Special Report: Actions Towards European Environmental Surveillance: Feasibility of Environmental Linkage (December 2013)

EUROCAT Central Registry
Room 12L09
University of Ulster
Newtownabbey, Co Antrim
Northern Ireland, BT37 0QB
Tel: +44 (0)28 90366639
Fax: +44 (0)28 90368341
Email: eurocat@ulster.ac.uk
Web: www.eurocat.ulster.ac.uk

Funded by the Public Health Programme 2008-2013 of the Executive Agency for Health and Consumers, European Commission

WHO Collaborating Centre for the Surveillance of Congenital Anomalies

Contents

Authored by Martine Vrijheid (WP6 Leader, leader small scale linkage feasibility study), Fabrizio Bianchi (leader hot-spot feasibility study) and the Air Pollution Working Group – Fabrizio Bianchi, Vera Nelen, Guy Thys, Judith Rankin, Carmen Martos.

1. Introduction

There are environmental exposures of important public health concern, such as air pollution from traffic and industrial sources, for which assessment of exposure largely relies on geographical methods, as questionnaire or biomarker methods are not appropriate. Geographically-based Europe-wide exposure databases are now available in relation to a number of environmental hazards, including air pollution and industrial toxic releases. These can be linked to individuals through geolocation of place of residence. The existence of exposure databases and congenital anomaly registry data in many regions of Europe, provides potential for the environmental surveillance of congenital anomalies. With this we mean the systematic and continuous monitoring of congenital anomaly prevalence in relation to potential pollution sources.

There are a number of issues that require clarification before the feasibility of such surveillance can be established, including a) the availability of place of residence (location) data in the registries; b) the level of spatial accuracy of the location data (i.e. residential address, postcode, census area, larger neighbourhood); c) the availability of data on control/denominator births with similar level of spatial accuracy; d) the availability of covariate data for cases and control births. These issues differ according to the nature of the environmental exposure of interest. For example, industrial releases are expected to give rise to concentrated exposure in a small area (hot-spots), whereas traffic-related air pollution (small size particulate matter – $PM_{2.5}$, PM_{10}, nitrogen dioxide – NO_2) is largely defined by intra-city, street-level, differences in traffic density. Yet other air pollutants (ozone – O_3, sulfur dioxide - SO_2) may be spread over larger areas with less intra-city variation.

The aim of this report, related to activity 6 in WP6 of the Joint Action, is to address these issues for two different exposure scenarios:

1) The feasibility of small-scale geographical (address) linkage studies (section 2 of the report)
2) The feasibility of epidemiological investigation in small polluted areas (hot-spots) (section 3 of the report)

2. Feasibility of small-scale geographical (address) linkage studies

2a. Background and Objectives

For this part of the feasibility work we have taken traffic-related air pollution as an example exposure. There is a growing number of studies on ambient air pollution and risk of congenital anomalies. In a recent meta-analysis, NO_2 and SO_2 exposures were related to increases in risk of coarctation of the aorta and tetralogy of Fallot, and PM_{10} exposure to an increased risk of atrial septal defects (Vrijheid et al 2011). So far, few studies have used refined spatial exposure models: exposure indices have been based on measurements from nearby fixed-site monitoring stations and were therefore of crude spatial resolution, measuring predominantly community-wide variations in air pollution. Such measures do not account for strong spatial determinants of intra-city air pollution variation, such as traffic density. Since traffic exhaust fumes are the main source of air pollution in urban areas, the use of more precise spatial air pollution models, based on dispersion or land-use regression models, are increasingly being recommended for urban air pollution assessment. In the study of birth outcomes, due to the very specific windows of exposure, spatial models would have to be combined with temporal ones.

In a number of European regions, detailed spatial air pollution models based on land-use regression (LUR) models have been developed as part of the ESCAPE study (European Study of Cohorts for Air Pollution Effects - www.escapeproject.eu). This projects aims to study the long-term effects on human health of exposure to air pollution in Europe and includes over 30 existing cohort studies. The development of ESCAPE air pollution models (for NO_2 and $PM_{2.5}$) in many regions following a common methodology opens the possibility of studying other health outcomes, such as congenital anomalies.

In order to establish the feasibility of using these types of exposure maps for linkage in the EUROCAT registries, we set the following objectives:

- To assess the feasibility of geographical linkage studies using address-level (instead of area-level) accuracy in EUROCAT registries. This has been done through a feasibility questionnaire and in-depth discussion with relevant registries (section 2b).
- To perform a pilot study in one EUROCAT region (Barcelona) linking the ESCAPE LUR models with the EUROCAT registry data. This registry was chosen as it had address data for cases and control births, the ESCAPE maps were ready to be used at the time of this study, and in-house expertise for the modelling of temporal and spatial exposure estimates was available (section 2c).

2b. Feasibility results across EUROCAT registries

A questionnaire was used as first evaluation to establish whether it would be feasible to conduct a study of the association between air pollution and congenital anomaly risk in the regions of Europe where ESCAPE and EUROCAT overlap. Registries in nine countries completed the questionnaire. In registries where it appeared possible to obtain address-level data (Antwerp, Tuscany, Valencia,

Barcelona, Basque Country, UK registries), we held further discussions during the EUROCAT Registry Leaders meetings in Dublin (2010), Antwerp (2011) and Zagreb (2013) to discuss protocol development issues for a potential study on traffic-related air pollution. Below is a summary of the results obtained in each registry and of the protocol development issues. Table 1 summarises results of the feasibility questionnaire.

Table 1: Results of feasibility questionnaire sent in 2009-2010 to regions of Europe where ESCAPE and EUROCAT were thought to overlap*

Country	EUROCAT Registry	Reply received	Summary feasibility (all depending on resources)
Belgium	Antwerp	Yes	Feasible. Need to go to hospital records to extract address data for cases. Address data for controls available.
Finland	Helsinki	Yes	Feasible. Address data can be obtained for cases and controls from the medical birth registry with extra permissions and resources. Significant cost attached to obtaining data.
France	Paris	Yes	Not feasible. No individual address data available for cases. Possibly in the future. Control births may be obtained through special recruitment.
Italy	Tuscany	Yes	Feasible. Case addresses available. Control addresses can be obtained from medical register (Certificate of attendance at birth) or Hospital Discharge Records.
Netherlands	Northern Netherlands	Yes	Feasibility unclear – address data available for cases, but probably only aggregate postcode data for controls births.
Spain	Barcelona	Yes	Feasible. Registry includes case and control births with address information.
	Valencia region	Yes	Feasible. Case addresses are available. Control addresses can be obtained through the live birth population-based registry
UK	All UK registries	Yes	Feasible, using postcode data. Help from GIS department needed.
Norway	Oslo	No	-
Sweden	Stockholm	No	-

*overlapping regions as established in 2009. Since then, changes in protocols and expansion of ESCAPE LUR models may have led to differences in the final coverage of the pollution maps. Also, it should be noted that in some countries, the Escape models started at city or regional level and are now being expanded to larger regions or countries (e.g. UK, Netherlands, Spain). Any new studies would have to evaluate latest coverage.

Case and control selection and geocoding

For this type of study it will be important to have address information or geolocation data with a high level of spatial accuracy (street name and number, street name only, UK postcodes) for cases. These addresses or locations, need a proper control of completeness and quality to be efficiently geocoded (transferred to x and y coordinates). The selection of cases for a potential study therefore depends on the efforts involved in obtaining addresses and geocodes:

1) Registries that already have addresses or postcodes will find it relatively easy to obtain geocodes for all their cases through automated linkage systems available in all countries. These registries include: Barcelona, Valencia, Basque Country, Tuscany, UK Registries.

2) Registries that do not currently have case addresses in their database, such as Antwerp, will need to obtain addresses from hospital records or other sources. This involves a much greater effort.

For a potential study, it will be necessary to obtain control births; these can be all births or a random sample. If a random sample is chosen it should be spatially random, i.e. it should not depend on location or hospital catchment areas. A random sample should include at least 1 control per case.

Locations of control births need to be available with the same level of spatial accuracy as the cases (street name and number, street name only, UK postcodes).

Table 2: Sources of controls in selected registries

	Control selection:	Location data
Barcelona	Controls (live births) are available as part of the registry: for each case, 2 control mothers are interviewed during maternity stay. This is randomly spread over city of BCN	Addresses are available on the registry, These have been geocoded. Covariate data available at individual level. Deprivation at area level
Valencia region	From live births registry	Possible to link to addresses (not for terminations). Covariables such as sex, length of gestation, birth weight, age of mother at delivery, mother's residence code and mather's birth country are available at individual level. Deprivation at area level.
Antwerp	From the medical births registry	Addresses can be extracted from hospital records. Maternal age available at individual level. Deprivation at area level.
UK registries	Controls (live births and stillbirths) from birth registry for whole of UK.	Geocoded postcodes available from previous study for certain years/regions. Geocodes to be obtained for rest. Maternal age available at individual level. Deprivation at area level.
Tuscany	Controls from birth registry	Addresses available on birth registry (Certificate of attendance at birth) or Hospital Discharge Records. Geocodes can be obtained. Maternal age available at individual level. Deprivation at area level.

Exposure estimation – linkage with exposure maps.

In Barcelona, traffic related air-pollution levels have been measured and refined exposure modelling techniques are employed to develop a detailed spatial land-use regression (LUR) model, within the framework of ESCAPE Project. The geocodes of the maternal residence at birth have been linked to exposure estimates for PM_{10}, $PM_{2.5}$, NO_x and NO_2 (see further section 2c). This provides spatial exposure estimates. Next, it is important to adjust the spatial estimates for temporal trends to account for day-to-day variation in pollution levels and estimate exposure during the sensitive time windows in pregnancy – for example weeks 3 to 8 of gestation when most major anomalies develop. For this it is important that the study region has at least one air pollution monitor in a background location that has been functional for all the years covering the study (see pilot study example in section 2c).

Specific feasibility issues in selected registries:

Antwerp

In Antwerp, a detailed air pollution study is feasible and would require the following steps:

- A detailed study protocol including scenario for the fieldwork (inclusion and exclusion criteria, number of cases and controls, timetable…)
- Approval by the ethical committee of each hospital involved
- Establishing collaboration with the Belgian partner of the Escape study: VITO. They hold the modeled air pollution data.
- Case/control finding, geocoding of the addresses, data linking with modeled pollution data and data analysis. Extra funding for the registry is necessary to carry out these tasks.

Tuscany

The linkage between addresses derived from the medical records and those in the GIS is an operation which can need a lot of time and staff, because many addresses have formal errors and others do not report the number. This means a manual search is needed when the roads are long or the address has to be assigned subjectively when the roads are short. It is estimated that less than 10% of these addresses have these problems. The cities of Florence and Pisa on the field of study may be considered the high quality of health data and systems geocoding of addresses. One person/year dedicated to the project seems necessary.

UK Registries

In the UK postcoded location data are available for cases on the congenital anomaly registries and for control births on the birth registration. Postcodes in the UK cover small geographical areas suitable for small-area studies; these have been used previously for other studies (e.g. Davand et al 2011a, b; Rankin et al 2009). A database covering several UK registries (Newcastle, Oxford, Wessex, Glasgow) and containing cases and control births between 1991-1999, with geocoded location data, is available from a previous study on geographic heterogeneity in congenital anomalies (Armstrong et al 2007) and on air pollution (Dolk et al 2010). Extension of this database covering more recent years would be feasible with sufficient support for the registries and a GIS technician.

Valencia region

Epidemiological investigations in small polluted areas could be carried out in Valencia Region. Case addresses are available in the Registry of Congenital Anomalies and control addresses can be obtained through the live birth population-based registry. A pilot study showed that about 96% of case and control addresses were geocoded . Nevertheless, due to address errors or incomplete information about 25% of them need a complementary data revision. Therefore, it is necessary the allocation of specific staff (at least one person/year, depending on the number of cases and controls) for carrying out this task. A software for automatic linkage between addresses and GIS would be necessary.

Concerning pollution data, an area of Valencia region was included in the ESCAPE project. This area consists of 33 municipalities, 300000 inhabitants and 1372 km^2. Therefore, spatial land-use regression could be applied to estimate the exposure to air pollution. In addition, the European Pollutant Release and Transfer Register (E-PRTR) can be used to obtain industrial pollution data for Valencia Region. Nevertheless, errors have been detected in the geocoding of the pollutant foci, so it is necessary to validate the accuracy of these co-ordinates (García-Peréz et al 2008).

2c. Traffic-related air pollution and risk of congenital anomalies in Barcelona

This section describes the methodology of the pilot study carried out in Barcelona. The results of this study have been published (Schembari, et al 2014 – Annex 1). Barcelona is among the most polluted cities in Europe. This is partly due to its geography, to its high traffic density, four times higher than London, and to its large proportion of diesel-powered vehicles, currently 50% (Reche et al. 2011). In Barcelona we developed a refined spatial air pollution exposure metric using a land use regression model (Eeftens et al. 2012). At the same time, Barcelona has a high-quality population-based congenital anomaly register, which has collected detailed data on malformed cases and control births for over 15 years (Greenlees et al. 2011). Using these two data sources, this pilot study aimed to investigate whether exposure to intra-urban, traffic-related air pollution during pregnancy is related to risk of congenital anomalies.

Study Population

This study used a population-based case-control design. The source population consisted of congenital anomaly cases and control births from the Barcelona congenital anomalies register, REgistro Defectios Congenitos Barcelona - REDCB that covers nearly all maternity units in the city since its start in 1992. The REDCB is part of the Service of Health Information Systems (Servei de Sistemes d'Informació Sanitaria) in the Public Health Agency of Barcelona (Agència de Salut Pública de Barcelona) and covers approximately 13,000 births per year (live births, stillbirths after 20 weeks of gestation, and terminations of pregnancy). It is also member of the European Surveillance of Congenital Anomalies – EUROCAT (Greenlees et al. 2011). Three full-time nurses actively search for new cases at delivery units, paediatric departments, cytogenetic laboratories, pathology departments, prenatal diagnosis units and paediatric cardiology services; cases of congenital anomalies not detected at birth are further included until age 1 year. Controls are continuously selected as a 2% representative sample of all live births in Barcelona hospitals, by random date of birth sampling, independently of the cases (non-matched) and proportional to the annual number of births in each hospital. Clinical information for cases and controls is collected from hospitals records. Information on obstetric and reproductive history, diagnostic information, socio-demographic variables, maternal tobacco smoking, alcohol consumption, medical drug use and parental education is collected by interview with the mother after delivery (live births only), using a standard questionnaire (Salvador et al. 2005). Parental consent is completed before the interview and all consenting cases and controls mothers are interviewed. We derived the MEDEA socio-economic deprivation index (Dominguez-Berjon et al. 2008) at census track level by linking this to the residential addresses of the cases and controls. Smoking during first trimester was calculated as the percentage of mothers who declared that they smoked for the first, the second or the third month of pregnancy. Ethical approval for the study was obtained from Clinical Research Ethics Committee (CEIC project 2008/3115/I and 2006/3394/I).

Definition of cases and controls

Eligible cases and controls were defined as those born between 1994 and 2006 and who had their residential address at birth in the city of Barcelona. The first two years of available REDCB data

were excluded because the case ascertainment was less complete and because around 1992 the Barcelona road network have sustained major changes which could have affected the spatial distribution of air pollution resulting in possible exposure misclassification.

Controls were all eligible live births on the REDCB. From a total of 3149 controls, 158 were excluded because of incorrect residential address or address outside Barcelona, giving a total of 2991 (95.0%) controls for analyses.

Cases were live births, stillbirths after 20 weeks of gestation, or terminations of pregnancy following prenatal diagnosis of congenital anomalies, with at least 1 major anomaly in the EUROCAT list of subgroups of congenital anomalies (EUROCAT, 2009). Cases with only minor congenital anomalies were excluded, following the EUROCAT exclusion list (EUROCAT, 2009). The range of codes for inclusion was, according to the International Classification of Disease (ICD) version 10, the Q-chapter except the Q86, Q87 and Q936. Cases with non-chromosomal anomalies (n=719), and teratogenic and genetic syndromes (n=72) were excluded. Twins were treated as one outcome (12 pairs), and classified as a case if one or both had a congenital anomaly; siblings were classified as separate outcomes, following the methodology in (Dolk et al. 2010). Cases with an incorrect residential address or address outside Barcelona were excluded (n=166), as were terminations before 20 weeks (n=5) and cases with missing information on birth date and gestational age and last menstruation period (n=74). Out of a total of 3295 cases, 2247 (68 %) were included in analyses. Cases were classified into anomaly subgroups following EUROCAT guidelines (EUROCAT, 2009). An a-priori decision was made to analyse the following, most frequent, subgroups of anomalies: neural tube defects, cardiac anomalies, respiratory system defects, orofacial clefts, digestive system defects, abdominal wall defects, urinary system defects, hypospadias, and limb reduction defects. To replicate results from previous studies (Vrijheid et al. 2011) eight subgroups of cardiac anomalies were also considered.

Exposure assessment

This study combined the spatial Land Use Regression (LUR) modelling developed in the European Study of Cohorts for Air Pollution Effects – ESCAPE project (ESCAPE project2009) with a temporal adjustment, arising both spatial and spatio-temporal exposure estimates. LUR models are commonly used to explain the small-scale within-city variation of traffic-related air pollutants; likewise temporal adjustment is needed to account for the exposure during organogenesis, i.e. weeks 3 to 8 of pregnancy (Moore and Persaud 1998).

Spatial estimates

Within the city of Barcelona, during the 2009, twenty sites were used to measure PM_{10}, PM_{coarse} (Particulate matter with aerodynamic diameter between 10μm and 2.5 μm), $PM_{2.5}$, and $PM_{2.5}$ absorbance; the absorbance of $PM_{2.5}$ filters was used as marker of black carbon. Forty sites were used to measure NO_2 and NO_x. Combinations of traffic and background locations were selected to maximize the spatial variability. The final LUR models explained the 74%, 73%, 87%, 75%, 83%, 86% of the variance in the measured NO_2, NO_x, PM_{10}, PM_{coarse}, $PM_{2.5}$, and $PM_{2.5}$ absorbance (supplemental material table 1 and Map 1), respectively; methodology and models specifications

were described in (Beelen et al. 2013; Cyrys et al. 2012; Eeftens et al. 2012). We assumed that the residential address at delivery was constant during all pregnancy and that the city spatial distribution of pollutants and their determinants remained constant over the study period. All addresses were geo-coded to assign the spatial exposure estimates which therefore reflect the annual average level of pollution for its location.

Spatio-temporal estimates

Weeks 3 to 8 of pregnancy were calculated from the date of birth and the gestational age recorded on the register (N=4866). When the data was not available, the declared date of last menstruation period was used (N=261). When both were missing, we imputed the gestational age using the mean gestational age for the specific type of birth (live birth, still birth or termination of pregnancy; N=111).

To pick up the exposure during the "critical window" for organogenesis (weeks 3 to 8), background routine daily ambient air pollution monitoring data were used. NO_2 and NO_x series were available for the complete study period, from 1994 to 2006 (29.3% of days with no measurement), and PM_{10} data from 2000 to 2006 (67.6% of days with no measurement). NO_2 and NO_x missing data were estimated using the multiple imputation method developed in the ICE function of the statistical package STATA versions 8 (Stata Corporation, College Station, Texas). PM_{10} missing data were not estimated; we restricted the study population to those pregnancies between 2000 and 2006 with data available on two or more days per week for at least 5 out of the 6-week period of interest, resulting with the 63% of the original population. Then, according to the ratio method procedure in the ESCAPE manual for extrapolation back in time, the daily spatio-temporal exposure estimates ($C_{extrapolated}$) for each pregnancy were the spatial exposure estimation (C_{ESCAPE}) multiplied for a daily temporal adjustment ($Ratio_{routine}$) that was calculated as the ratio between the daily NO_2, NO_x or PM_{10} measurements at the background routine monitoring station (C_{daily}) and its annual 2009 average ($C_{routine\_yearESCAPE}$). In formula:

$C_{extrapolated} = C_{ESCAPE} * Ratio_{routine}$

Where

$Ratio_{routine} = C_{daily} / C_{routine\_yearESCAPE}$

Daily spatio-temporal estimates were averaged over week 3 to 8 of each pregnancy to obtain the final exposure. We further applied the NO_x daily temporally adjustment to $PM_{2.5}$ absorbance spatial estimates, and the PM_{10} daily temporally adjustment to PM_{coarse} and $PM_{2.5}$ to obtain the respectively spatio-temporal exposure estimates, following the methodology in ESCAPE (ESCAPE project, 2011), with the exception of the re-scaling factor proposed.

Statistical Analysis

We examined the association between the spatial and spatio-temporal exposure estimates and non-chromosomal congenital anomalies using logistic regression models. Air pollution exposure estimates were entered into the model as continuous covariates. The odds ratios (ORs) were calculated for an inter-quartile range (IQR) increase in air pollutant concentration measured at the spatial level (Table 2), results are then comparable between spatial and spatio-temporal estimates.

Models were adjusted for year of birth, season of conception and maternal age, all as categorical variables, and for the MEDEA socio-economic deprivation index as a continuous variable. Maternal education was not included as covariate due to the large proportion of missing values; but its polychoric correlation with the MEDEA index was -0.4.

The potential confounding effect of smoking was tested in a sensitivity analyses, because there were many missing values (Table 1) in this variable. The assumption of a stable spatial exposure surface over the entire study period was verified stratifying the population by year of birth (before and after 2000). All analyses were performed using the statistical package STATA versions 8 and 10.1 (Stata Corporation, College Station, Texas).

Results

In spatial and spatio-temporal exposure models we found associations between coarctation of the aorta and NO_2 (adj.$OR_{spatio\text{-}temporal}$=1.15; 95%CI 1.01-1.31), digestive system defects and NO_2 (adj.$OR_{spatio\text{-}temporal}$=1.11; 95%CI 1.00-1.23), and abdominal wall defects and PM_{coarse} (adj.$OR_{spatio\text{-}temporal}$=1.93; 95%CI 1.37-2.73). Other statistically significant OR were found in the spatial model only or in the spatio-temporal model only, but not in both. (Annex 1)

These results overall do not indicate an association between traffic-related air pollution and most groups of congenital anomalies. Findings for coarctation of the aorta are consistent with the previous meta-analysis. Increased risks of digestive system anomalies and of abdominal wall defects are novel and call for confirmation.

2d. Potential role of EUROCAT

The pilot study in Barcelona shows that EUROCAT registry data can be used for investigation of environmental pollutants/hazards that vary on a small, within-city, spatial level. Apart from traffic-related air pollution such hazards may also include (traffic-related) noise, radiofrequency fields from mobile phone antennas, electricity powerlines (extremely low frequency and magnetic fields), etc. It should be noted that other studies, using EUROCAT data from UK registries, have previously shown that geographical linkage studies are possible to study the effects of pollutant variations at wider spatial level (e.g. community/city/neighbourhood-wide variations) (Davand et al 2011a, b; Dolk et al 2010, Rankin et al 2009).

The following lessons can be drawn from this work:

- In order for EUROCAT registries to contribute to small area environmental studies, their protocol needs to include collecting residential location routinely for cases, and having access to similar information for controls. In terms of areas which overlap with ESCAPE air pollution modeling, registries in UK, Spain, Italy and Finland have such information currently available.

- Links to a GIS department are needed. Geocoding of address data can be done automatically in all locations, but a GIS environment is needed to then process these data and specifically, to link the geocoded address data to pollution concentrations and geographical covariate data. A GIS environment may be set up centrally, and can be done at international level although some restrictions exist sending geocoded across borders – encryption and separation of the geocodes from the rest of the data will be required.

- Environmental exposure assessment expertise is necessary to obtain and process the correct pollution data, for example the temporal (daily) air pollution concentrations. This can only be done through local contacts with the pollution monitoring services. On the other hand, LUR air pollution maps from the ESCAPE project are now available on request from the project leaders (http://www.escapeproject.eu/).

- Collaboration is needed between environmental scientists and specialists in the epidemiology and surveillance of congenital anomalies in each country. The pilot study in Barcelona shows that where such collaborations exist, research projects can very successfully be completed.

3. Feasibility of epidemiological investigation in small polluted areas (hot-spots)

Currently, links between reproductive health and contaminated sites are studied in a non-extensive and non-integrated way in Europe. The topic deserves a European study and the EUROCAT network can be the engine taking advantage of the extensive and proven collaborative networking. This would involve exploiting available European pollutant register data (see E-PRTR below) and already available protocols from similar studies in Italy (see Sentieri Project below).

3a. European Pollutant Release and Transfer Register (E-PRTR) – Pilot Study in EUROCAT areas

The European Pollutant Release and Transfer Register (E-PRTR) is the Europe-wide register that provides easily accessible key environmental data from industrial facilities in European Union Member States and in Iceland, Liechtenstein, Norway, Serbia and Switzerland. It started up in 2009, replacing the previous European Pollutant Emission Registry (EPER). This register contains data reported annually by more than 30,000 industrial facilities covering 65 economic activities across Europe (http://prtr.ec.europa.eu/docs/Summary_activities.pdf). The activities are grouped in 9 activity sectors: 1) energy; 2) production and processing of metals; 3) mineral industry; 4) chemical industry; 5) waste and waste water management; 6) paper and wood production and processing; 7) intensive livestock production and aquaculture; 8) animal and vegetable products from the food and beverage sector; and 9) other activities. For each facility, information is provided concerning the amounts of pollutant releases to air, water and land as well as off-site transfers of waste and of pollutants in waste water from a list of 91 key pollutants including heavy metals, pesticides, greenhouse gases and dioxins for years 2007 onwards (http://prtr.ec.europa.eu/).

A facility has to report data under E-PRTR if it fulfills the following criteria:

- The facility falls under at least one of the 65 E-PRTR economic activities listed in Annex I of the E-PRTR Regulation and exceeds at least one of the E-PRTR capacity thresholds;
- The facility transfers waste off-site which exceed specific thresholds set out in Article 5 of the Regulation (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:033:0001:0017:EN:PDF#page=4);
- The facility releases pollutants which exceed specific thresholds specified for each media - air, water and land - in Annex II of the E-PRTR Regulation (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:033:0001:0017:EN:PDF#page=12).

Industrial facilities have to report data when the thresholds are exceeded for:

- Releases to air, water and land of any of the 91 E-PRTR pollutants;
- Off-site transfers of any of the 91 E-PRTR pollutants in waste water destined for waste-water treatment outside the facility;
- Off-site transfers of waste (reported as tonnes per year) for recovery or disposal. For transboundary movements of hazardous waste outside the reporting country, details of the waste receivers have to be provided;

The reported releases include any introduction of any of the listed pollutants into the environment as a result of any human activity, whether deliberate, accidental, routine or non-routine, at the site of the facility. E-PRTR also contains information on releases from diffuse sources into water which will be upgraded and extended gradually.

Pilot Study

We conducted a pilot study on the use of the *E-PRTR* for the environmental characterization of areas covered by Eurocat registries. :

Methods

The data are automatically downloaded using the following search criteria:

1) Facility level

The facility search allows the user to search and select E-PRTR data using almost all of its parameters. Default search criteria include country, year and region or river basin districts, facility name and town/village. The advanced search options allow the user to expand the search tool and use the criteria activity, pollutant releases and transfers and waste transfer. The outcome of this search option is a list of facilities fulfilling the criteria chosen by the user and a map display of these facilities. When clicking on the name of the facility or its location on the map, detailed information for the selected facility is shown, including its reported releases and transfers (where above the PRTR thresholds). If confidentiality has been claimed, the reason for this is provided.

2) Industrial activity

The industrial activity search allows the user to search data using the activity categories included in the E-PRTR Regulation, in the NACE economical classification and in Annex I of the IPPC Directive. The outcome of this search option is a report which displays the aggregated releases and transfers (pollutants and waste) of a specific industrial activity or a sector and the list of facilities fulfilling the criteria set out by the user.

3) Area overview:

This report will display the aggregated releases and transfers of a specific area

4) Pollutant releases

The pollutant releases option allows the user to search data using the groups of pollutants or each of the 91 substances of Annex II of the E-PRTR Regulation as main criterion. the outcome of this search option is a report of the aggregated releases of a specific pollutant. The information is provided on several sheets displaying a summary of releases of the selected pollutant per activity group, a table with those data, the total release of each pollutant per country (table and graph) and a list of facilities releasing the concerned pollutant.

5) Pollutant transfers

The pollutant transfers option allows the user to search data using the groups of pollutants or each of the 91 substances of Annex II of the E-PRTR Regulation as main criterion. The outcome of this search option is a report of the aggregated transfers of a specific pollutant. The information is provided on several sheets displaying a summary of transfers of the selected pollutant per activity group, a table with those data, the total transfer of each pollutant per country (table and graph) and a list of facilities transferring the concerned pollutant.

6) Waste transfers

The waste transfer option allows the user to retrieve data on waste movements within and outside the country. As main criterion the data can be searched by the type of waste (non hazardous or hazardous). For hazardous waste, a distinction is made between domestic (in the same country) or transboundary transfers. The outcome of this search option is a report of the annual waste transfers. The information is provided on several sheets displaying a summary of transfers by type of waste; by activity group; the total transfer of each category per country (table and graph); a list of facilities transferring each type of waste; a graph displaying hazardous waste transfers and a table of countries with the quantity of hazardous waste received. Clicking on the country a list of specific facilities within the country is displayed.

7) Map search

The map search option provides an entirely geographical approach to E-PRTR data.

Among the areas covered by Eurocat registries that have expressed interest in participating at the hot-spot pilot project, we analyzed the 2011 data of the Groningen (NL) and Comunidad Valenciana (SP) regions. Data were downloaded using the following search criteria:

- Facility level
- Industrial activity

Results

Comunidad Valenciana

In Valencia area were registered 360 industrial facilities. For each one we know the parent company name, the address, the town/village where it is sited, the activity code, the activity name.

Three industries released chlorinated organic substances, 34 released greenhouse gases, 18 heavy metals, 26 inorganic substances, 141 other gases e 2 other organic substances: the name and the amount of pollutant releases to air or water or land were reported.

Two hundred fifty three (253) industrial plants reported the information on the hazardous waste transfers, while 1 facility declared trans-boundary transfers. The non hazardous waste transfers was registered by 137 facilities.

Groningen

In Groningen area were reported 51 industrial facilities. For each one we know the parent company name, the address, the town/village where it is sited, the activity code, the activity name.

Two industries released chlorinated organic substances, 10 released greenhouse gases, 8 heavy metals, 12 inorganic substances, 15 other gases and 3 other organic substances: the name and the amount of pollutant releases to air or water or land were reported in the file.

The hazardous domestic waste transfers were reported by 41 industrial plants while 4 facility declared trans-boundary transfers. The non hazardous waste transfers was reported by 21 facilities.

Conclusions

- The bulk of information obtained from the two exercises summarized above, is indicative of a potential usefulness for the characterization of areas covered by population-based registries.

- Given the complexity of the environment and the relating exposure assessment, it is reasonable to think about the limitations of areas considering the area covered by the registry, and types of pollution or sources of pollution considering the potential hazard for birth defects.
- For this purpose a general protocol of investigation and an area-specific sub-protocol, must be defined.
- This activity requires a multidisciplinary approach, with the involvement of the environmental agencies with competence/responsibility in the territory, experts of the registry of congenital anomalies, environmental epidemiologists, toxicologists, environment and diseases mapping, at least.

3b. The Sentieri Project

The protocol of the Sentieri Project conducted in Italy represents a useful reference (Pirastu et al, 2010, 2011) (Annex 2). The SENTIERI Project "Mortality study of residents in Italian polluted sites" was conducted in 44 polluted sites of national interest, and is now extended to the study of cancer incidence, hospital admissions, and adverse pregnancy outcomes, including congenital anomalies. Exposure was referred to both environmental exposure in PS and other exposures. Environmental exposure in Polluted Sites included Production of chemical substance/s, Petrochemical plant and/or Refinery, Steel industry, Electric power plant, Mine/Quarry, Harbour area, Asbestos/ other mineral fibres, Landfill, Incinerator. It indicates the kind of production plant or any other source of environmental emission possibly affecting residents. Other exposures referred to air pollution, active and passive smoking, alcohol drinking, occupational exposure and socioeconomic status were considered.

3c. The role of EUROCAT

In the framework of WP6 a test of the main sources of emissions in the territories covered by the Eurocat registries has been developed. The results will be made available to the registers as a key element for deciding the membership and the activities to be undertaken, starting from the environmental characterization. The analysis of pollutants, their distribution in environmental matrices, the pathways of exposure, the exposure according to the definition of windows of susceptibility during embryonic and fetal development, the extension of the observation after birth, the definition of congenital abnormalities sensitive to pollutants, provide for the development of a specific protocol. The definition of the areas according to different levels of exposure is linked to the availability of information on the spread of pollutants in the air and the soil fallout, measured or estimated by diffusion models. This verification activity is site-specific and requires an interaction with regional and national environmental agenize. The participating areas will be characterized and homogeneous aggregated by type of industrial activity and characteristics of pollutants surveyed.

Using such a scheme and definitions a short questionnaire to verify the feasibility of a similar study in Europe was developed and is now ready to be proposed to the registers EUROCAT inside which falls one or more hot spots (Annex 3).

A recent WHO Report is relevant for collaborative work on contaminated sites and health and particularly useful for the present feasibility task (WHO, Contaminated sites and Health, Report of two WHO workshops: Syracuse, Italy, 18 November 2011; Catania, Italy, 21-22 June 2012. WHO Europe 2013). The WHO Regional Office for Europe (European Centre for Environment and Health) has expressed interest in collaboration on future EUROCAT related work in this area (Dr Martuzzi), as has the WHO Collaborating Centre for Environmental Health in Contaminated Sites (Dr Iavarone). Other data and methods of considerable interest are contained in the recent paper on the state of art on contaminated sites in Europe by the European Commission, Joint Research Centre, Institute for Environment and Sustainability, Ispra, Italy, summarizing the EIONET-SOIL project results (Panagos et al 2013).

4. Conclusions

Geographically-based Europe-wide exposure databases are now available in relation to a number of environmental hazards, including air pollution (e.g. Escape) and industrial releases (e.g. the European pollutant release and Transfer Registry http://prtr.ec.europa.eu/). The existence of exposure databases and congenital anomaly registry data in many regions of Europe provides great potential for the environmental surveillance and epidemiological research of congenital anomalies.

This report has evaluated the feasibility of small-scale geographical (address) linkage studies and of epidemiological investigation in small polluted areas (hot-spots). The following general conclusions can be drawn from this work:

1. It is feasible to link EUROCAT registry data to small-scale and hot-spot pollution maps.
2. By integrating environmental pollution surveillance knowledge into the existing EUROCAT network, an optimal resolution can be achieved to estimate the effect of environmental pollution on the prevalence of congenital anomalies. Due to the large number of annual births covered by EUROCAT in many European regions, such integration would have a large potential environmental health benefit.
3. Routine collection of residential location information for cases registered by EUROCAT is highly recommended to make the most of this potential. Control or denominator location data needs to be available at the same spatial scale.
4. There is an urgent need for collaborative structures involving, in each country, environmental scientists and specialists in the epidemiology and surveillance of congenital anomalies. Involvement from international organisations (such as the WHO and JRC) would also be of great benefit. This report clearly points towards the need for stronger collaborations between the two fields.

References

Armstrong BG, Dolk H, Pattenden S, Vrijheid M, Loane M, Rankin J, Dunn C, Grundy C, Abramsky L, Boyd PA, Stone D, Wellesley D. Geographic variation and localised clustering of congenital anomalies in Britain. Emerg Themes Epidemiol. 2007 Jul 6;4:14.

Beelen R, Hoek G, Vienneau D, Eeftens M, Dimakopoulou K, Pedeli X et al. 2013. Development of NO2 and NOx land use regression models for estimating air pollution exposure in 36 study areas in Europe – the ESCAPE project . Atmospheric ·Environment 72:10-23.

Cyrys J, Eeftens M, Heinrich J, Ampe C, Aarmengaud A, Beelen R et al. 2012. Variation of NO2 and NOx concentrations between and within 36 european study areas: results from the ESCAPE study. Atmospheric environment 62:374-390.

Dadvand P, Rankin J, Rushton S, Pless-Mulloli T. Ambient air pollution and congenital heart disease: a register-based study. Environ Res. 2011 Apr;111(3):435-41.

Dadvand P, Rankin J, Rushton S, Pless-Mulloli T. Association between maternal exposure to ambient air pollution and congenital heart disease: A register-based spatiotemporal analysis. Am J Epidemiol. 2011 Jan 15;173(2):171-82.

Dolk H, Armstrong B, Lachowycz K, Vrijheid M, Rankin J, Abramsky L et al. 2010. Ambient air pollution and risk of congenital anomalies in England, 1991-1999. Occup Environ Med 67:223-227.

Dominguez-Berjon MF, Borrell C, Cano-Serral G, Esnaola S, Nolasco A, Pasarin MI et al. 2008. Constructing a deprivation index based on census data in large Spanish cities (the MEDEA project). Gaceta Sanitaria 22:179-187.

Eeftens M, Beelen R, Bellander T, Cesaroni G, Cirach M, Declerq C et al. 2012. Development of land use regression models for PM2.5,PM2.5 absorbance, PM10 and PMcoarse in 20 European study areas; results of the ESCAPE project. Environ Sci Technol 46:11195-11205.

EUROCAT. 2009. EUROCAT Guide 1.3. Instructions for the Registration of Congenital Anomalies. http://www.eurocat-network.eu/aboutus/datacollection/guidelinesforregistration/guide1_3instructionmanual

García-Pérez J, Boldo E, Ramis R, et al. Validation of the geographic position of EPER-Spain industries. International Journal of Health Geographics 2008, 7:1-11.

Greenlees R, Neville A, Addor MC, Amar E, Arriola L, Bakker M et al. 2011. Paper 6: EUROCAT member registries: Organization and activities. Birth Defects Research Part A: Clinical and Molecular Teratology 91:S51-S100.

Moore KL, Persaud TVN. The Developing Human. Clinically Oriented Embryology. Philadelphia: 1998.

Panos Panagos, Marc Van Liedekerke, Yusuf Yigini, and Luca Montanarella. Contaminated Sites in Europe: Review of the Current Situation Based on Data Collected through a European Network (Review Article)Journal of Environmental and Public Health, Volume 2013 (2013), Article ID 158764, 11 pages, http://dx.doi.org/10.1155/2013/158764

Pirastu R, Pasetto R, Zona A, Ancona C, Iavarone I, Martuzzi M, Comba P. The health profile of populations living in contaminated sites: SENTIERI approach. J Environ Public Health. 2013;2013:939267. doi: 10.1155/2013/939267. Epub 2013 Jun 18.

Pirastu R, Ancona C, Iavarone I, Mitis F, Zona A, Comba P; SENTIERI Working Group. SENTIERI Project. Mortality study of residents in Italian polluted sites: evaluation of the epidemiological evidence. Epidemiol Prev 2010; 34(5-6 Suppl 3):1-96.

Rankin J, Chadwick T, Natarajan M, Howel D, Pearce MS, Pless-Mulloli T.Maternal exposure to ambient air pollutants and risk of congenital anomalies. Environ Res. 2009 Feb;109(2):181-7.

Reche C, Querol X, Alastuey A, Viana M, Pey J, Moreno T et al. 2011. New considerations for PM, Black Carbon and particle number concentration for air quality monitoring across different European cities. Atmospheric Chemistry and Physics 11:6207-6227.

Salvador J, Borrell A, Lladonosa A. 2005. Increasing detection rates of birth defects by prenatal ultrasound leading to apparent increasing prevalence. Lessons learned from the population-based registry of birth defects of Barcelona. Prenat Diagn 25:991-996.

Schembari A, Nieuwenhuijsen MJ, Salvador J, de Nazelle A, Cirach M, Dadvand P, Beelen R, Hoek G, Basagaña X, Vrijheid M. Traffic-related air pollution and congenital anomalies in Barcelona. Environ Health Perspect. 2014 Mar;122(3):317-23. doi: 10.1289/ehp.1306802. Epub 2013 Dec 23.

Vrijheid M, Martinez D, Manzanares S, Dadvand P, Schembari A, Rankin J, Nieuwenhuijsen M. Ambient Air Pollution and Risk of Congenital Anomalies: A Systematic Review and Meta-Analysis Environ Health Perspect 2011; 119 (5): 598-606.

WHO. Contaminated sites and Health, Report of two WHO workshops: Syracuse, Italy, 18 November 2011; Catania, Italy, 21-22 June 2012. WHO Europe 2013. http://www.euro.who.int/__data/assets/pdf_file/0003/186240/e96843e.pdf

Annex 1 – Barcelona study manuscript:

Schembari A, Nieuwenhuijsen MJ, Salvador J, de Nazelle A, Cirach M, Dadvand P, Beelen R, Hoek G, Basagaña X, Vrijheid M. Traffic-related air pollution and congenital anomalies in Barcelona. Environ Health Perspect. 2014 Mar;122(3):317-23. doi: 10.1289/ehp.1306802. Epub 2013 Dec 23.

Annex 2 – Sentieri Study Protocol

Annex 3 – Questionnaire for EUROCAT hot-spot investigations

ehp ENVIRONMENTAL HEALTH PERSPECTIVES
http://www.ehponline.org

Traffic-Related Air Pollution and Congenital Anomalies in Barcelona

Anna Schembari, Mark J. Nieuwenhuijsen, Joaquin Salvador, Audrey de Nazelle, Marta Cirach, Payam Dadvand, Rob Beelen, Gerard Hoek, Xavier Basagaña, and Martine Vrijheid

http://dx.doi.org/10.1289/ehp.1306802

Received: 14 March 2013
Accepted: 23 December 2013
Advance Publication: 3 January 2014

NIH National Institute of Environmental Health Sciences

Traffic-Related Air Pollution and Congenital Anomalies in Barcelona

Anna Schembari,[1,2,3] Mark J. Nieuwenhuijsen,[1,2] Joaquin Salvador,[2,4] Audrey de Nazelle,[1,2,5] Marta Cirach,[1,2] Payam Dadvand,[1,2] Rob Beelen,[6] Gerard Hoek,[6] Xavier Basagaña,[1,2] and Martine Vrijheid[1,2]

[1]Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain; [2]CIBER Epidemiologia y Salud Publica (CIBERESP), Spain; [3]Universitat Pompeu Fabra (UPF), Barcelona, Spain; [4]Servei de sistema d'Informació Sanitaria. Agencia de Salut Pública de Barcelona, Spain; [5]Centre for Environmental Policy, Imperial College London, UK; [6] Institute for Risk Assessment Sciences (IRAS), University of Utrecht, the Netherlands

Address correspondence to Anna Schembari, Center for Research in Environmental Epidemiology (CREAL), Parc de Recerca Biomèdica de Barcelona – PRBB, C. Doctor Aiguader, 88, 08003 Barcelona , Spain. Telephone: +34 93 214 7339. Fax: +34 93 214 7302. E-mail: aschembari@creal.cat

Running head: Air pollution and congenital anomalies

Acknowledgments, funding, and competing interests: This work was jointly supported by the EUROCAT Joint Action funded by the Public Health Programme 2008-2013 of the European Commission (Grant agreement number: 20102204), the ARIBA (Air Pollution and Pregnancy in Barcelona) project funded by a Fondo de Investigación Sanitaria (FIS) (Grant agreement number: PI081109) and by the ESCAPE project funded under the European Union's Seventh Framework Programme (Grant agreement number: 211250). Anna Schembari is funded by

Instituto de Salud Carlos III-FEDER fellowship (PFIS grant: FI 10/00476), Payam Dadvand is funded by a Juan de la Cierva fellowship (JCI-2011-09937). The authors declare no competing interests.

Abstract

Background*:* A recent meta-analysis suggested evidence for an effect of exposure to ambient air pollutants on risk of certain congenital heart defects. However, few studies have investigated the effects of traffic-related air pollutants with sufficient spatial accuracy.

Objectives: We estimated associations between congenital anomalies and exposure to traffic-related air pollution in Barcelona.

Method: Cases with non-chromosomal anomalies (n = 2247) and controls (n = 2991) were selected from the Barcelona congenital anomaly register between 1994 and 2006. Land use regression models from the European Study of Cohorts for Air Pollution Effects (ESCAPE), were applied to residential addresses at birth to estimate spatial exposure to nitrogen oxides and dioxide (NO_x, NO_2), particulate matter with diameter ≤ 10 μm (PM_{10}), 10 μm-2.5 μm (PM_{coarse}), ≤ 2.5 μm ($PM_{2.5}$), and $PM_{2.5}$ absorbance. Spatial estimates were adjusted for temporal trends using data from routine monitoring stations for weeks 3 to 8 of each pregnancy. Logistic regression models were used to calculate odds ratios (OR) for 18 congenital anomaly groups associated with an inter-quartile range (IQR) increase in exposure estimates.

Results: In spatial and spatio-temporal exposure models we estimated statistically significant associations between an IQR increase in NO_2 (12.2 μg/m^3) and coarctation of the aorta ($OR_{spatio-temporal}$ = 1.15; 95% CI: 1.01, 1.31) and digestive system defects ($OR_{spatio-temporal}$ = 1.11; 95% CI: 1.00, 1.23), and between an IQR increase in PM_{coarse} (3.6 μg/m^3) and abdominal wall defects ($OR_{spatio-temporal}$ =1 .93; 95% CI: 1.37, 2.73). Other statistically significant increased and decreased ORs were estimated based on the spatial model only or the spatio-temporal model only, but not both.

Conclusions: Our results overall do not indicate an association between traffic-related air pollution and most groups of congenital anomalies. Findings for coarctation of the aorta are consistent with the previous meta-analysis.

Introduction

There is a growing body of epidemiologic evidence suggesting that exposure to ambient air pollution may adversely affect the fetus and newborn. Recent studies have found association between Particulate Matter (PM) and increased risk of low birth weight, preterm birth and decrease in birth weight (Dadvand et al. 2012, Pedersen et al. 2013, Sapkota et al. 2010). Major congenital anomalies include structural defects such as heart defects and neural tube defects, and chromosomal abnormalities such as Down syndrome, and are diagnosed in 2 to 4% of births (WHO 2012). They are a main cause of infant mortality and important contributor to childhood and adult morbidity, but their etiology remains largely unknown (Dolk et al. 2003).

The evidence for an impact of ambient air pollution on congenital anomaly risk is still limited (Agay-Shay et al. 2013; Dadvand et al. 2011a and 2011b; Dolk et al. 2010; Gilboa et al. 2005; Hansen et al. 2009; Hwang et al. 2008; Kim et al. 2007; Marshall et al. 2010; Padula et al 2013a and 2013b; Rankin et al. 2009; Ritz et al. 2002; Strickland et al. 2009; Vrijheid et al. 2011). Previous studies have focused primarily on the routinely assessed pollutants; only four studies (Agay-Shay et al. 2013; Marshall et al. 2010; Padula et al 2013a and 2013b) included other specific traffic-related air pollutants such as $PM_{2.5}$. Cardiac anomalies or oral clefts were most frequently studied, but available evidence on other anomaly groups, such as defects of the nervous, digestive, or respiratory systems, is scarce (Dolk et al. 2010; Rankin et al. 2009; Padula et al 2013b). Summary estimates from a recent meta-analysis (Vrijheid et al. 2011) indicated that NO_2 and SO_2 were associated with two congenital heart anomalies, coarctation of the aorta and tetralogy of Fallot, and that PM_{10} was associated with atrial septal defects. With the exception of Dadvand et al. (2011b), exposure assessments in previous studies were based on monitoring data from a limited number of fixed-site stations, and thus did not account for the strong spatial intra-

city variation that characterizes traffic-related air pollution (Cyrys et al. 2012; Eeftens et al. 2012b). Dadvand et al. (2011b) estimated spatio-temporal exposure to black smoke and SO_2 with higher spatial resolution. The use of more precise spatial air pollution models in urban areas is increasingly recommended to reduce exposure misclassification (Hoek et al. 2008; Jerrett et al. 2004) in studies of traffic related air pollution and adverse birth outcomes (Aguilera et al. 2009; Ballester et al. 2010; Brauer et al. 2008). Moreover, in studies of congenital anomalies, spatial models need to be combined with temporal adjustments to account for the very specific etiologically relevant time windows of exposure (Ritz et al. 2008).

Barcelona is among the most polluted cities in Europe (Cyrys et al. 2012; Eeftens et al. 2012b). This is partly due to its geography; high traffic density (Ajuntament de Barecelona, 2007), which is four times higher than London; and large proportion of diesel-powered vehicles, currently 50% (Reche et al. 2011). In Barcelona we developed a refined spatial air pollution exposure metric using a land use regression model (Beelen et al. 2013; Eeftens et al. 2012a). At the same time, Barcelona has a high-quality population-based congenital malformation register, which has collected detailed data on cases of congenital anomalies and control births for over 15 years (Greenlees et al. 2011). Using these two data sources, we investigated associations between specific groups of congenital anomalies and intra-urban traffic-related air pollution exposures during sensitive time windows in pregnancy.

Methods

Study population

This study used a population-based case-control design. The source population consisted of congenital anomaly cases and control births from the Barcelona congenital anomalies register,

REgistro Defectios Congenitos Barcelona (REDCB), which has accrued approximately 13,000 births per year from nearly all maternity units in the city since its start in 1992. The REDCB is part of the Service of Health Information Systems (Servei de Sistemes d'Informació Sanitaria) in the Public Health Agency of Barcelona (Agència de Salut Pública de Barcelona) and a member of the European surveillance of congenital anomalies (EUROCAT) (Greenlees et al. 2011). For the REDCB, full-time nurses actively search for new cases at delivery units, pediatric departments, cytogenetic laboratories, pathology departments, prenatal diagnosis units and pediatric cardiology services; cases of congenital anomalies suspected but not detected at birth are further followed up until age 1 year. Controls are continuously selected as a 2% representative sample of all live births in Barcelona hospitals, by random date of birth sampling, independently of the cases (non-matched). Clinical information, including maternal age, is collected from hospitals records. As part of the REDCB, information on smoking and education is collected by interview with the mother using a standardized questionnaire (Salvador et al. 2005). Parental informed consent is completed before the interview and all consenting cases detected during the maternal period at the hospital and controls mothers are interviewed (35% and 95% respectively); interviews cannot be held with mothers of cases diagnosed or communicated to the registry authority after the maternity period. In these cases, smoking and maternal education information is abstracted from clinical history records. Further, for the purposes of the current study the residential addresses of the cases and controls were linked to the MEDEA socio-economic deprivation index (Dominguez-Berjon et al. 2008) at census tract-level.

The present study was approved by the Clinical Research Ethics Committee of PS - Mar (CEIC project 2008/3115/I and 2006/3394/I) and determined to be exempt from separate informed consent requirements.

Definition of cases and controls

Controls were all live births enrolled in the REDCB between 1994 and 2006 whit a residential address at birth in the city of Barcelona. Of the 3149 controls included in the REDCB during that time period, 158 were excluded because of a residential address that could not be geocoded or that was outside Barcelona, giving a total of 2991 (95.0%) controls for analysis.

Cases were live births, stillbirths after 20 weeks of gestation, or terminations of pregnancy following prenatal diagnosis of congenital anomalies, enrolled in the REDCB and born or terminated between 1994 and 2006, with at least 1 major anomaly in the EUROCAT list of subgroups of congenital anomalies (EUROCAT, 2009). Cases with only minor congenital anomalies, such as facial asymmetry (Q67.0) or talipes or pes calcaneovalgus (Q66.4) were excluded from the study, following the EUROCAT exclusion list (EUROCAT, 2009). The range of codes for inclusion was, according to the International Classification of Disease version 10 (ICD10), the Q-chapter. Cases with chromosomal anomalies (Q90-Q92, Q93, Q96-Q99, n = 719), and teratogenic and genetic syndromes (Q86, Q87, n = 72) were excluded. Twins were treated as one outcome (12 pairs), and classified as a case if one or both had a congenital anomaly; siblings were classified as separate outcomes. Cases with a residential address that could not be geocoded or that was outside Barcelona were excluded (n = 166), as were spontaneous abortion before 20 weeks of gestation (n=5). In addition we excluded cases that could not be classified according to the timing of the vulnerable time window of exposure (i.e., 3 to 8 weeks of gestation when organogenesis occurs) because any information on birth date,

gestational age (GA), and date of the last menstrual period (LMP) (n = 74) was available. Out of a total of 3295 cases, 2247 (68 %) were included in analysis. Cases were classified into anomaly subgroups following EUROCAT guidelines (EUROCAT, 2009). An *a priori* decision was made to analyze the following common subgroups of anomalies: neural tube defects (Q00, Q01, Q05), congenital heart disease (Q20-Q26), respiratory system defects (Q30-Q34), orofacial clefts (Q35-Q37), digestive system defects (Q38-Q38, Q402-Q409, Q41,-Q45, Q790), abdominal wall defects (Q792, Q793, Q795), urinary system defects(Q60-Q64, Q794), hypospadias (Q54), and limb reduction defects (Q650-652, Q658-Q659, Q660, Q681-Q682, Q688, Q69-Q74). To replicate results from previous studies (Vrijheid et al. 2011) eight subgroups of cardiac anomalies were also considered: transposition of great vessels (Q203), ventricular septal defect (Q210), atrial septal defect (Q211), atrioventricular defect (Q212), tetralogy of Fallot (Q213), tricuspid atresia and stenosis (Q224), pulmonary valve stenosis (Q221), and coarctation of aorta (Q251).

Exposure assessment

This study combined the spatial Land Use Regression (LUR) modeling developed in the European Study of Cohorts for Air Pollution Effects – ESCAPE (ESCAPE project 2009) with a temporal adjustment, providing both spatial and spatio-temporal exposure estimates. LUR models are commonly used to explain the small-scale within-city variation of traffic-related air pollutants; temporal adjustment is needed to account for the timing of exposure in relation to organogenesis, i.e. during weeks 3 to 8 of pregnancy (Moore et al.1998).

Spatial estimates

Land use regression (LUR) models were constructed in Barcelona for the year 2009 as part of the ESCAPE project. Pollutants included NO_2, $NO_{x,}$ PM_{10}, PM_{coarse} (particulate matter with

aerodynamic diameter between 10μm and 2.5 μm), $PM_{2.5}$, and $PM_{2.5}$ absorbance (as a marker of black carbon, Cyrys et al. 2003). The methodology has been described in detail elsewhere (Beelen et al. 2013; Cyrys et al. 2012; Eeftens et al. 2012a). All addresses were geo-coded to assign the spatial exposure estimates. We assumed that the residential address at delivery was constant during the whole pregnancy period and that the city spatial distribution of pollutants and their determinants remained constant over the study period.

Spatio-temporal estimates

The start and end dates of weeks 3 to 8 of pregnancy were determined from the date of birth and the GA recorded on the register (N=4866). When GA was not available, the declared date of LMP was used (N=261) to determine it. When only the birth date was available we imputed the GA with the mean GA for the specific type of delivery (live birth, still birth, or termination of pregnancy; N=111).

To estimate exposure during the "critical window" for organogenesis (weeks 3 to 8), background routine daily ambient air pollution monitoring data were used. NO_2 and NO_x series were available for the complete study period, from 1994 to 2006 (29% of days with no measurement), and PM_{10} data from 2000 to 2006 (68% of days with no measurement). On days with no measurement, NO_2 and NO_x data were estimated using the multiple imputation method developed in the ICE function of the statistical package STATA Version 8 (Stata Corporation, College Station, Texas). Because of the large number of days for which PM_{10} data were missing we did not impute missing PM_{10} data. Instead, we restricted our population to those pregnancies with data available on two or more days per week for at least 5 out of the 6 weeks of interest (week 3-8 of gestation). This resulted in 63% of the original population. Then, according to the

ratio method procedure in the ESCAPE manual for extrapolation back in time (ESCAPE project, 2009), we calculated the spatio-temporal exposure estimates as follow:

Procedure for extrapolation back in time

The daily spatio-temporal exposure estimates ($C_{extrapolated}$) for each pregnancy were the spatial exposure estimation (C_{ESCAPE}) multiplied by a daily temporal adjustment ($Ratio_{routine}$) that was calculated as the ratio between the daily NO_2, NO_x or PM_{10} measurements at the background routine monitoring station (C_{daily}) and its annual 2009 average ($C_{routine\_yearESCAPE}$). In formula:

$$C_{extrapolated} = C_{ESCAPE} * Ratio_{routine}, \quad [1]$$

where

$$Ratio_{routine} = C_{daily} / C_{routine\_yearESCAPE} \quad [2]$$

Daily spatio-temporal estimates were averaged over weeks 3 to 8 of each pregnancy to obtain the final exposure. We further applied the NO_x daily temporal adjustment to $PM_{2.5}$ absorbance spatial estimates because of their high correlation (Cyrys et al. 2003), and the PM_{10} daily temporal adjustment to PM_{coarse} and $PM_{2.5}$ (Pedersen et al 2013) to obtain the respective spatio-temporal estimates of exposure to air pollution, following the methodology in ESCAPE (ESCAPE project 2011).

Statistical analysis

We examined the association between the spatial and spatio-temporal exposure estimates and 18 groups of congenital anomalies using unconditional logistic regression models. Air pollution exposure estimates were entered into the model as continuous covariates. The odds ratios (ORs) were calculated for an inter-quartile range (IQR) increase in air pollutant concentration measured at the spatial level to ensure consistent exposure contrasts between spatial and spatio-temporal

estimates, and comparable contrasts among different pollutants. Models were adjusted for year of birth/termination, season of conception, and maternal age, all as categorical variables, and for the MEDEA socio-economic deprivation index as a continuous variable (Dadvand et al 2011a, Ritz et al 2002).

Potential confounding by maternal smoking and maternal education was tested in sensitivity analyses restricting to the populations with data available on these variables (70% and 80% of the full study population, respectively). Information on maternal smoking during each month of pregnancy was used to calculate the proportion of smokers during the first trimester as a 2 categories variable (Yes or quitted/ No). Maternal education was coded as a 4-category variable (Primary/ Secondary/ College/ University). The assumption of a stable spatial exposure surface over the entire study period was investigated by stratifying the population according to year of birth/termination (before and after 2000). All analyses were performed using the statistical package STATA versions 8 and 10.1 (Stata Corporation, College Station, Texas).

Results

The study included 2247 cases and 2991 controls. There were no statistically significant differences between cases and controls for season of conception, sex, maternal age, and socio-economic index (Table 1) but differences were seen for maternal smoking during first trimester and for maternal education: mothers of cases were lower educated and smoked more frequently than mothers of controls. Both these characteristics were derived from the interview with the mother completed by the 35% of cases and 95% of controls; in that subpopulation the exposure distribution was not differential among cases and controls (see Supplemental Material, Table S1).

Exposure distributions of the air pollutants are presented in Table 2. The inter-quartile ranges (IQR) of the spatio-temporal exposure estimates, which were averaged over the 6-week period of organogenesis for each observation, were wider than the IQRs of the spatial estimates, which were averaged over an entire year, due to the short averaging time and seasonal variation. Exposure estimates were somewhat higher among controls than among cases for all exposures. The range of correlations between spatial exposures (r = 0.16-0.93) was much wider than the corresponding range of correlations among the spatio-temporal exposures (r = 0.85-0.91) (Table 3) because of the high seasonal correlation between the pollutants (data not shown) and the use of NO_x and PM_{10} temporal trends to adjust the other air pollutants. Correlations between spatial and spatio-temporal estimates were moderate to low (r = 0.55 to 0.26 for NO_x and PM_{10} respectively).

We observed several statistically significant associations between IQR increases in spatial air pollutant exposure estimates and congenital anomaly groups (see Supplemental Material, Table S2): coarctation of the aorta and NO_2 (adj.$OR_{spatial}$ = 1.08; 95% CI: 1.00, 1.16), NO_x (adj.$OR_{spatial}$ = 1.06; 95%CI: 1.00, 1.13) and $PM_{2.5}$ (adj.$OR_{spatial}$ = 1.25; 95% CI: 1.00, 1.57); transposition of great vessels and PM_{10} (adj.$OR_{spatial}$ = 1.27; 95% CI: 1.03, 1.57); digestive system defects and NO_2 (adj.$OR_{spatial}$ = 1.07; 95% CI: 1.02, 1.13) and NO_x (adj.$OR_{spatial}$ = 1.06; 95% CI: 1.01, 1.10) and abdominal wall defects and PM_{coarse} (adj.$OR_{spatial}$ = 1.60; 95% CI: 1.04, 2.48). Furthermore, statistically significant negative associations with IQR increases in exposure were observed for all non-chromosomal anomalies and $PM_{2.5}$ absorbance (adj.$OR_{spatial}$ = 0.92; 95% CI: 0.86, 0.98), all congenital heart defects and $PM_{2.5}$ absorbance (adj.$OR_{spatial}$ = 0.91; 95% CI: 0.83, 0.99), and atrial septal defects and PM_{coarse} (adj.$OR_{spatial}$ = 0.73; 95% CI: 0.60, 0.89).

The association between an IQR increase in NO_2 (12.2 μg/m^3) and coarctation of the aorta was increased in the *spatio-temporal* exposure model (adj.$OR_{spatio\text{-}temporal}$ = 1.15; 95% CI: 1.01, 1.31) compared to the spatial model while it was somewhat reduced with an IQR increase in NO_x (27.1 μg/m^3, adj.$OR_{spatio\text{-}temporal}$ = 1.02; 95% CI: 1.00, 1.04) (Table 4). Similarly, digestive system defects showed a somewhat increased association with NO_2 (adj.$OR_{spatio\text{-}temporal}$ = 1.11; 95% CI: 1.00, 1.23) and decreased association with NO_x (adj.$OR_{spatio\text{-}temporal}$ = 1.02; 95% CI: 1.00, 1.04). The association between abdominal wall defects and an IQR increase in PM_{coarse} (3.6 μg/m^3) was also higher based on the spatio-temporal model (adj.$OR_{spatio\text{-}temporal}$ = 1.93; 95% CI 1.37, 2.73) (Table 5) compared with the spatial model. The spatio-temporal model also generated several statistically significant associations that were not observed in the spatial model, including significant positive associations between abdominal wall defects and PM_{10} and $PM_{2.5}$, and significant negative associations for ventricular septal defects and PM_{10}, PM_{coarse}, and $PM_{2.5}$.

Associations based on spatial models adjusted for maternal smoking (n = 3752) or maternal education (n = 4211) were consistent with estimates that were not adjusted for these variables when restricted to the population with available smoking or education data (see Supplemental Material, Table S3 and Table S4). However, some associations differed when based on the restricted populations compared with the full study population. In particular, there were more positive associations (ORs > 1) in the restricted population. The direction and magnitude of associations were comparable for anomalies identified from 1994 through 1999 (n = 2324) and 2000 through 2006 (n = 2913), consistent with our assumption of a stable exposure surface over the entire study period, though estimates based on the earlier subset were less precise (see Supplemental Material, Table S5).

Discussion

This study used both spatial and spatio-temporal exposure assessment frameworks to evaluate the association between traffic-related air pollution and groups of congenital anomalies. We included pollutants not previously studied in this field: PM_{coarse}, $PM_{2.5}$ and $PM_{2.5}$ absorbance, all of which are characterized by within-city variability (Eeftens et al. 2012b; Jerrett et al. 2005). We found little evidence for an association between most of the traffic-related air pollutants and most of the congenital anomaly groups studied. However, we observed statistically significant positive associations with both spatial and spatio-temporal exposure estimates for NO_2 and NO_x with coarctation of the aorta and digestive system anomalies, and for PM_{coarse} and abdominal wall defects.

Given the multiple comparisons involved in testing a large range of congenital anomaly subtypes against six pollution measures, our analyses are likely to have given rise to some chance associations and results should be interpreted with caution. To avoid errors due to false-positive statistically significant associations (type I errors) we emphasize statistically significant associations from the spatial model that persisted after temporal adjustment, in contrast with statistically significant positive or negative associations based on only one of the two exposure models, which we considered more likely to be due to chance. Evaluation of consistency with the previous meta-analysis has further been used to interpret the role of chance as an explanation of our main findings.

The positive association between coarctation of the aorta and NO_2 is consistent with a recent meta-analysis (Vrijheid et al. 2011) that combined results of four published studies and reported a summary odds ratio for coarctation of the aorta of 1.20 (95% CI: 1.00, 1.44) per 10 ppb

increase in NO_2 exposure. For comparison, in our study the odds ratio from the spatio-temporal model for a 10 ppb increment in NO_2 was 1.23 (95% CI: 1.02, 1.48). Although in our study the number of cases with coarctation of the aorta is small (N = 69), the consistency of findings between spatial and spatio-temporal models, and with the published meta-analysis, appears to strengthen evidence for an association. NO_2 and NO_x were highly correlated making it hard to separate their effect, but in the spatio-temporal exposure models NO_2 appeared somewhat more strongly associated with coarctation of the aorta than NO_x. We also found consistent results between the spatial and the spatio-temporal models when analyzing the association between NO_2, NO_x and digestive system anomalies. Only two previous studies evaluated these anomalies: Dolk et al. (2010) reported no association with NO_2, but the exposure assessment was based on annual mean levels only; Rankin et al. (2009) evaluated digestive system anomalies in relation to black smoke and also reported no association. In the present study, an association between abdominal wall defects and PM_{coarse} was observed in both spatial and spatio-temporal models. We are aware of only two previous studies that evaluated associations between air pollutants and abdominal wall defects (Dolk et al. 2010; Padula et al 2013b), and both reported non-significant associations except for the association between PM_{10} and omphalocele reported by Dolk et al. Therefore, further research on this outcome is needed.

The exposure assessment method used in this study was a temporal adjusted LUR built to capture and replicate the spatial variability within cities of traffic related air pollutants (Cyrys et al. 2012; Eeftens et al. 2012b). Additionally, for congenital anomalies, it is of great importance to assess exposure during the critical pregnancy weeks 3-8 (Moore et al. 1998), as any exposure after this period would not contribute to the etiology of a major congenital anomaly. Only recent studies on congenital anomalies and air pollution used a spatio-temporal exposure assessment,

but they were not covering the same range of pollutants (Dadvand et al. 2011b) or assessing the exposure at less refined spatial resolution (Agay-Shay et al. 2013; Padula et al 2013a and 2013b). The spatial LUR model we used for Barcelona resulted in a spatial exposure assessment with similar variability (i.e. similar width of the IQR) to previous studies in this field (Vrijheid et al 2011). After the temporal adjustment, the exposure variation increased, widening the IQR by more than 50% for all pollutants (Table 2), thus giving greater statistical power to detect associations in the spatio-temporal models compared with the spatial models. In particular, NO_2 and NO_x IQRs (reflecting within-city spatial variation) were larger than for particulate matter, partially explaining the null results for particulate matter in the spatial exposure models. One important assumption in using the LUR is that the city spatial distribution of pollutants and their determinants remained constant over the study period; if this assumption is violated, the ORs may be attenuated (Wu et al. 2011). To test this assumption we split the population by earlier and later years of termination/birth (before 2000 versus during or after 2000); results were consistent with the overall analyses, although earlier years had wider confidence intervals than the later years. Recently Cesaroni et al (2012) showed in Rome, a city with similar characteristics (i.e. climate, traffic, etc.) to Barcelona, a correlation of 96% for the exposure estimates from two LUR models produced 11 years apart. Furthermore we did not observe long-term trends in NO_2 and PM_{10} (data not shown). A limitation of our exposure assessment method is that we used NO_x and PM_{10} temporal trends to adjust other pollutant exposure estimates. This led to high correlations between the spatio-temporal estimates of these pollutants and thus difficulty in the interpretation of results from these pollutants independently. However we are following the approach developed in the ESCAPE protocol which has already been used in the recent publication on air pollution effect on pregnancy outcomes by Pedersen et al. (2013). Another

exposure limitation was related to the missing data on the PM_{10} temporal series which led to a loss of statistical power in the spatio-temporal models of pollutants temporally adjusted with that series (PM_{10} PM_{coarse} and $PM_{2.5}$).

Exposure misclassification could be due to the time spent in different environments, although we think that it is unlikely to be differential among cases and controls. Exposure misclassification could further have arisen because we estimated outdoor exposure at the residential address at termination/birth as a surrogate of the personal exposure during the first months of pregnancy. In our recent study in Barcelona (Schembari et al. 2013) among 54 pregnant women who carried a personal $PM_{2.5}$ sampler for two days and NO_x/NO_2 passive badges for one week, pregnant women reported time spent at home to be around 60-70% per day, and the correlation between personal exposure and outdoors levels of air pollution ranged from 0.39 for $PM_{2.5}$ and 0.78 for NO_x suggesting that, particularly for the latter, ambient outdoor levels could act as a good surrogate for personal exposure levels. Residual misclassification may have occurred if women changed residences during pregnancy; but this is unlikely to occur differentially among cases and controls, accordingly with results published by Miller et al. (2010). Residential mobility was estimated to be between 1% and 6% in a recent Spanish study based on fourth birth cohorts (Estarlich et al. 2011).

We examined a wide range of congenital anomalies that were subtyped following the classification proposed by EUROCAT (EUROCAT 2009). The REDCB includes cases identified among live births, stillbirths, and termination of pregnancy following prenatal diagnosis, which is particularly important (Ritz 2010) for some severe congenital anomalies such as neural tube defects or congenital heart disease (27% and 22.6% of anomalies, respectively, in our study). The register follows the EUROCAT guidelines, but ascertainment may be incomplete if the

congenital anomaly is not diagnosed prenatally or at birth, thereby the prevalence of all congenital anomalies (including live births, fetal deaths, still births and termination of pregnancy) for Barcelona was lower, during 1994 to 2006, than the European, 184/10,000 and 233/10,000 respectively (EUROCAT Website Database 2012). The register uses active case ascertainment and simultaneous ascertainment of population-based controls; it recodes the address at delivery allowing the geocoding used for the exposure assessment in this study. We adjusted for maternal age, conception season, year of birth, and socioeconomic status, although the latter was classified at census tract-level.

Only a subset of participants had data on smoking (70%) and education (80%). The sensitivity analyses on these sub-populations showed little impact of maternal smoking or education on the findings, thus indicating that their confounding effect is likely to be small even in the full study population. Nevertheless rely on these subpopulation could be misleading; missing information probably occurred not at random among cases and controls mainly because mothers of cases detected after birth were not interviewed. This may constitute a selective population due to the fact that only specific congenital anomalies are detected after birth, for example congenital heart defects are frequently detected in the first year of life (Todros et al 2010). The results of the sensitivity analyses differed for some congenital anomalies/exposure from those on the full population, in particular PM_{10} was statistically significantly associated to congenital heart defects in the smoking subpopulation (both adjusted and unadjusted) but not in the main analyses nor in the one adjusted for maternal education. Residual confounding by unmeasured risk factors such as alcohol consumption and dietary factors (e.g. folic acid) could have influenced our findings. However, it is unlikely that such factors would be strongly related to air pollution exposure, and

adjusting for social class on area level in the main analyses, and on individual level as sensitivity analysis, we can partially account for them.

The possible mechanisms and causes underlying the development of congenital anomalies are still unclear, because of their probable multifactorial aetiology (Ritz 2010) and because different types of anomalies are likely to have very distinct aetiology. Air pollution induced oxidative stress during pregnancy has been suggested as one possible mechanism behind pregnancy outcomes (Kannan et al. 2006; Slama et al. 2008), because it regulates the pulmonary and placental inflammation, the hemodynamic responses and thus the trans-placental oxygenation and transportation of nutrients. Oxidative stress may also affect organogenesis and neural crest cells migration and differentiation (Hassler et al. 1986; Ritz et al. 2002) which plays an important role in heart development (Keyte and Redmond Hutson 2012). More recently van Beynum et al. (2008) suggested a possible gene-environment interaction effect leading to an increased risk of congenital heart defects in mothers exposed to nitric oxide and smoking.

Conclusion

Our results overall do not indicate an association between exposure to traffic-related air pollution and many groups of congenital anomalies in Barcelona, even though the air pollution levels are some of the highest in Europe. The positive association of NO_2 and NO_x with coarctation of the aorta is consistent with a meta-analysis of previous studies and requires further study. Associations of digestive system anomalies with NO_2 and NO_x, and of abdominal wall defects with PM_{coarse}, also call for confirmation.

References

Agay-Shay K, Friger M, Linn S, Peled A, Amitai Y, Peretz C. 2013 Air pollution and congenital heart defects. Environ Res. 2013 Jul;124:28-34. doi: 10.1016/j.envres.2013.03.005. Epub 2013 Apr 25

Aguilera I, Guxens M, Garcia-Esteban R, Corbella T, Nieuwenhuijsen MJ, Foradada CM et al. 2009. Association between GIS-based exposure to urban air pollution during pregnancy and birth weight in the INMA Sabadell Cohort. Environ Health Perspect 117:1322-1327.

Ajuntament de Barecelona. 2007. Direcció de serveis de mobilitat - Dades Basiques 2007 http://w110.bcn.cat/portal/site/Mobilitat. [accessed 13 July 2013]

Ballester F, Estarlich M, Iñiguez C, Llop S, Ramón R, Esplugues A et al. 2010. Air pollution exposure during pregnancy and reduced birth size: a prospective birth cohort study in Valencia, Spain. Environ Health 9:6.

Beelen R, Hoek G, Vienneau D, Eeftens M, Dimakopoulou K, Pedeli X et al. 2013. Development of NO2 and NOx land use regression models for estimating air pollution exposure in 36 study areas in Europe – the ESCAPE project . Atmospheric Environment 72:10-23.

Brauer M, Lencar C, Tamburic L, Koehoorn M, Demers P, Karr C. 2008. A cohort study of traffic-related air pollution impacts on birth outcomes. Environ Health Perspect 116:680.

Cesaroni G, Porta D, Badaloni C, Stafoggia M, Eeftens M, Meliefste K et al. 2012. Nitrogen dioxide levels estimated from land use regression models several years apart and association with mortality in a large cohort study. Environ Health 11:48.

Cyrys J, Eeftens M, Heinrich J, Ampe C, Aarmengaud A, Beelen R et al. 2012. Variation of NO2 and NOx concentrations between and within 36 european study areas: results from the ESCAPE study. Atmospheric Environment 62:374-390.

Cyrys J, Heinrich J, Hoek G, Meliefste K, Lewné M, Gehring U et al. 2003. Comparison between different traffic-related particle indicators: elemental carbon (EC), $PM_{2.5}$ mass, and absorbance. J Expo Anal Environ Epidemiol. 13:134-143.

Dadvand P, Parker J, Bell ML, Bonzini M, Brauer M, Darrow LA et al. 2013. Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. Environ Health Perspect 121:267-373.

Dadvand P, Rankin J, Rushton S, Pless-Mulloli T. 2011a. Ambient air pollution and congenital heart disease: a registry-based study. Environ Res 111:435-441.

Dadvand P, Rankin J, Rushton S, Pless-Mulloli T. 2011b. Association Between Maternal Exposure to Ambient Air Pollution and Congenital Heart Disease: a Register-based spatio-temporal Analysis. Am J Epidemiol 173:171-182.

Dolk H, Armstrong B, Lachowycz K, Vrijheid M, Rankin J, Abramsky L et al. 2010. Ambient air pollution and risk of congenital anomalies in England, 1991-1999. Occup Environ Med 67:223-227.

Dolk H and Vrijheid M. 2003. The impact of environmental pollution on congenital anomalies. Br Med Bull 68:25-45.

Dominguez-Berjon MF, Borrell C, Cano-Serral G, Esnaola S, Nolasco A, Pasarin MI et al. 2008. Constructing a deprivation index based on census data in large Spanish cities (the MEDEA project). Gaceta Sanitaria 22:179-187.

Eeftens M, Beelen R, Bellander T, Cesaroni G, Cirach M, Declerq C et al. 2012a. Development of land use regression models for $PM_{2.5}$,$PM_{2.5}$ absorbance, PM_{10} and PM_{coarse} in 20 European study areas; results of the ESCAPE project. Environ Sci Technol 46:11195-11205.

Eeftens M, Tsai MY, Ampe C, Anwander B, Beelen R, Bellander T et al. 2012b. Spatial variation of $PM_{2.5}$, PM_{10}, $PM_{2.5}$ absorbance and PM_{coarse} concentrations between and within 20 European study areas and the relationship with NO2 - Results of the ESCAPE project. Atmospheric Environment 62:303-317.

ESCAPE project. 2009. ESCAPE http://www.escapeproject.eu/index.php [accessed 13 July 2013]

Estarlich M, Ballester F, Aguilera I, Fernandez-Somoano A, Lertxundi A, Llop S et al. 2011. Residential Exposure to Outdoor Air Pollution during Pregnancy and Anthropometric Measures at Birth in a Multicenter Cohort in Spain. Environ Health Perspect 119:1333-1338.

EUROCAT Website Database. 2012 Available: http://www.eurocat-network.eu/ACCESSPREVALENCEDATA/PrevalenceTables (accessed 03 April 2012).

EUROCAT. 2009. EUROCAT Guide 1.3. Instructions for the Registration of Congenital Anomalies. http://www.eurocat-network.eu/aboutus/datacollection/guidelinesforregistration/guide1_3instructionmanual [accessed 13 July 2013]

Gilboa SM, Mendola P, Olshan AF, Langlois PH, Savitz DA, Loomis D et al. 2005. Relation between ambient air quality and selected birth defects, seven county study, Texas, 1997-2000. Am J Epidemiol 162:238-252.

Greenlees R, Neville A, Addor MC, Amar E, Arriola L, Bakker M et al. 2011. Paper 6: EUROCAT member registries: Organization and activities. Birth Defects Research Part A: Clinical and Molecular Teratology 91:S51-S100.

Hansen CA, Barnett AG, Jalaludin BB, Morgan GG. 2009. Ambient air pollution and birth defects in brisbane, australia. PLoS One 4:e5408.

Hassler JA and Moran DJ. 1986. The effects of ethanol on embryonic actin: a possible role in teratogenesis. Cellular and Molecular Life Sciences 42:575-577.

Hoek G, Beelen R, de Hoogh K, Vienneau D, Gulliver J, Fischer P et al. 2008. A review of land-use regression models to assess spatial variation of outdoor air pollution. Atmospheric Environment 42:7561-7578.

Hwang B-F and Jaakkola JJK. 2008. Ozone and other air pollutants and risk of oral clefts. Environ Health Perspect 116:1411-1415.

Jerrett M, Arain A, Kanaroglou P, Beckerman B, Potoglou D, Sahsuvaroglu T et al. 2004. A review and evaluation of intraurban air pollution exposure models. J Expo Anal Environ Epidemiol. 15:185-204.

Jerrett M, Burnett RT, Ma R, Pope III CA, Krewski D, Newbold KB et al. 2005. Spatial analysis of air pollution and mortality in Los Angeles. Epidemiology 16:727-736.

Kannan S, Misra DP, Dvonch JT, Krishnakumar A. 2006. Exposures to airborne particulate matter and adverse perinatal outcomes: a biologically plausible mechanistic framework for exploring potential effect modification by nutrition. Environ Health Perspect 114:1636-1642.

Keyte A and Redmond Hutson M. 2012.The Neural Crest in Cardiac Congenital Anomalies. Differentiation 84(1):25-40.

Kim OJ, Ha EH, Kim BM, Seo JH, Park HS, Jung WJ et al. 2007. PM_{10} and pregnancy outcomes: a hospital-based cohort study of pregnant women in Seoul. J Occup Environ Med 49:1394-1402.

Marshall EG, Harris G, Wartenberg D. 2010. Oral cleft defects and maternal exposure to ambient air pollutants in New Jersey. Birth Defects Res A Clin Mol Teratol 88:205-215.

Miller A, Siffel C, Correa A. 2010. Residential mobility during pregnancy: patterns and correlates. Matern Child Health J 14:625-634.

Moore KL, Persaud TVN, Torchia MG, 1998. The Developing Human. Clinically Oriented Embryology. Philadelphia:.

Padula AM, Tager IB, Carmichael SL, Hammond SK, Yang W, Lurmann F, Shaw GM. 2013a. Ambient air pollution and traffic exposures and congenital heart defects in the san joaquin valley of california. Paediatr Perinat Epidemiol. 2013 Jul;27(4):329-39. doi: 10.1111/ppe.12055. Epub 2013 Apr 21.

Padula AM, Tager IB, Carmichael SL, Hammond SK, Lurmann F, Shaw GM. 2013b. The association of ambient air pollution and traffic exposures with selected congenital anomalies in the San Joaquin Valley of California. Am J Epidemiol. 2013 May 15;177(10):1074-85. doi: 10.1093/aje/kws367. Epub 2013 Mar 28.

Pedersen M, Giorgis-Allemand L, Bernard C, Aguilera I, f, Kogevinas M, Slama R. 2013. Ambient air pollution and low birthweight: a European cohort study (ESCAPE) The Lancet Respiratory Medicine 1:695-704.

Pernege TV. 1998 What's wrong with Bonferroni adjustments. BMJ 1998;316:1236

Rankin J, Chadwick T, Natarajan M, Howel D, Pearce MS, Pless-Mulloli T. 2009. Maternal exposure to ambient air pollutants and risk of congenital anomalies. Environ Res 109:181-187.

Reche C, Querol X, Alastuey A, Viana M, Pey J, Moreno T et al. 2011. New considerations for PM, Black Carbon and particle number concentration for air quality monitoring across different European cities. Atmos Chem Phys 11:6207-6227.

Ritz B. 2010. Air pollution and congenital anomalies. Occup Environ Med 67:221-222.

Ritz B and Wilhelm M. 2008. Ambient air pollution and adverse birth outcomes: methodologic issues in an emerging field. Basic Clin Pharmacol Toxicol 102:182-190.

Ritz B, Yu F, Fruin S, Chapa G, Shaw GM, Harris JA. 2002. Ambient air pollution and risk of birth defects in Southern California. Am J Epidemiol 155:17-25.

Rothman KJ. 1990. No adjustment are needed for multiple comparisons. Epidemiology 1:43-46.

Salvador J, Borrell A, Lladonosa A. 2005. Increasing detection rates of birth defects by prenatal ultrasound leading to apparent increasing prevalence. Lessons learned from the population-based registry of birth defects of Barcelona. Prenat Diagn 25:991-996.

Sapkota A, Chelikowsky AP, Nachman KE, Cohen AJ, Ritz B. 2010. Exposure to particulate matter and adverse birth outcomes: a comprehensive review and meta-analysis. Air Qual Atmos Health 5:369-381.

Schembari A, Triguero-Mas M, de Nazelle A, Dadvand P, Vrijheid M, Cirach M et al. 2013. Personal, indoor and outdoor Air pollution levels among pregnant Women. Atmospheric Environment 64:287-295.

Slama R, Darrow L, Parker J, Woodruff TJ, Strickland M, Nieuwenhuijsen M et al. 2008. Meeting report: atmospheric pollution and human reproduction. Environ Health Perspect 116:791-798.

Strickland MJ, Klein M, Correa A, Reller MD, Mahle WT, Riehle-Colarusso TJ et al. 2009. Ambient air pollution and cardiovascular malformations in Atlanta, Georgia, 1986-2003. Am J Epidemiol 169:1004-1014.

Todros T, Capuzzo E, Gaglioti P. 2001. Prenatal diagnosis of congenital anomalies. Images Paediatr Cardiol 3:3-18.

van Beynum IM, Mooij C, Kapusta L, Heil S, den Heijer M, Blom HJ. 2008. Common 894G> T single nucleotide polymorphism in the gene coding for endothelial nitric oxide synthase (eNOS) and risk of congenital heart defects. Clin Chem Lab Med 46:1369-1375.

Vrijheid M, Martinez D, Manzanares S, Dadvand P, Schembari A, Rankin J et al. 2011. Ambient air pollution and risk of congenital anomalies: a systematic review and meta-analysis. Environ Health Perspect 119:598-606.

WHO 2012. Media centre: Congenital Anomalies. Fact sheet nº370. http://www.who.int/mediacentre/factsheets/fs370/en/ [accessed 13 July 2013]

Wu J, Wilhelm M, Chung J, Ritz B. 2011. Comparing exposure assessment methods for traffic-related air pollution in an adverse pregnancy outcome study. Environ Res 111:685-692.

Table 1. Main characteristics of cases and controls for 1994-2006.

Characteristics	Controls, N (%)	Cases, N (%)	p-value[a]
Subjects	2991 (100%)	2247 (100%)	
Year of birth/termination			0.8
1994	228 (7.6)	189 (8.4)	
1995	220 (7.4)	152 (6.8)	
1996	211 (7.1)	142 (6.3)	
1997	217 (7.3)	164 (7.3)	
1998	224 (7.5)	167 (7.4)	
1999	224 (7.5)	187 (8.3)	
2000	222 (7.4)	184 (8.2)	
2001	227 (7.6)	176 (7.8)	
2002	246 (8.2)	182 (8.1)	
2003	231 (7.7)	163 (7.3)	
2004	249 (8.3)	169 (7.5)	
2005	250 (8.4)	199 (8.9)	
2006	242 (8.1)	173 (7.7)	
Season of conception			0.1
Winter	789 (26.4)	524 (23.3)	
Spring	727 (24.3)	565 (25.1)	
Summer	730 (24.4)	577 (25.7)	
Autumn	745 (24.9)	581 (25.9)	
Sex			0.6
Male	1540 (53.3)	1125 (52.0)	
Female	1348 (46.7)	1040 (48.0)	
(Missing)	105 (3.4)	84 (3.6)	
Type of birth			
Live birth	2991 (100.0)	1687 (75.1)	
Stillbirth		179 (8.0)	
TOP[b]		381 (17.0)	
Maternal age			0.6
< 25	298 (10.4)	207 (9.5)	
25-30	797 (27.8)	589 (27.1)	
30-35	1099 (38.3)	866 (39.9)	
> 35	675 (23.5)	511 (23.5)	
(Missing)	122 (4.1)	74 (3.3)	
Maternal education			0.00
Primary school	103 (3.6)	130 (9.5)	
Secondary school	699 (24.6)	388 (28.3)	
College	816 (28.7)	289 (21.1)	
University	1222 (43.0)	564 (41.1)	
(Missing)	151 (5.3)	876 (63.9)	

Characteristics	Controls, N (%)	Cases, N (%)	p-value[a]
Smoking 1st trimester			0.00
No	1767 (62.4)	481 (52.3)	
Yes + Quit	1066 (35.6)	438 (47.7)	
(Missing)	158 (5.3)	1328 (59.1)	
Medea index[c]			
Mean ± SD	0.02 ± 1.05	-0.01 ±1.00	0.2

[a]Chi-square test for equal distribution of categorical variables; t-test for equality of means of continuous variables, significant at α level (α = 0.05). [b]Termination Of Pregnancy (TOP). [c]Socio-economic index at census tract level. The lower the MEDEA index, the more deprived the census tract.

Table 2. Median and inter-quartile range (IQR) of spatial and spatio-temporal exposure of air pollutants, by cases and controls.

Pollutant	All median (IQR)	Controls median (IQR)	Cases median (IQR)
Spatial exposure[a]			
NO_2 μg/m^3	55.7 (12.2)	56.0 (11.8)*	55.4 (12.7)*
NO_x μg/m^3	88.7 (27.1)	89.8 (27.5)*	87.1 (27.2)*
PM_{10} μg/m^3	38.7 (3.0)	38.8 (3.0)	38.7 (2.8)
PM_{coarse} μg/m^3	21.7 (3.6)	21.7 (3.6)	21.7 (3.8)
$PM_{2.5}$ μg/m^3	16.6 (2.6)	16.6 (2.5)	16.5 (2.7)
$PM_{2.5}$ absorbance 10^{-5} m^{-1}	2.65 (0.73)	2.68 (0.71)*	2.62 (0.75)*
Spatio-temporal exposure			
1994-2006[a]			
NO_2 μg/m^3	53.6 (26.4)	54.1 (26.2)**	53.0 (26.3)**
NO_x μg/m^3	110.5 (78.1)	111.5 (77.4)**	108.5 (78.7)**
$PM_{2.5}$ absorbance 10^{-5} m^{-1}	3.21 (2.15)	3.24 (2.14)**	3.18 (2.19)**
2000-2006[b]			
PM_{10} μg/m^3	38.6 (12.1)	38.3 (11.9)	38.9 (12.4)
PM_{coarse} μg/m^3	21.1 (7.0)	21.1 (6.7)	21.1 (7.4)
$PM_{2.5}$ μg/m^3	16.6 (6.0)	16.6 (5.9)	16.6 (6.0)

[a]All subject n = 5238; controls n = 2991; cases n = 2247. [b]All subject n = 1665; controls n = 941; cases n = 724.

*Rank-sum test for difference in the distribution between cases and controls, significant at α level (α = 0.05). **Rank-sum test for difference in the distribution between two populations, significant at α level (α = 0.10).

Table 3. Correlation coefficients (Spearman, significant at α level=0.05) between spatial and spatio-temporal exposure estimates of air pollutants (from 1994 to 2006 for NO_2, NO_x and $PM_{2.5}$ absorbance, from 2000 to 2006 for PM_{10}, PM_{coarse} and $PM_{2.5}$).

Pollutant	**NO_2**	**NO_x**	**PM_{10}**	**PM_{coarse}**	**$PM_{2.5}$**	**$PM_{2.5}$ absorbance**
Spatial exposure (N=5238)						
NO_x	0.92					
PM_{10}	0.66	0.69				
PM_{coarse}	0.17	0.16	0.34			
$PM_{2.5}$	0.67	0.67	0.64	0.32		
$PM_{2.5}$ absorbance	0.93	0.92	0.68	0.17	0.70	
Spatio-temporal exposure, 1994-2006 (N = 5238)						
NO_2	0.53[a]					
NO_x	0.86	0.55[a]				
$PM_{2.5}$ absorbance	0.85	0.97				0.46[a]
Spatio-temporal exposure, 2000-2006 (N = 1665)						
PM_{10}			0.26[a]			
PM_{coarse}			0.89	0.41[a]		
$PM_{2.5}$			0.91	0.86	0.47[a]	

[a]Correlation between spatial and spatio-temporal exposure for each pollutant.

Table 4. Spatio-temporal exposure to NO_2, NO_x, and $PM_{2.5}$ absorbance: adjusted odds ratio (OR)[a] and 95% confidence interval for each inter-quartile range increase in exposure[b]. Study period 1994-2006.

Congenital anomaly	N Cases /N Controls[c]	NO_2 OR (95% CI)	NO_x OR (95% CI)	$PM_{2.5}$ absorbance OR (95% CI)
All cases	2173/2869	0.98 (0.92,1.04)	1.00 (0.99, 1.01)	0.95 (0.86, 1.04)
Neural tube defects	139/2869	1.01(0.83,1.22)	1.00 (0.96, 1.03)	1.09 (0.81, 1.47)
Congenital heart disease	823/2869	0.97 (0.89, 1.06)	1.00 (0.98, 1.01)	0.94 (0.83, 1.08)
Transposition of great vessels (complete)	69/2869	1.09 (0.93, 1.27)	1.01 (0.98, 1.04)	1.29 (0.88, 1.89)
Ventricular septal defect	351/2869	0.98 (0.86, 1.11)	0.99 (0.97, 1.02)	0.98 (0.81, 1.19)
Atrial septal defect	229/2869	0.94 (0.79,1.11)	0.98 (0.95, 1.02)	0.95 (0.76, 1.20)
Atrioventricular defect	30/2650	1.03 (0.77, 1.38)	1.00 (0.96, 1.06)	1.29 (0.70, 2.37)
Tetralogy of fallot	49/2650	0.96 (0.68, 1.35)	0.99 (0.93, 1.06)	0.92 (0.55, 1.52)
Tricuspid atresia and stenosis	59/2168	0.94 (0.67, 1.33)	0.98 (0.91, 1.05)	0.97 (0.61, 1.53)
Pulmonary valve stenosis	70/2869	0.95 (0.72, 1.27)	1.00 (0.95, 1.05)	1.08 (0.72, 1.63)
Coarctation of aorta	69/2869	1.15* (1.01, 1.31)	1.02* (1.00, 1.04)	1.28 (0.86, 1.90)
Respiratory system	138/2869	1.01 (0.85, 1.20)	1.00 (0.97, 1.03)	1.06 (0.79, 1.44)
Oro-facial clefts	130/2869	1.08 (0.93, 1.25)	1.00 (0.97, 1.03)	1.19 (0.89, 1.59)
Digestive system	191/2869	1.11* (1.00, 1.23)	1.02* (1.00, 1.04)	0.95 (0.74, 1.22)
Abdominal wall defects	55/2869	0.86 (0.58, 1.28)	0.97 (0.89, 1.05)	0.71 (0.42, 1.19)
Urinary system	494/2869	0.95 (0.85, 1.07)	0.99 (0.97, 1.01)	0.99 (0.84, 1.17)
Hypospadias	74/2423	1.02 (0.78, 1.34)	0.98 (0.91, 1.05)	0.89 (0.57, 1.39)
Limb reduction	308/2869	0.97 (0.85, 1.12)	0.99 (0.97, 1.02)	0.88 (0.71, 1.09)

[a]Model adjusted for maternal age, conception season, year of birth/termination, socio economic index. [b]Spatial exposure inter-quartile ranges for all subjects combined: NO_2 (12.2), NO_x (27.1), PM_{10} (3.0), PM_{coarse} (3.6), $PM_{2.5}$ (2.6), $PM_{2.5}$ absorbance (0.73). [c]The number of controls varies avoid collinearity when there were no cases in certain years. *Odd ratio significant at α level ($\alpha = 0.05$).

Table 5. Spatio-temporal exposure to PM_{10}, PM_{coarse} and $PM_{2.5}$: adjusted odds ratios (OR)[a] and 95% confidence interval (CI) for each inter-quartile range increase in exposure[b]. Study period 2000-2006.

Congenital anomaly	N Cases/N Controls[c]	PM_{10} OR (95% CI)	PM_{coarse} OR (95% CI)	$PM_{2.5}$ OR (95% CI)
All cases	695/903	1.00 (0.96, 1.04)	1.01 (0.93, 1.10)	0.97 (0.91, 1.04)
Neural tube defects	51/903	1.01 (0.89, 1.15)	1.08 (0.83, 1.39)	1.06 (0.86, 1.30)
Congenital heart disease	248/903	0.97 (0.91, 1.03)	0.94 (0.83, 1.07)	0.93 (0.84, 1.04)
Transposition of great vessels (complete)	26/890	1.03 (0.86, 1.24)	1.07 (0.75, 1.54)	0.99 (0.73, 1.33)
Ventricular septal defect	106/903	0.88* (0.81, 0.97)	0.79* (0.66, 0.94)	0.83* (0.72, 0.97)
Atrial septal defect	58/903	0.65 (0.84, 1.09)	0.84 (0.65, 1.09)	0.88 (0.72, 1.09)
Atrioventricular defect	13/903	0.93 (0.72, 1.20)	0.64 (0.36, 1.14)	0.83 (0.54, 1.28)
Tetragy of fallot	17/890	0.90 (0.73, 1.12)	0.86 (0.57, 1.30)	1.07 (0.76, 1.49)
Tricuspid atresia and stenosis	10/533	1.04 (0.76, 1.42)	1.26 (0.67, 2.34)	1.20 (0.74, 1.96)
Pulmonary valve stenosis	19/980	0.95 (0.76, 1.18)	1.03 (0.65, 1.61)	0.97 (0.68, 1.39)
Coarctation of aorta	28/890	0.99 (0.83, 1.18)	1.25 (0.88, 1.79)	1.08 (0.82, 1.42)
Respiratory	49/903	1.10 (0.98, 1.25)	1.14 (0.89, 1.47)	1.12 (0.92, 1.36)
Oro-facial clefts	40/903	0.98 (0.85, 1.13)	0.92 (0.70, 1.22)	0.99 (0.79, 1.24)
Digestive system	47/890	0.99 (0.87, 1.12)	1.09 (0.84, 1.42)	1.03 (0.83, 1.27)
Abdominal wall defects	22/890	1.36* (1.14, 1.62)	1.93* (1.37, 2.73)	1.33* (1.00, 1.76)
Urinary	179/903	1.00 (0.93, 1.07)	0.96 (0.83, 1.10)	0.96 (0.85, 1.07)
Hypospadias	23/700	1.15 (0.94, 1.41)	1.15 (0.77, 1.70)	1.18 (0.87, 1.60)
Limb reduction	109/903	0.94 (0.86, 1.03)	0.90 (0.75, 1.08)	0.92 (0.79, 1.06)

[a]Model adjusted for maternal age, conception season, year of birth/termination, socio-economic index. [b]Spatial exposure inter-quartile ranges for all subjects combined: NO_2 (12.2), NO_x (27.1), PM_{10} (3.0), PM_{coarse} (3.6), $PM_{2.5}$ (2.6), $PM_{2.5}$ absorbance (0.73).[c]The number of controls varies to avoid collinearity when there were no cases in certain years. *Odd ratio significant at α level ($\alpha = 0.05$).

Epidemiol Prev 2011; 35 (5-6) Suppl. 4: 1-204

WWW.EPIPREV.IT

Capitolo 12

Studio delle malformazioni congenite nei siti di interesse nazionale per le bonifiche di SENTIERI

The study of congenital anomalies in contaminated sites of interest for environmental remediation

Fabrizio Bianchi

Unità di ricerca "Epidemiologia ambientale e registri di patologia", Istituto di fisiologia clinica del CNR, Pisa

Corrispondenza
Fabrizio Bianchi
fabriepi@ifc.cnr.it

Riassunto

Gli effetti avversi sulla riproduzione rappresentano un importante campo d'azione per l'effettuazione di studi eziologici e per la sorveglianza di popolazioni definite a rischio. Una causa ambientale può agire con un'azione mutagena pre-concezionale (per esposizione materna o paterna) o un'azione teratogena post-concezionale. Sulla base della valutazione integrata di molteplici criteri, la US-Agency for Toxic Substances and Disease Registry (ATSDR) e la US-Environmental Protection Agency (USEPA), considerano prioritario lo studio delle malformazioni congenite e i disordini a carico dell'apparato riproduttivo. La scelta delle malformazioni congenite da includere nello studio è basata principalmente sui risultati della classificazione dell'evidenza realizzata per SENTIERI. In secondo luogo, in considerazione della ridotta numerosità degli studi epidemiologici sulle malformazioni congenite svolti in siti inquinati di diverso tipo, dei risultati ancora inadeguati o limitati conseguiti dalla maggior parte di essi, lo studio verterà anche sui principali gruppi di patologie a titolo descrittivo. I dati che saranno utilizzati sono quelli prodotti dai registri operanti in Regioni o aree sub-regionali, e aderenti al coordinamento nazionale dei Registri delle malformazioni congenite, istituito presso il Centro malattie rare dell'Istituto superiore di sanità.
Fanno parte del coordinamento sette registri distribuiti sul territorio nazionale. Sono scelti due periodi di studio: 1995-2002 (1996-2002 per la Campania), in analogia con il periodo di studio della mortalità in SENTIERI, e periodi di durata differente tra il 2003 e il 2008, secondo la disponibilità di dati da parte dei diversi registri. I Registri delle malformazioni sopra menzionati permettono di coprire 16 dei 44 SIN considerati da SENTIERI, includenti 119 Comuni. Per la stima dei casi attesi nelle aree dei SIN per ciascuna delle condizioni malformative selezionate saranno utilizzati i tassi di prevalenza alla nascita delle stesse malformazioni rilevati nelle aree regionali di registrazione includenti i SIN in studio.
La descrizione del Progetto SENTIERI è contenuta nel Supplemento ad esso dedicato pubblicato nel 2010 da *Epidemiologia & Prevenzione*.

Epidemiol Prev 2011; 35 (5-6) Suppl. 4: 199-204
Parole chiave: malformazioni congenite, registri malformazioni, siti contaminati

Abstract

SENTIERI Project (Mortality study of residents in Italian polluted sites) studies mortality of residents in 44 sites of national interest for environmental remediation (Italian polluted sites, IPSs). A development of the Project is the investigation of adverse reproductive effects. This issue is of the utmost importance in the field of environmental epidemiology, both in analytical studies and in surveillance activity. An environmental factor can be at play either as a preconception mutagen (maternal or paternal exposure)

e&p anno 35 (5-6) settembre-dicembre 2011 • Suppl. 4

or as a postconceptional teratogen. The US-Agency for Toxic Substances and Disease Registry (ATSDR) and the US-Environmental Protection Agency (USEPA), indicate as a priority the study of congenital anomalies (CA) and reproductive disorders. The choice of congenital anomalies to be included in the study is mainly based on the results of the evaluation of the epidemiological evidence completed for SENTIERI Project.
The epidemiological knowledge on congenital anomalies in polluted sites is lacking, therefore main groups of CA will also be included for descriptive purposes. Data on CA are produced by seven registers located in Italy, either in regional or sub-regional areas, which are included in the National Committee of Congenital Malformations Registers hosted by the National Center for Rare Diseases at Istituto Superiore di Sanità. The study periods are: a) 1995-2002 (1996-2002 for the Region Campania), namely the same years as SENTIERI mortality study; b) for the years 2003-2008 different time windows will be chosen on the basis of data availability in single registers. Registers of CA are active in 16 out of 44 polluted sites included in SENTIERI, for a total of 119 municipalities. In each polluted site the number of expected cases for each CA will be estimated from the prevalence at birth of the same anomaly as from regional registers active in the polluted site at study.
For a description of SENTIERI, refer to the 2010 Supplement of *Epidemiologia & Prevenzione* devoted to the Project.

Epidemiol Prev 2011; 35 (5-6) Suppl. 4: 199-204
Keywords: mammography screening, breast, survey, Italy

INTRODUZIONE

Gli effetti avversi sulla riproduzione sono un importante campo d'azione per l'effettuazione di studi eziologici e per la sorveglianza di popolazioni definite a rischio, principalmente in virtù del periodo breve di latenza tra inizio dell'esposizione e manifestazione dell'effetto.
I sistemi riproduttivi di donne e uomini sono sensibili all'esposizione ad agenti biologici, chimici e fisici che agiscono sul prodotto del concepimento con meccanismi complessi, diversi a seconda dell'esposizione, materna o paterna.
Una causa ambientale può agire con un'azione mutagena pre-concezionale (per esposizione materna o paterna) o un'azione teratogena post-concezionale. Il periodo della gravidanza di maggiore suscettibilità è quello dell'organogenesi, corrispondente al primo trimestre; esposizioni rilevanti possono verificarsi molto precocemente per effetti indiretti (es: effetti sul metabolismo endocrino) o anche per accumulo nei tessuti di sostanze chimiche con lunga emivita biologica, come per esempio i policlorobifenili (PCB). Alcuni effetti avversi, principalmente sullo sviluppo cerebrale, possono verificarsi a causa di esposizioni ambientali nel secondo trimestre di gravidanza od oltre.[1,2]
Un'origine multifattoriale prevalentemente non conosciuta, effetto di una combinazione o interazione tra fattori genetici e ambientali, è alla base della maggior parte delle malformazioni congenite, a fronte di una quota più ridotta di condizioni malformative a eziologia nota di tipo genetico (sindromi cromosomiche o da mutazione di un singolo gene) o di tipo ambientale per esposizione a teratogeni (es: talidomide). In questo contesto si inscrive l'accresciuto interesse per l'epigenetica anche nel campo delle malformazioni congenite.[3]
Sulla base della valutazione integrata di molteplici criteri, quali frequenza di associazioni tossicologiche o epidemiologiche con sostanze pericolose, gravità della condizione, entità della preoccupazione di medici, operatori della sanità pubblica e comunità, capacità di riduzione dell'impatto di malattia mediante attività di cura e prevenzione, la US-Agency for Toxic Substances and Disease Registry (ATSDR) e la US-Environmental Protection Agency (USEPA), considerano prioritario lo studio delle malformazioni congenite e dei disordini a carico dell'apparato riproduttivo.[4,5]
Nel Progetto SENTIERI è stata completata la valutazione *a priori* dell'evidenza epidemiologica di associazione tra le *esposizioni ambientali* nei SIN e i principali eventi avversi della riproduzione, tra cui le malformazioni congenite (MC). Le fonti utilizzate nella valutazione dell'evidenza epidemiologica tra i suddetti eventi e le *esposizioni ambientali* nei SIN sono state identificate interrogando la banca dati Pubmed, con le parole chiave "congenital malformations", "congenital anomalies", "congenital defects", "birth defects", "malformative syndromes". Le procedure per la selezione delle fonti (*primarie*, metanalisi quantitative, rassegne, studi multicentrici, singoli studi epidemiologici), i criteri e i risultati della valutazione dell'evidenza epidemiologica state descritte nel dettaglio in un Supplemento del 2010 di *Epidemiologia e Prevenzione*.[6] In sintesi, si ha una valutazione di evidenza Limitata di associazione delle malformazioni con la residenza in prossimità di impianti petrolchimici, raffinerie e discariche, e di evidenza Inadeguata per impianti chimici e inceneritori.[6]
I risultati delle valutazioni dell'evidenza completata da SENTIERI mostrano la limitatezza delle evidenze sulle malformazioni congenite fino a oggi disponibili e corroborano l'utilità di usare la metodologia SENTIERI per migliorare le conoscenze sul tema.

SELEZIONE DELLE MALFORMAZIONI CONGENITE

La studio delle malformazioni congenite è uno sviluppo del Progetto SENTIERI. La scelta delle MC da includere è basata principalmente sui risultati della valutazione dell'evidenza epidemiologica sopra esposti. Inoltre, in considera-

zione della insufficiente conoscenza epidemiologica relativa ai siti inquinati, conseguenza della scarsità degli studi condotti, lo studio esaminerà anche, a scopo descrittivo, i principali gruppi di malformazioni congenite. Pertanto, in conformità con questi due criteri e con quanto previsto da Eurocat (Sistema europeo di sorveglianza delle malformazioni congenite) si prevede di includere nello studio i gruppi di malformazioni elencati in tabella 1.
Inoltre, saranno analizzati sottogruppi specifici di malformazioni per le quali sono disponibili nella letteratura scientifica indicazioni di associazioni con fattori di rischio ambientale e che abbiano frequenze non particolarmente rare.

SELEZIONE DEI REGISTRI E DEI DATI

I dati utilizzati saranno quelli prodotti dai registri aderenti al coordinamento nazionale dei Registri delle malformazioni congenite, istituito presso il Centro malattie rare dell'Istituto superiore di sanità[7] e operanti nelle aree geografiche in cui sono ubicati i SIN.
Fanno parte del coordinamento i seguenti registri: Registro lombardo malformazioni congenite, Registro malformazioni Nordest Italia, Indagine malformazioni Emilia-Romagna, Registro toscano difetti congeniti, Registro campano difetti congeniti, Indagine siciliana malformazioni congenite, Registro malformazioni congenite dell'ASL di Mantova.

Anomalie congenite	Codice BPA-ICD 9*	Codice ICD 10
sistema nervoso	740, 741, 742	Q00-Q07
occhio	743	Q100, Q104, Q106-Q107, Q11-Q15
orecchio, faccia, collo	744	Q16, Q178, Q183, Q188
cuore	745, 746, 7470-7474	Q20-Q26
respiratorio	748	Q30-Q34
palato-labbro	7490, 7491, 7492	Q35-Q37
digerente	750, 751, 7566	Q38-Q39, Q402-Q409, Q41-Q45, Q790
parete addominale	75671, 75670, 75679	Q792, Q793, Q795
urinario	753, 75672, 75261	Q60-Q64, Q794
genitali	7520-7524, 75260, 75262, 7527-7529	Q50-Q52, Q54-Q56
arti	7543-7548, 755	Q650-Q652, Q658-Q659, Q660, Q681-Q682, Q688, Q69-Q74
muscolo-scheletrico	7540-7542, 7560-7565, 7568-7569, 76280	Q750-Q751, Q754-Q759, Q761-Q764, Q766-Q769, Q77, Q78, Q796-Q799
cromosomiche	7580-7583, 7585-7589	Q90-Q92, Q93, Q96-Q99

* International Classification of Diseases, 9th Revision, modificata dalla British Pediatric Association

Tabella 1. Gruppi di malformazioni selezionate.
Table 1. Congenital anomalies groups at study.

Registro	Acronimo	Anno diistituzione	Area coperta	Periodi di registrazione per SENTIERI	N medio nati/anno sorvegliati	Appartenenza a network internazionali*
Mantova	RMCPM	2006	ASL Mantova	2003-2008**	3 511	
Nordest Italia	RMC_NEI	1981	Prov. Bolzano e Trento, FVG, Veneto	1993-2002 2003-2007^	55 893 60 257	Eurocat (AM) ICBDSR
Emilia-Romagna	IMER	1978	intera Regione	1995-2002 2003-2008	25 737 37 415	Eurocat (FM) ICBDSR
Toscana	RTDC	1979	intera Regione	1995-2002 2003-2008	25 655 29 713	Eurocat (FM) ICBDSR
Campania	RCDC	1991	intera Regione	1996-2002 2003-2007	51 239 59 916	Eurocat (FM) ICBDSR
Sicilia	ISMAC	1991	Sicilia sudorientale§	1995-2002 2003-2004	17 141 20 165	Eurocat (AM) ICBDSR
Totale				1995-2002	175 664	
				2003-2008	211 466	

* Eurocat-European Surveillance of Congenital Anomalies; FM: full member; AM: associate member; ICBDSR: International Clearinghouse for Birth Defects Research and Surveillance
** 2003-2007 tramite SDO, 2008 tramite SDO e registrazione attiva
^ 2004-2007 dati di fonte registro non ancora inclusi nel database centrale Eurocat
§ alcune aree con copertura parziale sono integrate con dati di fonte locale, ottenuti da studi ad hoc (SDO, cartelle cliniche)

Tabella 2. Alcune caratteristiche dei Registri delle malformazioni congenite che coprono nascite residenti in aree entro le quali ricadono SIN di interesse per lo studio SENTIERI.
Table 2. Some characteristics of Congenital anomalies Registries serving areas that include IPSs at study in SENTIERI Project.

Nella prima fase dello studio saranno considerati i registri che aderiscono al sistema europeo di sorveglianza Eurocat, e pertanto utilizzano lo stesso protocollo d'indagine,[8] e il Registro dell'ASL di Mantova[9] che, pur non aderendo a Eurocat, viene incluso in considerazione della accertata qualità delle procedure impiegate e della rilevanza del SIN omonimo (tabella 2). Tutti i registri considerati includono casi con malformazioni congenite diagnosticate al momento della interruzione di gravidanza (IVG), nel nato morto (NM) o nel nato vivo, alla nascita o in periodo neonatale precoce (più propriamente, nei giorni di permanenza nella struttura ospedaliera dopo la nascita). In fase di analisi e discussione sarà tenuto conto della limitazione rappresentata dalla diversa capacità di registrazione delle IVG nel tempo all'interno dello stesso registro e tra registri.
Nei SIN siciliani di Gela e Priolo i dati del registro ISMAC potranno essere arricchiti con dati di indagini specifiche precedentemente effettuate nelle stesse aree e pubblicate.[10,11] Lo studio sulle malformazioni qui descritto, che si inserisce tra gli sviluppi di SENTIERI, considererà i casi diagnosticati in soggetti residenti nelle aree di registrazione.

PERIODO DI STUDIO

Come mostrato nella tabella 2, lo studio riguarderà due periodi: 1995-2002 (1996-2002 per la Campania), in analogia con il periodo di studio della mortalità in SENTIERI, e periodi di durata differente tra il 2003 e il 2008, secondo la disponibilità di dati da parte dei diversi registri. Nel primo periodo, di otto anni, i registri hanno sorvegliato complessivamente 1 354 075 nascite (175 664 nati/anno). Il secondo periodo è più breve, le nascite complessivamente sorvegliate dai registri sono state circa 823 998, pari a 210 977 nascite/anno, un numero più elevato di nascite sorvegliate annualmente, per effetto dell'incremento del numero di nascite che c'è stato in tutte le Regioni e in Italia nel suo complesso, e di una maggiore copertura territoriale da parte dei registri.
Altri registri in fase di avvio che coprono aree regionali in modo parziale (Piemonte, Calabria, Sicilia) o già avviati su aree sub-regionali (Lombardia) non saranno inclusi nello studio, perché per il loro uso si rende necessaria la preparazione di un protocollo di validazione e armonizzazione, che potrà essere sviluppato in parallelo alle altre attività dello studio. Questa attività potrà consentire, in una seconda fase, di includere numerosi altri SIN nelle analisi, aumentando la potenza di studio e la rappresentatività su scala nazionale.

SIN COPERTI DA REGISTRI

I registri delle malformazioni sopra menzionati permettono di coprire 16 dei 44 SIN considerati da SENTIERI,

Registro	SIN	Prov.	N Comuni	Tipo sito*	Nati sorvegliati nel periodo**			
					2002	1995-2002	2003-2008	1995-2008
ASL MN	Laghi di Mantova e polo chimico	MN	2	C, P&R, AP, D	457		2 742	2 742
NEI	Bolzano	BZ	1	C	888	7 104	4 440	11 544
	Trento Nord	TN	1	C	1 064	8 512	5 320	13 832
	Trieste	TS	1	C, P&R, S, AP	1 448	11 584	7 240	18 824
	Laguna di Grado e Marano	UD	6	C, AP	239	1 912	1 195	3 107
	Marghera	VE	1	C, P&R, E, AP, D	2 041	16 328	10 205	26 533
IMER	Fidenza	PR	2	C, D	307	2 456	1 842	4 298
	Sassuolo-Scandiano	RE, MO	3 + 3	C	1 122	8 976	6 732	15 708
RTDC	Massa Carrara	MS	2	C, P&R, S, AP, A, D, I	1 097	8 776	6 582	15 358
	Livorno	LI	2	P&R, AP	1 333	10 664	7 998	18.662
	Piombino	LI	1	C, S, E, AP, D	261	2 088	1 566	3 654
	Orbetello	GR	1	C	114	912	684	1 596
RCDC	Litorale vesuviano	NA	11	A, D	5 353	37 471	26 765	64 236
	Litorale Domizio Flegreo e Agro Aversano	CE, NA	49 + 28	D	25 473	178 311	127 365	305 676
	Priolo	SR	4	C, P&R, AP, A, D	1 734	13 872	3 468	17 340
	Gela	CL	1	C, P&R, D	987	7 896	1 974	9 870
	Totale		**119**		**44 211**	**316 862**	**216 118**	**532 980**

* acronimi delle esposizioni ambientali: **C** = "impianti chimici": nel suo complesso include impianti di produzione/utilizzo di sostanze chimiche eterogenee e impianti di produzione/utilizzo di singola sostanza chimica; esclude gli impianti petrolchimici; **P&R** = "impianti petrolchimici e raffinerie": include impianti petrolchimici e raffinerie, anche distinti; **S** = impianti siderurgici; **E** = centrale elettrica; **M** = miniere e/o cave; **AP**= area portuale; **A** = amianto o altre fibre minerali; **D** = discarica; **I** = inceneritore.

** stima sulla base dei nati nei Comuni appartenenti al SIN (fonte: Istat 2002).

Tabella 3. SIN coperti da Registri e relativo numero delle nascite sorvegliate.

Table 3. IPSs served by Registries and number of monitored births.

e&p anno 35 (5-6) settembre-dicembre 2011 • Suppl. 4

Tipo SIN*	Nati sorvegliati		Esempio 1 Attesi in caso di malformazione rara**		Esempio 2 Attesi in caso di malformazione non rara^		Esempio 3 Attesi in caso di malformazione frequente§	
	1995-2002	2003-2008	1995-2002	1995-2002	1995-2002	2003-2008	1995-2002	2003-2008
impianto chimico (C)	90 416	53 990	45	27	90	54	452	270
impianto petrolchimico e raffineria (P&R)	69 120	40 209	35	20	69	40	346	201
impianto siderurgico(S)	22 448	15 388	11	8	22	15	112	77
area portuale (AP)	65 224	40 996	33	20	65	41	326	205
discarica (D)	267 198	182 509	134	91	267	183	1336	913

* tipo di esposizione nel SIN;
** prevalenza alla nascita: 5 per 10 000;
^ prevalenza alla nascita: 10 per 10 000;
§ prevalenza alla nascita: 50 per 10 000.

Tabella 4. Nascite e malformazioni attese in aggregati di diverso tipo di SIN per tre diverse frequenze di malformazione.

Table 4. Expected births and congenital anomalies in different type of IPSs for three different anomaly frequencies.

includenti 119 Comuni, come riportato nella tabella 3.
In tabella 4 sono riportati i numeri di eventi stimati sulla base delle nascite sorvegliate nei due periodi considerati negli aggregati diversi di SIN, con tre esempi concernenti malformazioni con frequenza rara, intermedia e non rara.
Per calcolare la capacità dei registri di evidenziare come statisticamente significativi i rischi relativi stimati dal rapporto osservati/attesi, la tabella 4 presenta la stima degli attesi nelle diverse tipologie di SIN.
Nel primo esempio di una malformazione più rara, nel caso del numero minimo di casi attesi pari a 8 il sistema permette di evidenziare un rapporto O/A pari a 1.88 (IC 95% 1.05-2.94), con 11 casi attesi il rapporto O/A evidenziabile scende a 1.73 (IC 95% 1.04-2.59); nel secondo esempio, al numero minimo di attesi di 15 corrisponde un rischio relativo minimo di 1.60 (IC 95% 1.02-2.30). Nel terzo esempio, riferito a una malformazione non rara, il numero minimo atteso di 77 permette di rilevare un rischio di 1.23 (IC 95% 1.01-1.49).
Dagli esempi emerge come al crescere della dimensione della popolazione (nascite) e/o della frequenza della condizione malformativa si possono identificare come significativi incrementi di rischio sempre più contenuti. Per esempio: N attesi ≥20, O/A ≤1.50; N attesi ≥50, O/A ≤1.30; N attesi ≥100, O/A ≤1.21.

I dati presentati mostrano come complessivamente il sistema sarà in grado di porre in evidenza incrementi di rischio anche di moderata dimensione per tutte le tipologie di SIN considerate, mettendo in luce una minore potenza solo per l'aggregato dei SIN con impianti siderurgici, mentre ancora minore sarebbe per gli altri tipi di SIN previsti da SENTIERI, poco rappresentati dai 16 SIN analizzabili e che quindi non sono stati riportati in tabella.

POPOLAZIONI STANDARD E CALCOLO DEI RAPPORTI DI RISCHIO

Per la stima dei casi attesi nelle aree dei SIN per ciascuna delle condizioni malformative selezionate saranno utilizzati i tassi di prevalenza alla nascita delle stesse malformazioni rilevati nelle aree regionali di registrazione includenti i SIN in studio. Per il SIN di Mantova si utilizzeranno i tassi forniti dal registro IMER riferiti alla regione Emilia-Romagna, non essendo disponibili dati della Regione Lombardia.
E' previsto il calcolo dei rapporti O/A grezzi sia aggiustati per indice di deprivazione socioeconomica materiale (O/A ID), calcolato al 2001 con la stessa procedura messa a punto *ad hoc* in SENTIERI per lo studio di mortalità. I rapporti O/A saranno corredati di intervallo di confidenza al 90%. Una trattazione dettagliata dell'analisi è esposta nel Capitolo 3 del presente Supplemento.

Bibliografia/References

1. Otake M, Schull WJ. In utero exposure to A-bomb radiation and mental retardation; a reassessment. *Br J Radiol* 1984; 57: 409-414.
2. Evrard P, Kadhim HJ, Sasint-Goerges P, Gadisseux JF. Abnormal development and destructive processes of the human brain during the second half of gestation. In: Evrard P, Minkowski A (eds). *Developmental neurobiology*. Raven Press, NewYork 1989.
3. Martinez-Frias ML. Can our understanding of epigenetics assist with primary prevention of congenital defects? *J Med Genet* 2010; 47: 73-80.
4. US Environmental Protection Agency – USEPA http://www.epa.gov/superfund/sites/npl
5. Johnson BL. Impact of hazardous waste on human health: hazard, health effects, equity, and communication issues. Lewis Publishers, Boca Raton (USA) 1999.
6. Pirastu R, Ancona C, Iavarone I, Mitis F, Zona A, Comba P, SENTIERI Working Group. SENTIERI Project. Mortality study of residents in Italian polluted sites: evaluation of the epidemiological evidence. *Epidemiol Prev* 2010; 5-6 (Suppl. 3): 1-96.
7. Pagina dei Registri malformazioni congenite presso il sito del Cen-

tro nazionale malattie rare. Istituto superiore di sanità http://www.iss.it/cnmr/regi/cont.php?id=861&lang=1&tipo=14 (ultima consultazione 27 luglio 2011).
8. EUROCAT – European Surveillance of Congenital Anomalies http://www.eurocat-network.eu (ultima consultazione 27 luglio 2011).
9. Azienda sanitaria locale della Provincia di Mantova. Sezione epidemiologia. http://www.aslmn.it/t_dat_epid_malformazioni.asp?IDLivello1=3&IDLivello2=60&IDLivello3=179 (ultima consultazione 27 luglio 2011).
10. Bianchi F, Bianca S, Linzalone N, Madeddu A. Surveillance of congenital malformations in Italy: an investigation in the province of Siracusa. *Epidemiol Prev* 2004; 28: 87-93.
11. Bianchi F, Bianca S, Dardanoni G, Linzalone N, Pierini A. Congenital malformations in newborns residing in the Municipality of Gela (Sicily, Italy). *Epidemiol Prev* 2006; 30: 19-26.

Eurocat pre-survey on Polluted Sites (PSs) in the area covered by the registry

Background

In the SENTIERI Project "Mortality study of residents in Italian polluted sites", conducted in 44 polluted sites of national interest, the following definitions have been adopted and used for the analysis:

The polluted sites (PSs) were classified according 9 types:

- C = production of chemical substance/s
- P&R = petrochemical plant and/or refinery
- S = steel industry
- E = electric power plant
- M = mine/quarry
- HA= harbour area
- A = asbestos/other mineral fibres
- L = landfill
- I = incinerator

Exposure was referred to both environmental exposure in PS and other exposures.

Environmental exposure in PS included Production of chemical substance/s, Petrochemical plant and/or Refinery, Steel industry, Electric power plant, Mine/Quarry, Harbour area, Asbestos/ other mineral fibres, Landfill, Incinerator. It indicates the kind of production plant or any other source of environmental emission possibly affecting residents.

Other exposures referred to air pollution, active and passive smoking, alcohol drinking, occupational exposure and socioeconomic status were considered.

Using such a scheme and definitions a short questionnaire to verify the feasibility of a similar study in Europe is proposed:

1. Name of the Eurocat Registry ……..

2. Presence of PS in the area covered by the Eurocat registry
No
Yes, specify:

…… operating time (year) from …….. to ……

…… operating time (year) from …….. to ……

…… operating time (year) from …….. to ……

3. Amount of the population residing in the smaller administrative territory (municipality, district, county, other) including the PS
Exact data …… source of information ……

Estimated data ……. way of estimation ……..

4. Availability of personal data/vital statistics in the same area
No
Yes
Source …….

5. Information of the residence address of births used as denominator for prevalence
No
No, but recoverable by GIS/geocoded map/other ……
Yes, municipality/district/county/other ……
Yes, street and number, post-code, other …….

6. Information of the residence address of malformed cases included in the Eurocat registry
No
No, but recoverable by GIS/geocoded map/other ……
No, but recoverable by health documents as medical birth record/hospital admission or discharge record/other ……
Yes, municipality/district/county/other ……
Yes, street and number, post-code, other …….

7. Information on plant's emission data in:

	Air	Soil	Surface water	Groundwater
No				
Yes				
N.K.				

8. Information on ambient contamination (measured in the known or potentially polluted area**):**

	Air	Soil	Surface water	Groundwater	Food chain	Human biomonitoring
No						
Yes						
N.K.						

9. Information on diffusion data

No

Yes by measurements, specify ……..

Yes by diffusion models, specify …….……

10. Information on other exposure data

No

Yes at aggregated level (community defined by administrative boundary)

	air pollution
	active and passive smoking
	alcohol drinking
	occupational exposure
	socioeconomic status

Yes at individual level for:

Cases		Controls (normal births)	
	air pollution		air pollution
	active and passive smoking		active and passive smoking
	alcohol drinking		alcohol drinking
	occupational exposure		occupational exposure
	socioeconomic status		socioeconomic status

11. Privacy restrictions in using personal data by the registry personnel

No

Yes, type …….

12. Willingness to participate:

No

Yes

13. Notes and considerations

……

.....