds (HVOC), Hydrocarbons (C5-C10), phthalates (8), PCBs (9) and pesticides (12).

Lichen, soil and water samples will be analyzed in a COFRAC-accredited analytical laboratory. For each cluster, we plan to collect 20 water samples (total = 160 samples) and a minimum of 30 soil and lichen samples (total = 240 samples, plus 10 samples to distribute across the largest clusters covered). To guarantee homogeneity, all samples from a given cluster will be collected in the same week. The samples will be collected over a 2-month period, depending on the weather. A database will be built in order to characterize the CD clusters; all the HEROIC consortium members will be able to access it.

⇒ Task led by the LGCgE: the technician to be recruited, A. Deram, D. Cuny, C. Lanier, F. Occelli, M. Paumelle, and L-M Wakim.

Task 2.2. Historical survey. The goal of the historical survey is to establish an environmental diagnosis specifying the transformation of the environment in these areas since the 1950s. Thanks to the 3-month Masters project supervised by B. Touchelay (funding: I-Site, Lille University), the survey has already begun with a brief analysis of the major sociodemographic characteristics (lifestyle, life condition, economic activities, level of income, owner-occupiers/tenants, etc.) of the cluster populations, based on the available regional data. The historical survey will innovate by meticulously examining three sources of data describing the environment of these populations. The so-called *commodo and incommodo* enquiries - systematically initiated after a claim against a company or prior to the setting-up of a new craft-based or industrial activity - constitute the basis for our enquiry. These enquiries are registered and documented in the city of Lille's archives. The French historical inventory of industrial sites and service activities (BASIAS) is an open-access database (available via the Géorisques website) that describes geolocalized historical activities. The activity-pollutant matrix is an open-access database (available via the InfoTerre website) that ranks the pollutants potentially emitted from each industrial activity. All industrial activities observed in CD clusters will be linked to a list of these potential pollutants. The sociodemographic characteristics of the population and a pollution profile will be described for each cluster. We will outline the main characteristics of the clusters' inhabitants and the transformation of their living and working conditions, and will measure and track the changes in their environment quality since the end of the Second World War. More broadly, the historical approach is valuable because it can (i) analyze people's resilience when faced with transformations of their environment (Heuguebart and Touchelay, 2020), and (ii) provide insights into profound regional inhomogeneities in health conditions (Aprile et al., 2015).

⇒ Task led by the IRHis: L. Heuguebart, the research engineer to be recruited, and B. Touchelay

Deliverables. (i) A descriptive database for air, soil and water contamination by cluster, (ii) a historical research booklet and database, (iii) publication of a manuscript by L. Heuguebart in 2024.

WP3: Construction of a socio-environmental spatial database (led by the LGCgE).

The diversity of factors involved in environmental health, the complexity of the interactions to be considered, and the spatial and temporal variability in the phenomena observed mean that multidimensional approaches are essential. In this project, we shall build a unique, multidimensional database in order to characterize the EPIMAD area's outdoor environment on the municipality scale. This database will include spatialized indicators of the population's exposure to long-term air, water and soil pollution, as well as indicators of land use, proximity to sources of pollution, and access to environmental amenities.

Task 3.1. Sources of open-access data.

The first step is to collect data that describe each of the six dimensions identified as characterizing all the determinants involved in environmental health at the population level, and acknowledged to have a role in health inequalities: health, the environment, social aspects, economics, services, and policy (Brousmiche et al., 2020). The data will have to meet four inclusion criteria:

- open-access on the national scale;
- a plausible association with environmental health in the literature;
- comprehensive, spatially contiguous, contemporary, and available for the entire study area;
- production and regular updating by a reliable organization (thereby ensuring acceptable data quality).

We have already identified several French and European open-access data sources: GeodataGouv, the French National Institute of Statistics and Economic Studies, the French National Institute for Geographic and Forest Information, Open Street Map, the Permanent Equipment Base, the French National Spatial Inventory, the Observatory of French Regions, and the Environmental European Agency.

To provide a complete dataset and avoid bias due to missing values, a data management step (using spatial imputation) will be necessary. Ensuring the spatial and temporal interoperability of data from different sources and that differ in their nature and format is a key issue in this WP.

⇒ Task led by the LGCgE: F. Occelli, A. Deram, D. Cuny and C. Lanier

Task 3.2. Construction of spatial indicators.

Some of these data can be used directly in WP4 (e.g. the unemployment rate for each municipality). For other data, building a robust environmental indicator will require a spatial analysis. For example, long-term exposure to PM_{10} will be assessed by aggregating the spatial models for air contamination in space (from a 1x1 km grid to the municipality scale) and in time (from a one-year average to a ten-year average). Moreover, the Euclidian distance between the municipalities' populations and industrial, road, railway and crop sources will be computed using ESRI ArcGIS 10.7 Spatial Analyst tools.

⇒ Task led by the LGCgE: M. Paumelle, F. Occelli, A. Deram, D. Cuny and C. Lanier

Task 3.3. The open-access socio-environmental database.

The socio-environmental database will be populated with open data and our scientific work. That is why the database will be distributed in an open-access format at the end of the project. Moreover, to describe this database in a specific way and to make it citable, we will publish a data paper that explain the raw data's organizational structure. If the dataset is not accepted by the data journal, we will deposit it in a general repository (e.g. Zenodo).

⇒ Task led by WP3's scientific leader: F. Occelli

Task 3.4. Composite index. Outdoor environmental contamination is a complex phenomenon that involves chronic exposure to many different pollutants. Hence, environmental pollution must be considered holistically and in the long term. To date, very few studies have assessed the spatialized, cumulative exposure to multiple pollutants. We intend to build a composite index of multiple exposure. Composite index groups will serve as indicators of the various facets of multiple exposure to environmental pollutants (Lanier et al., 2019). We shall generate a composite index of the population's exposure to multiple environmental contamination or the municipality's sociodemographic characteristics. More widely, a vulnerability index will reflect the cumulative threat to which populations are exposed. A resilience index will reflect a given territory's ability to cope with health inequalities. The resilience/vulnerability balance will take account of the territory's disadvantages (according to the vulnerability index) and advantages (according to the resilience index).

⇒ Task led by the LGCgE: F. Occelli, A. Deram, D. Cuny and C. Lanier

Deliverables. (i) Publication of a data paper, (ii) maps of the socio-environmental indicators and the composite index.

WP4: Statistical analyses (led by the METRICS and INFINITE).

Task 4.1. Spatial regressions. An ecological spatial regression at the municipality scale will be used to explain the spatial heterogeneity of the standardized incidence ratios (SIRs), using the environmental and socio-environmental database generated in WP3. The spatial distribution of CD was recently assessed by computing SIRs for each spatial unit. The SIR is defined as the ratio between the observed number of CD cases and the expected number after indirect standardization for age and gender (i.e. well-known confounding factors in CD incidence). Given that the SIRs were unstable (due to low frequencies and spatial autocorrelation), the ratios were smoothed using a Bayesian Poisson regression model taking into account both the extra-Poisson dispersion and the municipalities' spatial structure. Associations between the age- and-gender-standardized incidence of CD and ecological indicators will be assessed using an extension of the previous model, namely ecological regression (i.e. the inclusion of ecological covariates as fixed effects). For each covariate, the relative risk of CD incidence and its 95% Bayesian credibility interval will be computed, using forest plots.

⇒ Task led by METRICS: M. Salem and M. Genin

Task 4.2. Cluster comparisons. High-incidence clusters and low-incidence clusters will be compared in terms of the factors characterized in WP2 and WP3, using classical statistical tests of comparison and multilevel logistic regressions for spatial data aggregated at different geographical scales.

⇒ Task led by INFINITE and METRICS: H. Sarter and M. Genin

Deliverables. Bivariate and multivariate forest plots

WP5: Expert analysis of the highlighted environmental pollutants by toxicologists and physiologists (led by INFINITE).

The environmental pollutants identified in WP4 will be hierarchized by expert toxicologists and physiologists. The experts will take account of the exposure routes, the toxicodynamics in the context of IBD, and potential links to autoimmunity.

⇒ Task led by INFINITE: C. Vignal

Deliverables. A list of environmental risk factors.

<table>
<tr><td>AAPG2020</td><td colspan="2">CROPS</td><td>PRC</td></tr>
<tr><td>Coordinated by:</td><td>Corinne GOWER</td><td>Duration : 48 months</td><td>334 k€</td></tr>
<tr><td colspan="4">scientific evaluation committee : CES 34 : contaminants, écosystèmes et santé</td></tr>
</table>

Risk analysis

The major risk in our project is temporal bias, which might limit the impact of our results. Previous studies performed by Epimad Register on conjugal forms of CD found that the time interval between exposure to an environmental risk factor and the appearance of CD appears to be around 8-10 years (Comes et al., 1994; Laharie et al., 2001). The clusters identified to date concern the period from 1990 to 2014. The environmental data that we are going to exploit will cover the period from 2010 to 2022 (open access databases available since the early 2010s; field campaigns performed from 2021). Several approaches will enable us to reduce this bias.

Firstly, we have checked the spatial clusters' temporality by using a spatiotemporal detection method. Some clusters were observed consistently from 1990 to 2014, which suggests that the areas of above-average incidence and below-average incidence were stable over time. At the start of the project, we will be able to check this stability over time by adding incidence data for 2015, 2016 and even 2017 (currently being validated). The clusters' geographic boundaries will then be specified.

Furthermore, we have chosen to use dedicated methods for the evaluation of long-term environmental impregnation by pollutants. Lichen-based biomonitoring of air quality provides information on cumulative exposure to atmospheric pollutants over 10 years or so, whereas surface soil quality is a good indicator of long-term environmental contamination – mainly due to human activities. Our historical analysis of the clusters' industrial and agricultural past will reinforce the field observations.

Risk analysis by WP

WP2 - This project is based on the acquisition of environmental field data. The major risk is a problem that arises during our analysis. However, the parameters to be analyzed here are conventional and several laboratories are able to provide these analyses. The main difficulty in the historical survey is almost complete absence of sources on agricultural practices (e.g. fertilizer and pesticide use by farmers) and eating habits in the selected territories. Neither the archives nor the environmental databases provide information on these aspects, which can only be clarified by indirect means (e.g. assessment of the accounts of agricultural cooperatives or companies, municipal archives on school meals, and company archives on canteen menus).

WP3 - The database will be built with data from the open-access databases listed above. The construction of composite indices has already generated publications within our group. This WP does not present any major risks.

WP4 - Similarly, WP4 is based on a long-standing collaboration (as evidenced by several publications).

WP5 - WP5 relates to the specific interpretation of the results and so does not constitute a major risk.

GANTT diagram

	Year 1												Year 2												Year 3												Year 4											
Task	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
WP1 - Scientific and administrative management																																																
1.1 Scientific management	X					X						X						X						X						X						X						X						X
1.2 Risk management	X					X						X						X						X						X						X						X						X
1.3 Open science	X					X						X						X						X						X						X						X						X
WP2 - Characterization of CD clusters																																																
2.1 Environmental monitoring and biomonitoring																																																
2.1.1 Sample plan			X	X	X																																											
2.1.2 Field sampling (lichens, soil, water)						X	X								X	X				X	X																											
2.1.3 Sample preparation						X	X	X							X	X	X			X	X	X																										
2.1.4 Laboratory analysis									X									X					X																									
2.2 Historical survey																																																
2.2.1 Sociodemographic survey	X	X	X	X	X	X	X	X	X	X	X	X																																				
2.2.2 Survey of commodo and incommodo enquiries	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																		
2.2.3 Construction of an emission indicator (BASIAS and activity-pollutant)				X	X	X	X	X	X	X	X	X																																				
WP3 - Construction of a socio-environmental database																																																
3.1 Spatial data collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																								
3.2 Construction of spatial indicators				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X																								
3.3 Open-access socio-environmental database																						X	X	X																								
3.4 Construction of a composite index																									X	X	X	X	X	X																		
WP4 - Statistical analyses																																																
4.1.1 Bivariate spatial regressions																															X	X	X	X	X	X												
4.1.2 Multivariate spatial regressions																																					X	X	X	X	X							
4.2.1 Bivariate cluster comparisons																									X	X	X	X	X	X	X	X	X	X	X	X												
4.2.2 Multivariate cluster comparisons																																					X	X	X	X	X							
WP5 - Expert analysis of the highlighted environmental pollutants																																																
5 List of environmental risk factors																																									X	X	X	X	X	X		
Productions																																																
Intermediate and final report																						X	X	X																						X	X	X
Data management plan						X															X																												X
Dissemination plan						X												X												X												X						X

II. Organisation and implementation of the project

a. Scientific coordinator and its consortium / its team

The HEROIC interdisciplinary consortium was formed in 2018 and headed by Corinne Gower-Rousseau. It comprises clinicians, toxicologists, epidemiologists, environmentalists, statisticians, historians, and sociologists.

Description of Partner 1 – INFINITE (the Principal Investigator)

Affiliation: Univ. Lille, Inserm, UMR 1286 INFINITE: Institute of Translational Research in Inflammation, U1286 Inserm Univ. Lille

Topics: Environmental risk factors associated with IBDs: from epidemiology to functional analyses

Leader: Corinne Gower-Rousseau, MD, PhD, HDR (CV in the appendix).

Task contributors: Hélène Sarter (research engineer in biostatistics and epidemiology, Lille), Cécile Vignal (Associate Professor in functional analyses/basic science), and the project manager to be recruited (34 months, part time)

Corinne Gower-Rousseau is the principal investigator and leader at Partner 1. She is currently a Senior Clinical Lecturer in Epidemiology at Lille University Hospital. She is the Scientific Head of the EPIMAD prospective, population-based registry in northern France, and manages the registry's logistics, methodology, scientific strategy, and publications.

Corinne Gower-Rousseau is also a lecturer and research in the UMR 1286 INFINITE INSERM unit at the University of Lille. She has expertise in the environmental factors of IBD, from epidemiology to functional analyses (i.e. cell-based and animal models). Her group comprises 11 staff: fundamental scientists, a data manager, a statistician, interviewer practitioners, and a technician. She specializes in the epidemiology of IBDs (CD and ulcerative colitis) in general, and their causes and progression over time and in space in particular in time and space. IBDs belong to the spectrum of IMIDs – diseases of unknown etiology that emerged in the 20th century and that cause high levels of disability. Corinne Gower-Rousseau is also joint head of Lille University Hospital's federative project on inflammatory disorders (FHU IMMINeNT). She is member of the French Scientific Advisory Board on Registries (at the French Ministry of Health) and is an internationally acknowledged expert in the epidemiology of IBDs. Between 2013 and 2016, she led a European research taskforce on epidemiology (the ECCO/EPI-IBD European cohort/). She has given over 20 guest lectures around the world, and has published 238 international papers (total citations: 10,132; mean citation number: 42.57; H Index: 35).

Starting from the population-based EPIMAD registry of IBD cases, Corinne Gower developed several multidisciplinary multicenter projects on specific cohorts (e.g. pediatric-onset IBD and elderly-onset IBD). She recently built the HEROIC consortium, which is developing a novel approach to territorial diagnosis of IBDs at a population level. The consortium includes historians, ecologists, toxicologists, mathematicians, epidemiologists, clinicians and socio-anthropologists. It is part-funded by a specific research program from University of Lille North Europe (ULNE), a European research foundation (DigestScience) and a IBD patient association (Association François Aupetit).

Corinne Gower-Rousseau is actively involved in translational research. Her main collaborations are with the group led by Professor JP Hugot (Robert-Debré Hospital, Paris), with whom she developed an e-cohort of adolescents and young adults with IBD in order to identify a possible nutritional profile associated with disease relapse (the MIKINAUTE program). She also developed major collaborations with microbiologists specializing in the microbiota: INRA units in Jouy en Josas (led by Dr Patricia Lepage and Professor Joël Doré), Saint-Antoine Hospital, Paris (led by Professor Harry Sokol) and Clermont Ferrand (led by Professor Nicolas Barnich). These collaborators are currently performing two large studies; the first on the microbiota in healthy first-degree relatives of patients with CD (the

MAGIC project, a national hospital-based research program), and the second on differences in the microbiota as a function of age at disease onset (the COMeBACk project, funded by the French National Research Agency). She also collaborates extensively with epidemiology research groups in Scandinavia (Professor Tine Jess in Copenhagen and Aalborg, and Professors Ebbe Langholz and Professor Johan Burisch in Copenhagen) and with Professor Jean-Frédéric Colombel (Director of The Susan and Leonard Feinstein Inflammatory Bowel Disease Center and Director of The Leona M. and Harry B. Helmsley Inflammatory Bowel Disease Center in New-York, USA), with 76 publications together. She supervised 6 PhD thesis and many Masters students 1 and 2). She has submitted a European ERC SYNERGY program which is awaiting the result.

Hélène Sarter (an epidemiologist, data manager and biostatistician), and **Cécile Vignal** (an expert in the toxicology and physiopathology of the highlighted environmental pollutants) will assist with WP1, WP4 and WP5.

Description of partner 2 – LGCgE (characterization of the environment in epidemic CD areas, and the development of spatial indicators)

Affiliation: ULR 4515 - LGCgE, Laboratoire de Génie Civil et géo-Environnement, Univ. Lille

Topics: Our group is part of the LGCgE Unit, which specializes in ecotoxicology, air and soil biomonitoring, and spatial analysis in environmental health. Over the last 40 years, the group has carried out several biomonitoring campaigns of environmental contamination in the north of France.

Leader: Professor Annabelle Deram, PhD (CV in the appendix)

Task contributors: Florent Occelli PhD (Associate Professor specializing in environmental health sciences and spatial analysis), Professor Damien Cuny PhD (specializing in ecotoxicology and air pollution biomonitoring), and Caroline Lanier PhD (Associate Professor specializing in toxicology, ecotoxicology, and food science), Martin Paumelle (PhD student 2020-2023), Lara-Maria Wakim (the PEARL PhD student 2020-2023) to be recruited with funding from PEARL, and the environmental field study technician to be recruited (17 months).

Annabelle Deram is the project leader at Partner 2. She is the scientific coordinator of the LGCgE biomonitoring group (10 people) and is part of the laboratory's scientific council (90 people). She was appointed as Dean of the Faculty of Engineering and Health Management in January 2020. She is an ecotoxicologist, with a particular interest in plants growing in contaminated soils. Her research theme concerns the development of tools for the assessment of health and environmental risks. As such, she supervised 4 PhD theses and has led a large number of projects dealing with the genotoxic effects of contaminated soil or the effect of mixtures of pollutants (MarGeEn - ANSES ADEME). She is an expert reviewer for grant applications in these fields (GESIPOL ADEME most lately). Together with Florent Occelli, she is developing a database on the quality of urban soil (CARBUR - not publically available at present). Annabelle Deram will coordinate WP2 and will assist with WP3.

For the last 20 years, **Damien Cuny** has been involved in air pollution biomonitoring programs based on lichens or higher plants. He has worked on the environmental effects of ozone pollution (using tobacco plants), heavy metals (using lichens) and organic compounds (using cabbages). He is involved in a large study that combines lichen-based air pollution biomonitoring and epidemiological population surveys. He is part of various European and French working groups on standards. He has previously led a research program on indoor air pollution biomonitoring. Damien Cuny will assist with WP2 and WP3.

Florent Occelli is involved in environmental epidemiology programs (e.g. coronary heart disease, chronic kidney disease, preterm birth, obesity, and CD) and studies of environmental inequalities (e.g. the spatial distribution of environmental and socioeconomic risk factors). His main research themes are (i) the development of spatial indicators for the characterization of environmental quality and the population's exposure to environmental contaminations, and (ii) the spatial interoperability of environmental, health and socioeconomic data. He recently studied exposure to multiple air pollutants through the use of monitoring and biomonitoring data, and he is currently researching the Euclidian distance between populations and multiples sources of burdens. He will coordinate WP3 and will assist with WP2.

Caroline Lanier was appointed Vice-Dean of the Faculty of Engineering and Health Management in January 2020. She studies the cumulative effects of health determinants, and environmental and social inequalities in health. Caroline Lanier previously led a research program on the development of composite spatialized indices to characterize vulnerability and resilience at the local scale. She will assist with WP2 and WP3.

The four researchers involved in the present project have developed a scientific transdisciplinary program (*Systèmes d'Information Géographique et Liens Environnement-Santé*, SIGLES, www.sigles-sante-environnement.fr) that assesses spatial statistics in environmental health and generates etiological hypothesis for several chronic diseases (cancer, chronic kidney disease, male infertility, and cardiovascular diseases). The researchers are also involved in a regional environmental health program.

Description of partner 3 – IRHiS (sociologic and historical investigations in epidemic CD areas)

Affiliation: UMR-CNRS 8529, Institut de Recherches Historiques du Septentrion (IRHiS), Univ. Lille.

Topics: This group (led by Béatrice Touchelay, Professor of Contemporary History at the University of Lille) specializes in contemporary economic and social history

Leader: Professor Béatrice Touchelay PhD (CV in the appendix)

Task contributors: Léo Heuguebart (PhD student) and the research engineer in Digital Humanity and Contemporary History to be recruited (7 months)

Béatrice Touchelay (Professor of Contemporary History at Lille University) specializes in the history of public data and the industrialization process in the north of Europe. She is very familiar with the regional and national archives. Her research group focusses on contemporary economic and social history and performs demographic, historical and environmental surveys at the territorial scale. The historical surveys are based on careful interpretation of various sources of data (archives, the local and national press, other media, reports from "experts" such as agricultural engineers, town planners, trade unionists, etc.) on agricultural, craft-related and industrial activities in the north of France in general and in CD clusters in particular. Béatrice Touchelay will coordinate the historical research.

Léo Heuguebart's PhD in Contemporary History is devoted to the review of the three databases presented above for the most prominent CD clusters.

Description of partner 4 – METRICS (statistical methodology, space-time statistics, and specific statistical models of the epidemic CD areas)

Affiliation: ULR 2694 METRICS - Evaluation des technologies de santé et des pratiques médicales. Univ. Lille.

Topics: The ULR 2694 METRICS unit (led by Alain Duhamel, Professor of Biostatistics at the Lille Faculty of Medicine) comprises 46 researchers and 18 PhD students, and includes methodologists, data managers, biostatisticians and specialists of spatial and space-time statistics and their application to epidemiology.

Leader: Michaël Genin PhD (Associate Professor of Statistics, CV in the appendix).

Task contributor: Mohamed-Salem Ahmed (Postdoctoral researcher, PhD in statistics)

Michaël Genin's research focuses on spatial and space-time statistics and their applications in epidemiology. For the past 10 years, he has been developing models of spatial statistics (scan statistics) and spatial database interoperability methods for use in epidemiology research. He is now an acknowledged national-level specialist in geospatial biostatistics and has highlighted spatial clusters of various diseases (particularly IBD) using isotonic spatial scan statistics models. These methods are well known, very powerful, and frequently used in the field of epidemiology. He has collaborated with the EPIMAD Registry team for the last 8 years, following his PhD. His collaboration with French experts in IBD has led to several international publications. He is also a member of Lille University Hospital' clinical research department, and so the present project will benefit from the department's expertise in methodological aspects.

Mohamed-Salem Ahmed develops statistical methods that take account of both spatial heterogeneity and dependence of spatiotemporal epidemiologic data.

Implication of the scientific coordinator and partner's scientific leader in on-going project(s)

Name of the researcher	Person. month	Call, funding agency, grant allocated	Project's title	Name of the scientific coordinator	Start - End
Corinne GOWER	3	French Health Ministry Population-based registry	Epidemiological Population-based study in northern France Epimad Registry	Corinne GOWER	1992-Now
Corinne GOWER	3	National Research Agency	Comparison of microbiota according to age in Crohn's disease (COMeBACk)	Corinne GOWER	2014-Now
Corinne GOWER	3	ISITE AND Lille European Metropole (168K€)	Health and environment: from the territory to the individual	Corinne GOWER & Luc DAUCHET	2019-2023
Corinne GOWER	1	European Charity DigestScience Fundation	Highlighting Environmental features in epidemic areas of CD	Corinne GOWER	2018-2020
Corinne GOWER	3	Association François Aupetit	Food risk factors associated with relapse from an e-cohort of paediatric intestinal chronic inflammatory diseases (MIKINAUTES)	Corinne GOWER & Jean-Pierre HUGOT	2018-2021
Annabelle DERAM	3	ISITE AND Lille European Metropole (168k€)	Health and environment: from the territory to the individual	Corinne GOWER & Luc DAUCHET	2019-2023
Annabelle DERAM	2	Regional Health Agency Hauts-de-France (100k€)	Biosurmonitoring (BILIV)	Caroline LANIER	2019-2021
Annabelle DERAM	2	RECORD network (42k€)	Exposure to atmospheric particles - Link between physico-chemical characterization and impact on health	Annabelle DERAM	2019-april 2020
Annabelle DERAM	3	City of Lille (105k€)	Environmental diagnosis of the territory - influence of the fine geographical scale on the informative quality of the data, in environmental health	Annabelle DERAM & Florent OCCELLI	2020-2023

Name of the researcher	Person. month	Call, funding agency, grant allocated	Project's title	Name of the scientific coordinator	Start - End
Florent OCCELLI	3	Regional Health Agency Hauts-de-France (100k€)	Biosurmonitoring (BILIV)	Caroline LANIER	2019-2021
Florent OCCELLI	6	ISITE AND Lille European Metropole (168K€)	Health and environment: from the territory to the individual	Corinne GOWER & Luc DAUCHET	2019-2023
Florent OCCELLI	3	City of Lille (105k€)	Environmental diagnosis of the territory - influence of the fine geographical scale on the informative quality of the data, in environmental health	Annabelle DERAM & Florent OCCELLI	2020-2023
Beatrice TOUCHELAY	3	ISITE AND Lille European Metropole (168K€)	Health and environment: from the territory to the individual	Corinne GOWER & Luc DAUCHET	2019-2023
Michaël GENIN	2	Regional Health Agency Hauts-de-France	Spatial analysis of vaccination coverage rates in the Hauts-de-France region.	Benoit Dervaux & Michaël Genin	2019-2021
Michaël GENIN	1	Regional Health Agency Hauts-de-France (100k€)	Biosurmonitoring (BILIV)	Caroline LANIER	2019-2021
Michaël GENIN	6	ISITE AND Lille European Metropole (168k€)	Health and environment: from the territory to the individual	Corinne GOWER & Luc DAUCHET	2019-2023

b. Implemented and requested resources to reach the objectives

Partner 1 - INFINITE: 90,720€

Staff expenses

Project manager

Even if the HEROIC consortium has existed for 2 years, a project manager is essential for the implementation and coordination of this interdisciplinary project.

General and administrative costs & other operating expenses

Environmental costs (8%).

Partner 2 – LGCgE : 198,612 €

Staff expenses

The technician will be responsible for preparing and (with group members) collecting all of the abovementioned samples (lichens, soil, and water). The duration of the technician's employment contract will make it possible to prepare and deploy the campaign during the second year of the overall program. An additional campaign (risk management) could be added in the following year in the event of difficulties (bad weather, samples not analyzed, a need for additional samples, etc.). The technician will reinforce the group during WP2 and WP3.

Instruments and material costs

These costs will be low because since the bottles and transport required for sample analysis are included in the laboratory's service provision. The laboratory already has the necessary sampling equipment.

Outsourcing / subcontracting

The planned number of samples is 30 per cluster for soils and lichens and 20 for water samples. The samples will be distributed over 8 clusters (in a regular square mesh), corresponding to 240 soil and lichen samples and 160 water samples (110,000€). Fees for publication in open science revues (5,000€).

General and administrative costs & other operating expenses

This item includes the vehicle rental costs for the two sampling campaigns, travel and accommodation costs, part of the costs linked to open access, and environmental costs (8%).

Partner 3 - IRHiS: 23,350 €

Staff expenses

A research engineer specializing in digital humanities will be recruited for 7 months to support Léo Heuguebart in the review of the three databases presented above for the most prominent CD clusters.

General and administrative costs & other operating expenses

Environmental costs (8%).

Partner 4 - METRICS: 16,200 €

Instruments and material costs

The spatial statistical methods used in this project are based on hierarchical Bayesian models that are very time-consuming to compute. Given the large number of models (spatial ecological regressions) to be estimated, an information technology (IT) infrastructure dedicated to parallelised high-performance computing is required.

General and administrative costs & other operating expenses

Environmental costs (8%).

⇒ Table of requested founds is given at the end of the document (p18)

III. Impact and benefits of the project

Scientific, economic, social and cultural impacts

The present research project on environmentally-driven CD is truly innovative and transdisciplinary, with the involvement of clinicians, toxicologists, epidemiologists, environmentalists, statisticians, historians, and sociologists. The most novel features of the CROPS project are its analysis of the effects on ecosystems, the identification of environmental indicators of these effects, the remote sensing of new indicators, the mapping of environmental quality, and assessment of links with human health. To the best of our knowledge, CROPS will be the first project to implement an integrated approach to the study of health hazards associated with environmental contamination in general and the soil pollution in particular. Moreover, several of the proposed approaches (i.e. chemical screening in soil and water) have never previously been applied to this topic. This exceptional breadth and commitment to state-of-the-art work will place CROPS at the forefront of health ecology studies internationally. Although most of the work is truly innovative, the conceptual and methodological aspects of the research will build on the PI's extensive expertise.

Data and results dissemination strategy

The outcomes of this research will be high-level scientific outputs that go far beyond the state of the art. It will be the first time that detailed data on the fate of chemicals in soils and water (as a special case of chemical pollutants incorporating themselves into the environment) will be combined with state-of-the-art technologies to accurately assess the etiology of CD (as a special case of an environmentally-driven chronic disease). CROPS will involve observational, experimental and modelling work at the frontier between ecology and public health, thereby responding to the call for more integrated "health ecology" ways of understanding the role of human-modified environments in the recent emergence of diseases like CD. Each WP in this cutting-edge project will result in several publications in top-ranked, multidisciplinary journals. We expect to open up new research perspectives beyond the project's direct scope. For instance, CROPS will provide conceptual and methodological frameworks for research on the causal relationships between environmental pollutants and chronic diseases in general.

Data generated through CROPS will be managed according to the FAIR principles: the data must be findable, accessible, interoperable and re-usable. The DMP will describe the data management life cycle at an appropriate level of detail for the project, including (i) identification of data and metadata collected, processed and/or generated, (ii) how research data will be handled, curated and preserved – even after the end of the project for possible reusability, and (iii) which methodology and standards will be applied to ensure data interoperability. The relevance of sharing some of the scientific output on open data storage platforms will be confirmed.

When disseminating our research results, we will follow the ANR recommendations on open science. All of the peer-reviewed scientific publications will be made available on an open-access basis. As stipulated by French legislation, these publications will be uploaded to open-access repositories such as the HAL national repository no later than 6 months after their publication on the publisher's website. This open-access strategy will allow broad, free dissemination of our publications. We shall not seek to publish in journals requesting an article processing charge.

Technology transfer and innovation

The new insights provided by CROPS will also help policymakers and land/water managers to develop urgently needed strategies for preventing emerging health hazards associated with chemicals in the environment. The CROPS project's goal fits perfectly with the European Union's strategy on the "prevent-detect-respond" concept and with the One Health European Joint Programme adopted by the European Commission in October 2018, which seeks to reduce human exposure to environmentally-driven health hazards (currently limited to infectious diseases). Lastly, the CROPS results will be particularly suitable for communication to the general public via the press/media, to students in university lectures, and to stakeholders at informal study days. The fate of chemicals released into the environment by human activities and the chemicals' effects on human heath are key concerns for the general public, as witnessed by extensive coverage in the press and on national and international television, radio and web-based media.

Promotion

In summary, this project will constitute a clear conceptual advance in our understanding of the relationships between environmental chemical pollutants and the occurrence of certain chronic diseases. We expect it to spark the interest of the general public, policy makers, land/water managers, clinicians, life science researchers, students, and other groups. If we confirm that several pollutants are indeed involved in the pathogenesis of CD, CROPS will set the stage for a major revision of the effects of historical soil pollution on chronic diseases, and will strongly shape future assessments of environment-health relationships. Future projects would probably adopt a similar holistic, multidisciplinary approach, in order to (i) make accurate, robust predictions about the long-term effects of environmental pollutants on ecosystem function and human health, (ii) create indices and tools for the effective monitoring of exposure, and ultimately (iii) avoid preventable health threats. The impact of CROPS will therefore extend far beyond the stated system, study area and project lifetime.

Requested means by item of expenditure and by partner*

		Partner *INFINITE*	Partner LGCgE	Partner IRHiS	Partner METRICS
Staff expenses		85,000€	45,900€	26,250€	0
Instruments and material costs (including the scientific consumables)		0	5,000€	0	15,000€
Building and ground costs		0	0	0	0
Outsourcing / subcontracting		0	121,000€	0	0
General and administrative costs & other operating expenses	Travel costs	0	12,000€	0	0
	Administrative management & structure costs**	6,720€	14,712€	2,100€	1,200€
Sub-total		90,720€	**198,612€**	**28,350€**	**16,200€**
Requested funding		**333,882€**			

* The amounts indicated here must be strictly identical to those entered on the website. If both information are not consistent, if they were badly filled in or lacking, the information entered online will prevail on those reported in the submission form / scientific document.

** For marginal cost beneficiaries, these costs will be a package of 8% of the eligible expenses. For full cost beneficiaries, these costs will be a sum of max. 68% of staff expenses and max. 7% of other expenses.

IV. References related to the project

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