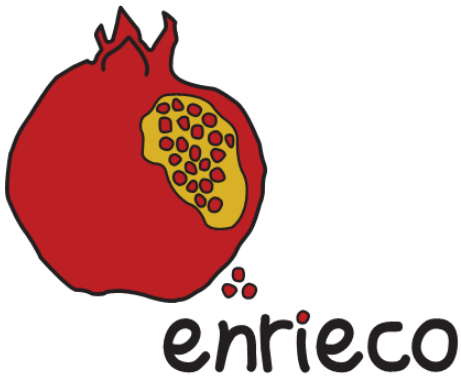
The ENRIECO Project:
ENVIRONMENTAL HEALTH **R**ISKS IN **E**UROPEAN BIRTH **CO**HORTS



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Report

Methods and Approaches of Evaluating Occupational Exposures in European Birth Cohorts

Work Package 2

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Table of Contents

Summary

Background
Occupational parental exposures before conception or during pregnancy may be hazardous to fertility and optimal child development and a number of agents, chemical, physical or related to work organization, have been suspected to interfere with normal reproduction process. The potential added value of a joint analysis of European birth cohorts to study the risk of adverse outcomes following parental occupational exposures has been acknowledged. It offers a prospective collection of occupational data for both mother and father before birth and records a number of confounders, often missing when administrative records are used. It will allow also the study of long term consequences of these exposures on child development.

Methods
The quality of occupational data collected in ENRIECO cohorts (job title, questionnaire on specific exposures, use of a job-exposure matrix or expert evaluation, biological markers of exposure) was assessed. The distribution of the main occupational groups present in five cohorts was checked. An inventory of existing job-exposure matrices was also made. Finally the feasibility of pooling occupational data was discussed and a protocol was proposed.

Results
Most Enrieco cohorts (36 out of 47) have recorded at least maternal occupation at one point in time and 20 have collected some additional information concerning a number of maternal occupational exposures . Information on paternal occupation has been recorded in 29 cohorts. Five cohorts have collected detailed information on paternal exposures, for five additional cohorts it is not clear if paternal occupational exposure has already been collected or not.
The description of the main maternal occupational groups in a selected number of cohorts show that industrial and agricultural occupations are relatively rare and that health care sector and service occupations are the ones where most occupational exposures will be found.
Applying one existing JEM to ENRIECO birth cohorts was not judged appropriate because too many different countries and work environments are represented. Building one detailed "European" JEM would require a huge amount of work for a questionable result, it could only be country-specific agent-specific JEMs.

Recommendations
For existing cohorts
The agreement was to conduct a pooled/meta-analysis of the risk of adverse outcomes in the various cohorts for selected "at risk" occupations (both mothers and fathers) during the period of vulnerability (pregnancy for mother, before pregnancy for father). Fourteen cohorts that have recorded maternal occupations held at any time during pregnancy (including collected at birth) or paternal occupation at the beginning of pregnancy and have already translated this information into (occupational) codes are eligible, 12 have already expressed their interest for this project (N= 260,000 births). A protocol for pooled analysis has been proposed.
For future cohorts
In order to avoid any influence of birth outcome on the availability of occupational information and on its quality, we recommend that data should be collected before birth. This is mandatory when questionnaires on occupational exposures are used and optional for job title.
For mothers, the period of interest is around conception and each trimester - or at least one trimester of pregnancy (depending on the health outcome studied), and before conception for fathers.
For an adequate data collection on occupational exposures job title is not sufficient. In addition, one should collect description of task, type of industry, number of hours per week, and if possible name of company, existence of biomonitoring data. Free text should be kept in the data base for additional details. A good training of coders should be organized for standardization.

Introduction

Occupational exposures differ from environmental exposures due to the nature of the compounds involved and to the level of exposure. In industrialized countries, occupational exposures during pregnancy are restricted since a number of compounds classified as developmental toxicants are officially banned from work environment or, alternatively, women are moved to a less exposed job after pregnancy recognition. There are however multiple exceptions to this rule especially in small workshops or among self-employed women. Also some women decide to hide their pregnancy as long as possible due to threat to employment. In addition, except in countries where preventive withdrawal (before pregnancy recognition) is organized, exposure may still occur during the first crucial weeks of pregnancy.
Epidemiological studies that have been conducted on the association between occupational exposures and pregnancy outcomes usually suffer from the cross-sectional or retrospective character of exposure assessment or from lack of power for rare outcomes. Use of existing birth cohorts to improve knowledge on these issues is therefore particularly relevant and should allow the study of the long term consequences of both maternal and paternal occupational exposure.
The aim of this case study was to evaluate the different occupational exposure assessments conducted in European birth cohorts and their potential use in analyses of occupational exposures and to make recommendations.

Available tools for Assessment of occupational exposures

Occupational exposures are more or less precisely defined by the knowledge of the occupation held: this is the principle of job-exposure matrices (JEM) that automatically assign a probability of exposure to a list of compounds for a given occupation. For some occupations, exposures may however vary across different settings or countries and according to the chemical composition of the products used (ie. pesticides, cleaning agents, disinfectants…). In that situation the precise identification of chemicals present in the workplace is not easy in the absence of external information about usual practice or measurements on site (atmospheric or biological monitoring). It is nevertheless usually possible to identify the chemical class of products likely to be present (i.e. organophosphate insecticides, oxygenated solvents…) or even the specific compound (i.e. mercury...). Job-specific questionnaires inquiring about specific tasks in a given job have been built for some largely female occupations such as hairdressers (Kersemaekers et al., 1998) or health-care workers (Delclos et al., 2009) providing a set of key questions allowing a classification of levels of specific exposures within these occupations.

Coding occupation
The first and simplest information characterizing an occupational environment is the job title. It is however not sufficient since it depends on the overall environment (the activity of the company where the job is held i.e. a secretary working in a garage may be indirectly exposed to exhaust fumes) and because a same job can be handled in many different ways in terms of types and frequency of occupational exposures depending of the task really performed. Ideally for a given job, both occupation and industrial activity should be recorded in order to better apprehend the work environment. Occupation title should record the maximum level of details about the work really done (task, tools, number of hours per week) and should not be limited to the level of qualification (ex: labourer).
To be able to analyze all occupations within a cohort, or to pool occupations from various cohorts and eventually to make use of Job Exposure Matrices (JEM), there needs to be a translation of job titles (and industrial activity) into a common coding system. This task is a delicate one since it may induce measurement errors, propagated all along the analysis, if done wrongly.
The choice of the coding system is also difficult. It appears that within ENRIECO cohorts, the code that has been most commonly used is ISCO (International Standard Classification of Occupations) 1988 or a national adaptation of it. As mentioned above the coding of industrial activity allows a better description of the work environment, capturing in particular indirect

exposures. Each country in Europe has a national translation of the NACE and its use is recommended whenever information on economic activity has been recorded in addition to occupation.

Using questionnaire data

Due to the prospective nature of data collection in most ENRIECO cohorts, pooling exposure data collected through self-reports can be considered if collected before knowledge of the outcome. In order to do that, individual questionnaires should be checked by experts in order to decide the subset of exposures that could be pooled. There has been an abundant literature about questionnaire validity (Tielemans, 1999; Teschke, 2002) showing that one should ask questions about usages (ie window cleaners) or working conditions rather than precise chemicals (ie glycol ethers). These questionnaires are also useful complements of the description of the work environment when applying JEMs.

Using Job Exposure Matrices

For chemical agents

A number of JEMs have been built in Europe that cover different periods of time, different types of exposure with various degrees of detail (see Annex I). The focus should be on contemporary exposures to compounds or physical constraints that may affect child development after preconceptual or prenatal exposure. The list of these compounds keeps increasing. A JEM focusing on endocrine disrupters (Van Tongeren 2002; Brouwers, 2009) would be particularly relevant to our objective.

There are however a number of challenges to overcome before applying these JEMs. First there is a need for a validation of these matrices in their different applications, that is compare the estimate of exposure provided by the JEM to some objective measure of exposure (work environment, biomarkers) (Tielemans, 1999; Garlantezec, 2010). From this exercise it may turn out that some JEMs and/or exposures will be more reliably assessed than others.
Most JEMs have been built by experts in one country relying on their knowledge of work processes in their own country. Extrapolation of this translation to all European countries if possible should require a consensus between European experts in work environment.

For non chemical agents

Assessment of physical characteristics of work has presented a challenge in epidemiologic community-based studies assessing the associations of physical load and reproductive outcomes. In particular, collection of information about physical load at work has been restricted to questionaires, since observations and direct registration techniques have seldom been used. Within other areas of work-related exposure job exposure matrices are often applied. Such matrices provide exposure information based on occupational title and they present a promising source of exposure estimates in large-scale epidemiologic studies. However, with respect to physical load there are very few examples of job-exposure matrices for physical load (Bosma et al. 2003, Leino-Arjas 2004). So far, their use in such research fields has been rather limited.
A first step in the development is to compare existing questions used to assess characteristics of physical load. Most often, questions on physical load at work concern manually handling loads, awkward postures, prolonged periods of standing. Typically a four-point scale is used with ratings 'seldom or never', 'now and then', 'often', and 'always' during a regular workday and subjects with answers ‘often’ or ‘always’ classified as exposed (Elders et al., 2001). The evaluation of comparability across studies will be guided by the consensus document of Griffith et al 2008.
The second step is the within- and between job evaluation within each birth cohort. For each mother with a paid job occupation shortly before or during pregnancy was classified at 3 to 5 digit level according to the International Standard Classification of Occupations 1988 or comparable schemes. For each job the proportion of exposed subjects and the average exposure will be the exposure measures of interest. The average exposure will be derived from scores given to the exposure rank in the answering scale. The statistical analysis will evaluate

within- and between job variance components for jobs coded at 5 digits, at 4 digits, and at 3 digits. This allows to evaluate the sensitivity of the JEM for detail of occupation.
The third step is an evaluation across different birth cohorts in order to evaluate consistency of jobs with high exposure and high proportion of exposed subjects. This will facilitate insight into the exportability of a JEM from one birth cohort to another birth cohort.

Strengths of general population cohorts for the study of occupational exposures

Several epidemiological studies have been conducted to investigate reproductive risks in specific occupational cohorts such as dry cleaners (Doyle et al., 1997), semiconductor workers (Swan SH et al., 1995), hairdressers and beauticians (Halliday-Bell et al., 2009). Usually this requires pooling data relative to groups of workers from different companies or countries and the study design is often a retrospective cohort. Other designs pertinent for rare outcomes are case-control studies based on birth defects registries for instance.
The principal strength of cohorts from the general population such as ENRIECO cohorts is the prospective collection of occupational data before birth. This is especially important when one wants to make use of exposure data collected by questionnaire. The prospective collection of health data will allow the study of long term consequences of preconceptual and prenatal occupational exposures. It will in particular allow to explore with reasonable power, data relative to father's occupational exposures that have not received much attention until now.
Among the weaknesses is the fact that some occupational groups, such as industrial and agricultural groups, may not be well represented in these cohorts. In addition similar occupations in different European countries may use different agents and mixtures.

Inventory of existing occupational data and interest in ENRIECO cohorts

Most ENRIECO cohorts (36 out of 47) have recorded at least maternal occupation at one point in time (Table 1 and 2a) and 20 have already collected some additional information concerning some maternal occupational exposures (Table 2b). Information on paternal occupation has been recorded in 29 cohorts (Table 3a). Five cohorts have collected detailed information on paternal exposures, for five additional cohorts it is not clear if paternal occupational exposure has already been collected or not (Table 3b).

Criteria for selecting cohorts that could be included in a common work on occupational exposures are the following:
- Timing of data collection
In order to avoid any influence of birth outcome on the availability of occupational information and on its quality, we recommend that data should be collected before birth. This is mandatory when questionnaires on occupational exposures have been used and optional for job title.
This is the case for 17 cohorts for mothers' occupational exposures, 6 cohorts for fathers' occupational exposures (uncertain for 5 cohorts).
- Period covered
For mothers, the period of interest is around conception and each trimester - or at least one trimester of pregnancy (depending on the health outcome studied), and before conception for fathers.
- Status of information on occupation
Coding of occupations should be completed or on-going. If a checklist of occupations or activity sectors has been used, data collection form should be provided and checked to see if usable. Similarly, questionnaires collecting information on occupational exposures should be checked for comparability.

The main occupations potentially entailing occupational exposures and held by at least 1% of the working mothers are described below for a selected number of cohorts.

Main occupations (potentially entailing occupational exposures) present in six ENRIECO cohorts and proportion of working mothers concerned

	ABCD (n = 8266)	Generation R (n=9778)	INMA (n=2269)	INUENDO (n=2269)	PELAGIE (n=3421)	RHEA (n=1606)
Chemists/ Biologists	-	-	-	-	2.5%	-
Healthcare workers	5%	4.7%	3.5%	12%	14%	3%
Housekeepers /cleaners	0.8%	2.5%	5.8%	-	6%	2.3%
Hairdressers	1%	0.5%	1.7%	-	1.6%	2.6%
Daycare workers	3.2%	3.1%	-	-	-	-
Cooks-bartenders	1.6%	1%	3.8%	2.7%	-	4.4%
Agricultural workers (incl. gardeners)	-	-	-	-	1.5%	2.4%

less than 1%

As expected, this table shows that investigation of maternal occupational risk factors in ENRIECO cohorts will mainly relate to service occupations.

Recommendations

Recommendations for future collection of occupational data

In addition to the criteria mentioned above concerning the timing of data collection and period covered, additional recommendations were made. For an adequate data collection on occupational exposures job title is not sufficient. In addition, one should collect description of task, type of industry, number of hours per week, and if possible name of company, existence of biomonitoring data. Free text should be kept in the data base for additional details. A good training of coders should be organized for standardization.

Plans for future work with existing ENRIECO cohorts

A number of cohorts respecting the inclusion criteria described above are willing to participate in a "pooling exercise" with the objective of assessing the association between parental occupational exposures and the risk of adverse birth outcomes and impairment of child development.

Lessons from the Utrecht meeting

In the Utrecht meeting, experts in occupational exposure assessment (Joelle Févotte, Lyon; Hans Kromhout, Utrecht; Nels Roeleveld, Nijmegen; Martie Van Tongeren, Edinburgh) were invited to discuss the opportunity of applying or adapting an existing JEM, or building a new JEM applicable to the various cohorts. Invited experts felt that it would not be appropriate to apply one existing JEM to ENRIECO birth cohorts because these cohorts cover different countries and potentially different work environments. The experience of Dutch scientists in the update of the "Van Tongeren JEM" (see Annex I) resulting in the creation of the "Brouwers JEM" (see Annex II) shows how information varies according to time period and country. This may be especially true for certain compounds (phthalates for instance) for which occupation is not the main source of exposure. Building one detailed "European" JEM would require a huge amount of work for a questionable result. It should be a country-specific agent-specific JEM. The agreement was to conduct a meta-analysis of the risk of adverse outcomes in the various cohorts for selected "at risk" occupations (both mothers and fathers) during the period of vulnerability (pregnancy for mother, before pregnancy for father).

Protocol for a meta-analysis

A draft protocol of the proposed Meta-analysis was circulated in July 2010 (see Annex II). The main options need to be further discussed, in particular concerning the need and the feasibility to centralize raw data, taking into account lessons from the two Case studies that did this pooling exercise (Asthma, POP and Birth Weight).

Tools for occupational exposure assessment

A list of ISCO88 codes describing 12 occupational sectors to be investigated in priority for maternal or paternal occupations is in preparation by Joelle Févotte in Lyon. It includes 1) medical ; 2) social + preschool ; 3) scientific occupations (laboratories, chemical industry…); 4) electricity/electronics ; 5) food production ; 6) cleaning ; 7) agriculture ; 8) hairdressing/beauticians; 9) printing; 10) mining; 11) transport; and 12) welding sectors.

In parallel, assignment of 14 tasks or exposure mixtures to individual ISCO88 codes (in order to propose a "gross" European JEM) is also in preparation. The tasks chosen include: 1) cooking; 2) housecleaning; 3) disinfection; 4) laboratory work; 5) chemical work; 6) biological risks; 7) pharmaceutical compounds; 8) cosmetics; 9) solvents (incl use of paints, inks, dyes, glues, varnishes); 10) food additives; 11) pesticides; 12) ionizing radiations; 13) electric welding; 14) second-hand smoke. This "E"JEM will then be circulated to experts in occupational exposure assessment for validation and to specialists in occupational environment of the participating cohorts.

Operational definition of physical factors (exposure to noise, heat), physical load (handling burden, standing…), factors related to work organization (shift work, night work…) need to be built to complete the tools applicable for occupational exposure assessment. This part could be

developed under the responsibility of Generation R (Lex Burdorf) and INMA (AM Garcia) scientists.

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association between maternal occupational exposure and hypospadias. Annals Occup Hyg 46:465-477,2002

Tables

Table 1: Description of ENRIECO birth cohorts evaluating occupational exposure.

Cohort		Country	Calendar period of enrolment	Enrolment			N Children	N Mothers	N Fathers
				Pregnancy	Birth	Posnatal			
1.	Aarhus	Denmark	1990-on going	√	-	-	93000	93000	-
2.	ABCD	Netherlands	2003-2004	√	-	-	7863	8266	-
3.	ALSPAC	UK	1991-1992	√	-	-	14062	14541	9957
4.	APREG	Hungary	2000-2006	√	-	-	2800	2800	-
5.	BAMSE	Sweden	1994-1996	-	√	√	4089	4089	4089
6.	BiB	UK	2007-2010	√	-	-	13000	13000	3000
7.	C. Faroe I	Faroe Islands	1986-1987	√	-	-	1022	1022	?
8.	C. Faroe II	Faroe Islands	1994-1995	√	-	-	182	182	?
9.	C. Faroe III	Faroe Islands	1997-2000	√	-	-	656	656	?
10.	C. Faroe V	Faroe Islands	2007-2009	-	√	-	491	491	250
11.	CONER	Italy	2004-2005	-	√	-	654	651	593
12.	Czech EC	Czech Republic	1994-1999	-	√	-	4883	6866	-
13.	DNBC	Denmark	1996-2002	√	-	-	96986	100418	?
14.	Duisburg	Germany	2000-2003	√			234	232	-
15.	EDEN	France	2003-2006	√			1873	2002	1850
16.	EFESE/ELFE	France	2011-2012	-	√	-	20000	20000	20000
17.	FLEHS	Belgium	2002-2004	-	√	-	1196	1200	-
18.	Generation R	Netherlands	2001-2005	√	√	-	9778	9778	6748
19.	Generation XXI	Portugal	2004-2006	√ (n=349)	√		8654	8493	4351
20.	HUMIS	Norway	2002-2009	-	-	√	2500	2400	?
21.	INMA	Spain							
	Asturias		2004-2007	√	-	-	485	494	494
	Gipuzkoa		2006-2008	√	-	-	600	639	626
	Granada		2000-2002	-	√	-	668	668	668
	Menorca		1997-1998	√	-	-	482	475	?
	Ribera Ebre		1997-1999	-	√	-	102	102	102
	Sabadell		2004-2006/2007	√	√	-	749	787	657
	Valencia		2004-2005	√	-	-	787	855	827
22.	INUENDO	Greenland, Sweden, Poland, Ukraine	2002-2004	√	-	-	1322	2269	1172
23.	KANC	Lithuania	2007-2009	√	-	-	4000	4000	4000
24.	KOALA	Netherlands	2000-2003	√	-	-	2834	2834	2700
25.	LUKAS	Finland	2002-2005	√	-	-	442	442	418
26.	MAS	Germany	1990	-	√	-	1314	1314	1250

27.	MoBa	Norway	1999-2008	√	-	-	107400	107000	72000
28.	NINFEA	Italy	2005- on going	√	-	-	7500	7500	-
29.	NFBC 66	Finland	1965-1966	√	-	-	12058	12055	12000
30.	NFBC 86	Finland	1985-1986	√	-	-	9432	9362	9000
31.	PCB cohort	Slovakia	2001-2003	-	√	-	1134	1134	1134
32.	PÉLAGIE	France	2002-2006	√	-	-	3460	3421	3421
33.	REPRO PL	Poland	2007-2011	√	-	-	1300	1300	-
34.	RHEA	Greece	2007-2008	√	-	-	1500	1606	1376
35.	SNiP	Germany	2003-2008	-	√	-	4840	4783	?
36.	The Leicester RC	UK	1996-1997	-	-	√	5400	4247	4247

Table 2a: Assessment of maternal occupation in ENRIECO birth cohorts				
Cohort	Type of instrument	Coding and Status	Timing of data collection	Period covered
Aarhus	Job title		1rst T	1st T
ABCD	Job title	CBS-SBC 1992 (eq ISCO 1988)	2nd T	Before pregnancy?, 1st T
ALSPAC	Job title	SOC1990 (partly done for pregnancy)	3rd T and after birth	Before pregnancy, 1st, 2nd , 3rd T
APREG	Job title		1rst T	Before pregnancy, 1st, 2nd T, 3rd T
BAMSE	Job title	Nordic Occupant coding (NYK)	At birth, 8 years	Current occupation
BiB	Job title	SOC2000	3rd T	Current occupation
C. Faroe I	Job title	-	At birth	1st, 2nd, 3rd T
C. Faroe II	Job title	-	At birth	1st, 2nd, 3rd T
C. Faroe III	Job title	-	At birth	1st, 2nd, 3rd T
C. Faroe V	Job title	-	At birth	1st, 2nd, 3rd T
CONER	Checklist Occupations (nsp)	-	At birth	Before pregnancy, 1st, 2nd, 3rd T
Czech EC	Job title		At birth	Before pregnancy
DNBC	Job title	D ISCO (Danish version)	2nd T (16w) 3rd T (30w)	Before pregnancy and 1st T 3rd T
Duisburg	Job title	-	3rd T	Before pregnancy, 3rd T
EDEN	Job title	-	End of 2nd T	Before pregnancy, 1st, 2nd T
EFESE/ELFE	planned	-	At birth	
FLEHS	Check list activity sectors: textile industry, lab work, chemical industry, metal industry, rubber/ plastic, wood industry, paper industry,		At birth	Pregnancy?
Generation R	Job title	WHO standard classification of occupations	2nd trimester	2nd trimester
Generation XXI	Job title	ISCO	At birth	Current occupation
HUMIS	Job title	ISCO88 + Industrial activity (subsample?)	1rst T (medical record??)see	1st T

			above inclusion postnatal	
INMA				
Asturias	Job title	ISCO 88, CNO-94, CNAE-93	1st T 3rd T	Before pregnancy, 1st T 2nd , 3rd T
Gipuzkoa	Job title	ISCO 88, CNO-94, CNAE-93	1st T 3rd T	Before pregnancy, 1st T 2nd , 3rd T
Granada	Job title	ISCO 88, CNO-94, CNAE-93	At birth	Before pregnancy, 1st, 2nd , 3rd T
Menorca	Job title	ISCO 88, CNO-94, CNAE-93	One time during pregnancy	1st, 2nd , 3rd T
Ribera Ebre	Job title	ISCO 88, CNO-94, CNAE-93	At birth	?
Sabadell	Job title	ISCO 88, CNO-94, CNAE-93	1st T 3rd T	Before pregnancy, 1st T 2nd , 3rd T
Valencia	Job title	ISCO 88, CNO-94, CNAE-93	1st T 3rd T	Before pregnancy, 1st T 2nd , 3rd T
INUENDO	Job title	ISCO? + NACE	During pregnancy	Before pregnancy + pregnancy?
KANC	Job title	ISCO88	3rd T	Before pregnancy, 1st T, 2nd T, 3rd T
KOALA	Job title		1rst T 3rd T (+ after birth)	1st T 3rd T
LUKAS	Job title		1rst T, 2nd T, 3rd T	5 years during pregnancy, 3rd T
MAS	Job title		At birth	Current occupation
MoBa	Job title	Coding planned	2nd T	1st T, 2nd T
NINFEA	Job title + questions occupations (cleaning, hairdressing, dry cleaning, health care workers, gardening/farming, photographic printing	ISCO + ISIC planned	1st-2nd T	Before pregnancy?, beginning of pregnancy, last job during pregnancy
NFBC 66	Job title	Statistics Finland	2nd T	1st T
NFBC 86	Job tittle	Statistics Finland	1st T	1st T
PCB cohort	Job title		At birth	Before

				pregnancy, 1st, 2nd T
PÉLAGIE	Job title	ISCO68 + ISIC	1st T 2 years after birth (n=1506)	Present or previous occupation 2nd, 3rd T
REPRO PL	Job title		1st T 2nd T 3rd T	Before pregnancy, 1st T 2nd T 3rd T
RHEA	Job title	ISCO88	1st T 3rd T	Before pregnancy, 1st T 3rd T
SNiP	Job title		At birth	Before pregnancy, 1st, 2nd, 3rd T
The Leicester RC	Job title		At birth	

Table 2b: Assessment of maternal occupational exposures in ENRIECO birth cohorts			
Cohort	Type of instrument: Agents	Timing of data collection	Period covered
Aarhus	planned		
ABCD	Questionnaire: working hours, standing/walking, physical load, job strain Questionnaire: cytostaics, biological agents, anesthetics, solvents, metals, pesticides, X-ray, hours working, physical workload, hours standing + JEM	2nd trimester 5 years after pregnancy	1rst trimester 1rst trimester, 2nd trimester, 3rd trimester
ALSPAC	Check list self report: hairspray, carpet cleaner etc…	3rd trimester	Before pregnancy, 1rst trimester, 2nd trimester, 3rd trimester
APREG	Questionnaire: ?	?	?
BiB	JEM Brouwers	3rd trimester	current
DNBC	Questionnaires specific for some occupations: painters, greenhouse workers, farm workers, hospital workers, laboratory workers, daycare institutions, graphic industry + JEM	1rst trimester	1rst trimester
Duisburg	Questionnaire: Oil residues; benzole; flying ash; halogenated alipathic hydrogencarbons; wood preservatives; hydraulic liquids; biocids; heavy metals; products of tar coatings; herbicides; transformer liquids; softeners for plastics.	3rd trimester	Before pregnancy 3rd trimester
EDEN	Questionnaire: Exposure to heat, radiations, anaesthetic products, pesticides, paints, industrial cleaning, metal welding, physical strain, stress at work (woman).	End of 2nd T	Before pregnancy, 1rst T
EFESE/ELFE	Biological monitoring	At birth	
FLEHS	Questionnaire: Cleaning products, pesticides, stains, solvents, fuel damps, hair-care products, dry cleaning products.	At birth	Pregnancy
Generation R	JEMs (Van Tongeren, Browers) + handling of burdens Questionnaire : list JEMs + nb hours per week Urine samples (N=100): pesticides, phthalates, bisphenol A, PCB 153	2nd trimester 1rst T, 2nd T, 3rd T	1rst-2nd T Pregnancy?
HUMIS	Questionnaire: Metals (lead, chrome, arsenic, mercury,...), gasoline, disinfectants, pesticides, paints, industrial syes	2nd T (18w)	Last 6 months (=before pregnancy, 1rst T, 2nd T)

	or ink, oils, photographic chemicals, chemotherapy substances, substances used in welding and soldering, etc.		
INMA			
Asturias	Questionnaire: Solvents, benzene, lead, mercury, cadmium, arsenic, formaldehyde, oxide nitrate, oxide ethylene, antineoplasics, EMF, ionizing radiations, etc.	1st T 3rd T	1st T 3rd T
Gipuzkoa	Questionnaire: Solvents, benzene, lead, mercury, cadmium, arsenic, formaldehyde, oxide nitrate, oxide ethylene, antineoplasics, EMF, ionizing radiations, etc.	1st T 3rd T	1st T 3rd T
Granada	Questionnaire: Metals, paints, dyes, anaesthetics, radiations, photographical chemical products, pesticides, solvents, hair sprays, cleaning products, etc. + JEM (nsp)	At birth	Before pregnancy, 1st, 2nd ,3rd T
Sabadell	Questionnaire: Solvents, benzene, lead, mercury, cadmium, arsenic, formaldehyde, oxide nitrate, oxide ethylene, antineoplasics, EMF, ionizing radiations, etc.	1st T 3rd T	1st T 3rd T
Valencia	Questionnaire: Solvents, benzene, lead, mercury, cadmium, arsenic, formaldehyde, oxide nitrate, oxide ethylene, antineoplasics, EMF, ionizing radiations, etc.	1st T 3rd T	1st T 3rd T
INUENDO	Questionnaire: Paints, varnish, lacquer, glues, solvents, welding fumes, metal dusts, fumes, engine exhaust, pesticides, fungicides, insecticides, weedkillers, anaesthetic gases, radioactivity or x-rays, cytostatic drugs.?? For mothers also?	During pregnancy	Before pregnancy
KANC	Questionnaire: Solvents, paints.	3rd T	Before pregnancy
MoBa	Questionnaire: Lead or mercury vapours, chrome, gasoline, disinfectants, paint, industrial dyes, photographic chemicals, substances used in welding or soldering, anaesthetic gases.	1st T	Last 6 months
NINFEA	Questionnaire: lead, chromium, diesel exhausts, pesticides, paints, solvents, inks, industrial oils and lubricants, formaldehyde, chemotherapic substances, anesthetic drugs, any other chemicals, shift	1st -2nd T	Before pregnancy?, beginning of pregnancy, last job during pregnancy

	working, physical demanding work + JEM (Milan) planned		
NFBC 66	Questionnaire: glues, lead, fuels, paints, varnish, colour substance, solvents (e.g thinner, turpentine), pesticides	2nd T	1st T
PÉLAGIE	Questionnaire: solvent containing compounds, welding, EMF, standing, handling weight, shift work + JEM (solvents): Milan	1st T	Current occupation
REPRO PL	Questionnaire: Solvents, X, electromagnetic fields, disinfection substances, heavy metals, biological samples (urine, blood), pesticides, paintings.	1st T 2nd T 3rd T	1st T 2nd T 3rd T
RHEA	Questionnaire: Noise, shift work, pesticides, farm work Biomarkers: urine (pesticides, phthalates, BFR) Blood: BFR, metals	1st T	1st T

Table 3a: Assessment of paternal occupation in ENRIECO birth cohorts				
Cohort	Type of instrument	Coding and Status	Timing of data collection	Period covered
ABCD	Job title	CBS-SBC 1992 (eq ISCO 1988) Planned june 2011 (N=5000)	2nd T	Before pregnancy, 1st T
ALSPAC	Job title	SOC1990 (partly done for pregnancy)	3rd trimester and after birth	Before pregnancy, 1st, 2nd T, 3rd T
BAMSE	Job title	Nordic Occupant coding (NYK)	At birth, 8 years	Current occupation
BiB	Job title	SOC2000	3rd T	Current occupation
C. Faroe I	Job title		At birth	1rst, 2nd, 3rd T
C. Faroe II	Job title		At birth	1rst, 2nd, 3rd T
C. Faroe III	Job title		At birth	1rst, 2nd, 3rd T
C. Faroe V	Job title		At birth	1rst, 2nd, 3rd T
CONER	Checklist Occupations		At birth	Before pregnancy, 1rst, 2nd, 3rd T
Czech EC	Job title		At birth	Before pregnancy
DNBC	Job title	D ISCO (Danish version)	2nd T (16w)	1rst T
EDEN	Job title		pregnancy	Before pregnancy
EFESE/ELFE	Planned?			
Generation R	Job title ??	WHO standard classification of occupations	2nd trimester	2nd trimester
Generation XXI	Job title	ISCO	At birth	Current occupation
HUMIS	Job title	ISCO88 + Industrial activity (subsample?)	1rst T	1rst T
INMA				
Asturias	Job title	ISCO 88, CNO-94, CNAE-93	1st T	Before pregnancy, 1st T
Gipuzkoa	Job title	ISCO 88, CNO-94, CNAE-93	1st T	Before pregnancy, 1st T
Granada	Job title	ISCO 88, CNO-94, CNAE-93	1st T	Before pregnancy, 1st
Menorca	Job title	ISCO 88, CNO-94, CNAE-93	One time during pregnancy	1st, 2nd , 3rd T
Ribera Ebre	Job title	ISCO 88, CNO-94, CNAE-93	At birth	?
Sabadell	Job title	ISCO 88, CNO-94, CNAE-93	1st T	Before pregnancy, 1st T

Valencia	Job title	ISCO 88, CNO-94, CNAE-93	1st T	Before pregnancy, 1st T
INUENDO	Job title	ISCO? + NACE	During pregnancy	Before pregnancy + pregnancy?
KANC	Job title	ISCO88	3rd T	Before pregnancy, 1rst T, 2nd T, 3rd T
KOALA	Job title		At 5-7 years postpartum	
LUKAS	Job title		1 year after birth	5 year period before pregnancy
MAS	Job title		At birth	Current occupation
MoBa	Job title	Coding planned	2nd T	1st T, 2nd T
NFBC 66	Job title	Statistics Finland	2nd T	1st T
NFBC 86	Job tittle	Statistics Finland	1st T	1st T
PCB cohort	Job title		At birth	Before pregnancy
PÉLAGIE	Job title	ISCO + ISIC	1st T	Beginning of pregnancy
RHEA	Job title	ISCO88	1st T 3rd T	Before pregnancy, 1st T 3rd T
SNiP	Job title		At birth	Before pregnancy, 1st, 2nd, 3rd T
The Leicester RC	Job title		At birth	

Table 3b: Assessment of paternal occupational exposures in ENRIECO birth cohorts			
Cohort	Type of instrument: Agents	Timing of data collection	Period covered
ALSPAC	Check list self report: hairspray, carpet cleaner etc…	3rd T	Before pregnancy, 1rst T,2nd T, 3rd T
BiB	JEM applicable?? (see mother)	3rd T	current
DNBC	Questionnaires specific for some occupations: painters, greenhouse workers, farm workers, hospital workers, laboratory workers, daycare institutions, graphic industry + JEM	1rst trimester 1rst trimester	1rst trimester 1rst trimester
EDEN	Questionnaire: Exposure to heat, radiations, anaesthetic products, pesticides, paints, industrial cleaning, metal welding, physical strain	Pregnancy	Before pregnancy
Generation R	Same as mother??		
HUMIS	Same as mother??		
INUENDO	Questionnaire: Paints, varnish, lacquer, glues, solvents, welding fumes, metal dusts, fumes, engine exhaust, pesticides, fungicides, insecticides, weedkillers, anaesthetic gases, radioactivity or x-rays, cytostatic drugs.?? For mothers also?	During pregnancy	Before pregnancy
KANC	Same as mother	3rd T	Before pregnancy
MoBA	Same as mother?		
NFBC 66	Same as mother?	2nd T	1st T

ANNEX I - INVENTORY OF AVAILABLE JOB EXPOSURE MATRICES

Characteristics of job-exposure matrices (JEM) available are listed below starting with the most recently published. All of them have been built in Europe except Hoar JEM which is cited here because it has been applied to European populations. All except one apply to the general population. One industry-specific JEM is cited ("Health-Care workers JEM"), although built in the US, because of its potential usefulness for future data collection.
Except for MatGéné and Milan JEMs which use international codes, all other JEMs use national codes: UK codes at different periods or Finnish codes. Most JEMs assessed exposure to chemical agents, FINJEM is the only JEM assessing psychosocial stress factors. The three more recent matrices assess exposure to a limited number of agents such as endocrine disrupters or solvents, but these agents appear to be particularly relevant to the study of female exposures and their impact on reproductive outcomes. Some older ones (Milan JEM) have also had recent applications in this domain of research.

I- General population JEMs

1- Name: Brouwers JEM (updated version of van Tongeren JEM)
Reference: Brouwers MM, van Tongeren M, Hirts AA, Bretveld RW, Roeleveld N. Occupational exposure to potential endocrine disruptors: further development of a job exposure matrix. *Occupational and Environmental Medicine* 66:607-614, 2009
Job codes: UK SOC2000
Agents (10): polycyclic aromatic hydrocarbons, polychlorinated organic compounds, pesticides, phtalates, organic solvents, bisphenol A, alkylphenolic compounds, brominated flame retardants, metals, miscellaneous.

2- Name: van Tongeren JEM
Reference: van Tongeren M, Nieuwenhuijsen MJ, Gardiner K, Armstrong B, Vrijheid M, Dolk H, Botting B. A job-exposure matrix fro potential endocrine-disrupting chemicals developed for a study into the association between maternal occupational exposure and hypospadias. *Annals of Occupational Hygiene* 46:465-477,2002.
Job codes: OC80, presumably UK 1980 version of Categories of Occupations (348 job titles)
Agents(7): pesticides, polychlorinated organic compounds, phtalates, alkylphenolic compounds, bi-phenolic compounds, heavy metals, other substances (parabens, butylated hydroxyanisole, phytoestrogens and synthetic steroids).
Recent application : Ormond G, Nieuwenhuijsen M, Nelson P, Toledano MB, Iszatt N, Geneletti S, Elliott P. Endocrine disruptors in the workplace, hair spray, folates supplementation, and risk of hyspospadias: case-control study. *Environmental Health Perspectives* 117:303-307, 2009.

3- Name: MatGéné (Institut de Veille Sanitaire – France)
Reference : http://www.invs.sante.fr/surveillance/matgene/index.htm (may 2009)
Job codes : ISCO-ILO 1968 and ISIC-UN 1975 (or French codes also available)
Agents:
. Solvents: 1) petroleum-based (5): benzene; other aliphatic mineral spirits; motor gasoline; white- spirits and other light aromatic mixtures; gasoil, fuels and kerosene. 2) chlorinated (6): trichloroethylene, tetrachloroethylene, methylene chloride, chloroforme, carbon tetrachloride, at least one.
. Dusts: leather, flour, cement.
. Fibers: Mineral wool
. Pesticides: arsenic-based

4- Name: FINJEM
Reference: Kauppinen T, Toikkanen J, Pukkala E. From cross-tabulations to multipurpose exposure information systems: a new job-exposure matrix. *American Journal of Industrial Medicine* 33:409-417, 1998.

Job codes: Finnish Census Classification of Occupations
Agents (74): physical (9), chemical (47), microbiological (2), ergonomic (8), psychosocial stress factors (8)
Recent application: Alguacil J, Porta M, Kauppinen T, Malats N, Kogevinas M, Carrato A. Occupational exposure to dyes, metals, polycyclic aromatic hydrocarbons and other agents and K-ras activation in human exocrine pancreatic cancer. *International Journal of Cancer* 107:635-641, 2003.
NB: a translation of this matrix for Spain is now available (see INMA cohort)

5- Name : Milan JEM
Reference : Ferrario F, Continenza D, Pisani P, Magnani C, Merletti F, Berrino F. Description of a job exposure matrix for sixteen agents which are or may be related to respiratory cancer. In: Hogstedt C, ed. *Progress in Occupational Epidemiology*. Amsterdam: Elsevier Publications Company, pp. 379-382, 1988.
Job codes: ILO 1968 and ISIC 1975
Agents (16): asbestos, arsenic, chromium and its compounds, diethylsulphate, formaldehyde, isopropyl alcohol, leather dust, man-made mineral fibers (MMMF), naphthalene, nickel and its compounds, PAH, sulphuric acid, wood dust, dusts (other than asbestos, MMMF, leather and wood dust), gases, organic solvents.
Recent application: Garlantezec R , Monfort C, Rouget F, Cordier S. Maternal occupational exposure to solvents and congenital malformations : a prospective study in the general population. *Occupational Environmental Medicine* 66:456-463, 2009.
Berrino F, Richiardi L, Boffetta P et al. Occupation and larynx and hypopharynx cancer : a job-exposure matrix approach in an international case-control study in France, Italy, Spain and Switzerland. *Cancer Causes and Control* 14:213-223, 2003.

6- Name: Pannett JEM
Reference: Pannett B, Coggon D, Acheson E. A job-exposure matrix for use in population based studies in England and Wales. British Journal of Industrial Medicine 42:777-783, 1985.
Job codes: Registrar's General Classification of occupations (1966) and Classification of industries (1968)
Agents (49): chemical, physical and biological agents
Recent application: Seidler A, Raum E, Arabin B, Hellenbrand W, Walter U, Schwartz FW. Maternal occupational exposure to chemical substances and the risk of infants small-for-gestational-age. *American Journal of Industrial Medicine* 36:213-222, 1999.

7- Name: Hoar JEM
Reference: Hoar SK, Morrison AS, Cole P et al. An occupational linkage system for the study of occupational carcinogens. *Journal of Occupational Medicine* 22:722-726, 1980.
Job codes: US occupation code
Agents (334)
Recent application: Tielemans E, Heederik D, Burdorf A at al. Assessment of occupational exposures in a general population: comparison of different methods. *Occupational Environmental Medicine* 56:145-151, 1999.

II- Industry specific JEMs

8- Name: Health-Care Workers JEM
Reference: Delclos L, Gimeno D, Arif AA, Benavides FG, Zock J-P. Occupational exposures and asthma in health-care workers: comparison of self-reports with a workplace-specific job exposure matrix. *American Journal of Epidemiology* 169: 581-587, 2009.
Job codes: Job-practice setting combinations (139)
Agents (5): use of cleaning products/disinfectants, use of powdered latex gloves, administration of aerosolized medications, use of adhesives or solvents, exposure to gases/vapors

ANNEX II - Pooled/Meta-analysis of the risk of adverse birth outcomes associated with occupational exposure across ENRIECO birth cohorts

Draft Protocol

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July 2010

Background

Occupational parental exposures before conception or during pregnancy may be hazardous to fertility and optimal child development and a number of agents, chemical, physical or related to work organization, have been suspected to interfere with normal reproduction process (Burdorf, 2006; Figa-Talamanca, 2006).

The potential added value of a joint analysis of European birth cohorts to study the risk of adverse outcomes following parental occupational exposures has been acknowledged. It offers a prospective collection of occupational data for both mother and father before birth and records a number of confounders, often missing when administrative records are used. It will allow also the study of long term consequences of these exposures on child development.

Assessment of occupational exposures in ENRIECO cohorts has been summarized. It is very diverse and ranges from simple occupational title, to questionnaires on specific exposures, application of job-exposure matrices or biological markers of exposure. The feasibility of applying a "European job-exposure matrix (JEM)" focused on some compounds of interest (i.e endocrine disrupters) to existing data has been discussed in a Workshop convened in Utrecht on May 25, 2010 where invited experts of JEMs were present. The consensus was that applying a common JEM to work situations covering different time periods and different European countries as they occur in ENRIECO cohorts would not be appropriate and therefore the effort of building such a JEM was not justified. It was proposed instead to perform a meta-analysis of risk of adverse reproductive outcomes for a number of groups of occupations potentially "at risk" with a parallel evaluation of broad classes of exposures for these occupations in the European countries represented.

Objectives

The general objective of the project will be to assess the relationship between parental occupational exposure and the risk of adverse birth outcomes and impairment of child development.

A pilot meta-analysis will first be conducted to estimate risks of decrease in duration of gestation, intrauterine growth retardation and stillbirth in a number of selected maternal and paternal occupation groups.

The feasibility of studying the impact of physical factors (noise, heat), physical load (handling burden, standing…) or work organization (shift work, night work…) will also be evaluated.

Cohorts included

Selection criteria

Cohorts having recorded maternal occupations held at any time during pregnancy (including collected at birth) or paternal occupation at the beginning of pregnancy and having already translated this information into (occupational) codes are eligible.

Fourteen cohorts are eligible according to these criteria (Table A), 12 have already expressed their interest for this project. ALSPAC and BAMSE are to be approached.

Outcomes variables (Table B)

Stillbirth(SB)
Definition of stillbirth varies according to countries with criteria relative to birthweight or duration of gestation or both. For example, stillbirth in France is defined as "*any 'child' expelled or issued forth from its mother after the 22th week of pregnancy or weighting more than 500 grams that did not breathe or show any other signs of life".* Each cohort will have to provide its definition of stillbirth.

Gestational Age (GA)
The estimation of gestational age (or gestational duration) can be based on the last menstrual period (LMP) or ultrasound measurements (US) (before 20 weeks of gestation).
- Dating based on LMP is the most widely available, simple, low cost method of estimating GA (GA=(date of delivery – LMP date)/7). Limitations associated with LMP dating include variation of the normal cycle length between women, irregular menstrual cycles or the possibility that an ovulation may not adhere to the often presumed 14-day interval for onset of ovulation, the early bleeding in pregnancy that may often be mistaken for a delayed menstrual period thereby offsetting the date of LMP by as much as 4 weeks and finally the errors in the woman's recall of her date of last menstrual period. In addition, if occupational exposure affects ovarian function and the duration of the menstrual cycle, using the LMP would be problematic (Windham et al. 2003).
- To calculate GA with the use of ultrasounds, foetal measurements are compared with a GA-specific reference. Ultrasound-based estimates of GA (conducted before 20 weeks' gestation) are considered more accurate than LMP-based estimates derived from irregular cycles (Olsen and Basso 2005). A limitation of this method is the fact that if the occupational exposure or environmental pollutant considered can restrict fetal growth as early as the first trimester, correcting GA using first-trimester ultrasound measurements will erroneously shorten the GA of these small-for gestational-age fetuses and introduce systematic bias.
- In usual practice, the estimation of GA results from the combination of information from the LMP and US made by the clinician (at the beginning of the pregnancy and at birth).

In the European ESCAPE/HiWate joint protocol, R. Slama and M. Kogevinas propose to adopt the following decision process to determine GA :
- If the LMP-based GA estimation is consistent by 7 (14 days?) or less days with the US-based estimation (US realized before <20 weeks of gestation), take the LMP-based estimation.
- If estimations are inconsistent by more than 7 days, or LMP date is unavailable, take the US-based estimation
- If US results are not available, take the available GA estimated in each cohort from the medical records. The obstetrician estimation is based both source on information and corrected for long durations.

A variable will indicate the type of GA estimation finally used in the cohorts. If several methods of estimation are available in some cohorts, some sensitivity analyses may be performed.

It is to note that GA estimation impacts several other indicators (SGA variables, preterm delivery, subgroups of premature rupture of membranes).

Birth weight (BW)
In addition to birthweight, a number of outcomes can be defined. A low BW (LBW) is generally defined using WHO criteria as a BW below 2500g. It is the result of either premature birth or intrauterine growth retardation. A very low birth weight (VLBW) is defined as BW below 1500g. Term low birth weight (TLBW) is defined as a low birth weight (<2500 g) despite a gestational age greater than 37 weeks.

Head Circumference (HC)
Abnormal head circumference at birth can reflect brain damage or the presence of entities that could involve varied degrees of neurological dysfunction in childhood (and associations have been reported between large head circumference and brain cancer, see Samuelsen attached). In addition to a number of factors of variation common to biometric measurements at birth, HC

is influenced by the mode of delivery (vaginal delivery or caesarean section and PROM) which will have to be taken into account.

Preterm delivery (PTD)
Preterm delivery is defined as GA<37 gestational weeks. Very preterm delivery is defined as GA<34 gestational weeks.
Whenever this is known, pre-planned deliveries for non-medical reasons should be excluded from the analysis (and analyzed separately..).

Small for gestational age (weight, head circumference, length)
Small for Gestational Age (SGA-BW) is defined as a liveborn infant below the 10 th percentile of birth weight (respectively head circumference (SGA-HC) or birth length (SGA-LG)) for gestational age and sex in the referent population. This referent population is defined at national level in each cohort.

Exposure assessment

A number of groupings of occupations will be proposed, for mothers and for fathers, according to ISCO88 code. ISCO88 was chosen because this occupation coding system has many national equivalents and appears to be the most frequently reported in the participating cohorts. Each cohort will have, if necessary, to translate the ISCO88 codes into their own codes to build the occupation groups. Some translations exist, for example between ISCO68 and ISCO88.

Two strategies for groupings will be used, one by activity sector, one by task.

Example of list of activity sectors:
1**)** Medical ; 2) Social + preschool ; 3) scientific occupations (laboratories, chemical industry…); 3) Electricity/Electronics ; 4) Food production ; 5) Cleaning ; 6) Agriculture ; 7) Haidressing/Beauticians; 8) Printing; 9) Mining; 10) Transport; 11) Welding.

Tentative list of tasks or exposures
1) cooking; 2) housecleaning; 3) disinfection; 4) laboratory work; 5) chemical work; 6) biological risks; 7) pharmaceutical compounds; 8) cosmetics; 9) solvents (incl use of paints, inks, dyes, glues, varnishes); 10) food additives; 11) pesticides; 12) ionizing radiations; 13) electric welding; 14) second-hand smoke.

A first version of these grouping strategies is being finalized using ISCO88 codes, it will first be circulated to experts in occupational exposure assessment present at the Utrecht meeting for validation. It will then be proposed to participating cohorts for discussion.

Operational definition of physical factors (exposure to noise, heat), physical load (handling burden, standing…), factors related to work organization (shift work, night work…) will be built according to the strategy defined in the working group (see page 8).

Confounding variables (Table C)

Gender of the child
Maternal parity before this pregnancy
Maternal age at birth
Maternal ethnicity
Maternal marital status
Maternal education
Paternal education
Socio-economic level of the family
Maternal active smoking during pregnancy and the third trimester

Average number of cigarettes smoked during pregnancy and the third trimester
Maternal passive smoking
Maternal alcohol drinking during pregnancy
Maternal height
Maternal pre-pregnancy weight
Father's height
Maternal hypertension during pregnancy
Maternal diabetes (chronic or gestational)
Other maternal chronic diseases (epilepsy, HIV, autoimmune disease, asthma…)
Previous preterm deliveries
Previous low birth weight babies

Data analysis

A standardized program could be sent to all the participating cohorts that will then run it. The standardized listings produced by the program will be sent back to the coordinating team in order to be meta-analyzed. A meta-analysis will be conducted. Heterogeneity will be tested and explored using relevant available variables in the cohort. When possible (if enough cohorts have such data), sensitivity analyses will be conducted.
Alternatively, raw data and appropriate data transfer agreement will be sent to the coordinating team where the analysis will be conducted.

Statistical analysis for each cohort
Selection of subjects
For the study of maternal occupations, only mothers who have been working at the beginning of the pregnancy will be included in the analysis. Similarly, only fathers working at the beginning of pregnancy will be included in the analysis of paternal occupations.

Definition of variables
Variables (outcomes, exposures, covariates) will have to be defined and (re)named according to tables provided (exposure variables to come).
Separate models for each outcome will be used. Gestational Age, Birth Weight, Head Circumference will be considered as continuous variables and analyzed with multivariate regression models including the same covariates for all the cohorts. Stillbirths, SGA variables, pre-term births will be analyzed as dichotomous outcomes and modelled by multivariate logistic regression models. At this stage, no automatic selection of variables to be kept is decided. For each activity sector exposure group, the reference (non-exposed) group will be constituted of mothers (resp fathers) working in an occupation outside these 11 activity sectors. Similarly for each task exposure group, the reference (non-exposed) group will be constituted of mothers (resp fathers) handling a task outside these 14 task/exposure groups.
The output will include descriptive statistics about outcome, exposure and confounding variables, and some additional analyses in order to make sure the conditions of modelling are verified and to document the potential heterogeneity that will be observed in the meta-analysis.
Strategies for handling missing data will have to be discussed between participants.

Table A: Description of ENRIECO birth cohorts with coded maternal and/or paternal occupation at time of pregnancy

Cohort		Country	Calendar period of enrolment	Enrolment			N Children	N Mothers	N Fathers
				Pregnancy	Birth	Posnatal			
1.	ABCD	Netherlands	2003-2004	√	-	-	7863	8266	-
2.	ALSPAC	UK	1991-1992	√	-	-	14062	14541	9957
3	BAMSE	Sweden	1994-1996	-	√	√	4089	4089	4089
4.	BiB	UK	2007-2010	√	-	-	13000	13000	3000
5.	DNBC	Denmark	1996-2002	√	-	-	96986	100418	?
6.	Generation R	Netherlands	2001-2005	√	√	-	9778	9778	6748
7.	Generation XXI	Portugal	20042006	√ (n=349)	√		8654	8493	4351
8.	HUMIS	Norway	2002-2009	-	-	√	2500	2400	?
9.	INMA	Spain							
	Asturias		2004-2007	√	-	-	485	494	494
	Gipuzkoa		2006-2008	√	-	-	600	639	626
	Granada		2000-2002	-	√	-	668	668	668
	Menorca		1997-1998	√	-	-	482	475	?
	Ribera Ebre		1997-1999	-	√	-	102	102	102
	Sabadell		2004-2006/2007	√	√	-	749	787	657
	Valencia		2004-2005	√	-	-	787	855	827
10.	INUENDO	Greenland, Sweden, Poland, Ukraine	2002-2004	√	-	-	1322	2269	1172
11.	KANC	Lithuania	2007-2009	√	-	-	4000	4000	4000
12.	MoBa	Norway	1999-2008	√	-	-	107400	107000	72000
13.	PÉLAGIE	France	2002-2006	√	-	-	3460	3421	3421
14.	RHEA	Greece	2007-2008	√	-	-	1500	1606	1376

Table B: Outcome variables and corresponding coding

Outcome variable	Variable name	Categories	Comments
Stillbirth	SB	0-No	
		1-Yes	
Birth weight	BW	Continuous (grams)	
Low birth weight	LBW	0-No	BW ≥ 2500 g
		1-Yes	BW < 2500 g
Very low birth weight	VLBW	0-No	BW ≥ 1500 g
		1-Yes	BW < 1500 g
Head circumference	HC	Continuous (cms)	
Gestational age	GA	Continuous (weeks of amenorrhea)	See definition part. When priority is set as follows: 1. LMP, 2. US, 3. Medical
Method used to estimate gestational age	GA_meth	1-Last Menstrual Period only	
		2-UltraSound only	
		3-Medical (from LMP, and US)	
		4-Other or unknown	
Preterm delivery	PTD	0-No	GA ≥ 37 weeks
		1-Yes	GA <37 weeks
Small for gestational age – weight	SGA_W	0-No	BW < 10^{th} percentile of birth weight of children of the same gestational age in the reference population (cohort-specific reference)
		1-Yes	
Small for gestational age – head circumference	SGA_HC	0-No	HC < 10^{th} percentile of head circumference of children of the same gestational
		1-Yes	

			age in the reference population (cohort-specific reference)
Small for gestational age – length	SGA_LG	0-No 1-Yes	Length < 10^{th} percentile of length of children of the same gestational age in the reference population (cohort-specific reference)

Table C: Confounder variables and corresponding coding

Adjustment factor	Variable name	Categories	Comments
Region	Region	To define for each cohort	Sample design of each cohort
Gender of the child	Sex	Male	0
		Female	1
Maternal parity before the index pregnancy	Parity	No child	0
		≥1 child	1
Mode of delivery	Delivery	Vaginal	0
		Caesarean section	1
Maternal age	Age	<20, 20-24, 25-29, 30-35, >35	At birth
Maternal race / Ethnicity	Race	To define for each cohort	
Maternal marital status	Marital	Living with the father	0
		Living alone	1
Maternal education	M_edu	primary school	0
		secondary school	1
		university degree or higher	2
Paternal education	P_edu	primary school	0
		secondary school	1
		university degree or higher	2
Socio economic status of the parents (levels to be defined for each cohort)	Ses	Low income Medium income High income	Terciles of the most relevant proxy of social status of the child's family in each cohort. If too many missing values, paternal and/or maternal levels of education will be used
Maternal active smoking during the pregnancy	Smok	No	0
		Yes	1

during 3rd trimester of pregnancy	smok3	No	0
		Yes	1
Mean average number of cigarettes smoked per day			
during the pregnancy	Cig	Continuous	
during 3rd trimester of pregnancy	cig3	Continuous	
Maternal passive smoking			
during the pregnancy	Psmok	No	0
		Yes	1
during 3rd trimester of pregnancy	psmok3	No	0
		Yes	1
Maternal alcohol drinking	Alc	No	0
		Yes (at least one drink per week)	1
Maternal height	m_height	Continuous (cm)	
Maternal pre-pregnancy weight	m_weight	Continuous (kg)	
Maternal pre-pregnancy BMI	m_bmi	Continuous (kg/m^2)	
Father's height (cm)	p_height	Continuous	
Maternal hypertension during pregnancy	HTA_preg	No	0
		Yes	1
Maternal diabetes (chronic or gestational)	Diab	No	0
		Yes	1
Other chronic maternal pathologies (epilepsy, HIV, autoimmune disease, asthma…)	patho_chro	No	0
		Yes	1
Previous pre-term birth	Pv_prema	No	0
		Yes	1
Previous low birth weight	Pv_LWB	No	0
		Yes	1