ENRIECO EU project

Work package 3

Evaluation of health outcomes

Protocol

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1. Introduction

1.1. Context

There are many pregnancy and birth cohorts in Europe, with sample sizes ranging from a few hundred to tens of thousands. A number of them aim to examine environment and health relationships, but the sample sizes are often too small to lead to conclusive results on their own, or have led to inconsistent and sometimes opposite results.

Generally, combined analyses have several potential advantages:

- To allow a higher statistical power than analyses based on each cohort considered separately
- To yield a more accurate estimate (i.e., narrower confidence interval)
- To allow studying if there is evidence for heterogeneity of effects of environmental exposures between cohorts
- To allow subgroup analyses to try identifying effect measure modifications (interactions) or more sensitive populations, which may not always be possible in a single cohort.

However, combined analyses also have potential limitations, linked among others to potential differences in study protocol, and in particular in the assessment of the health outcomes.

The ENRIECO project will make inventories of birth outcomes; assure quality and interoperability; validate exposure, health and exposure-response data; obtain data access; build databases and conduct analyses. In the context of this project, work package 3 is focused on health outcomes.

1.2. Aims of work package 3 (health outcomes)

The overall aim of this work package is to evaluate existing health information, including protocols, methods tools and protocols of the birth cohorts included in ENRIECO and to make recommendations for further analyses. Specifically, the aims of the work package are:

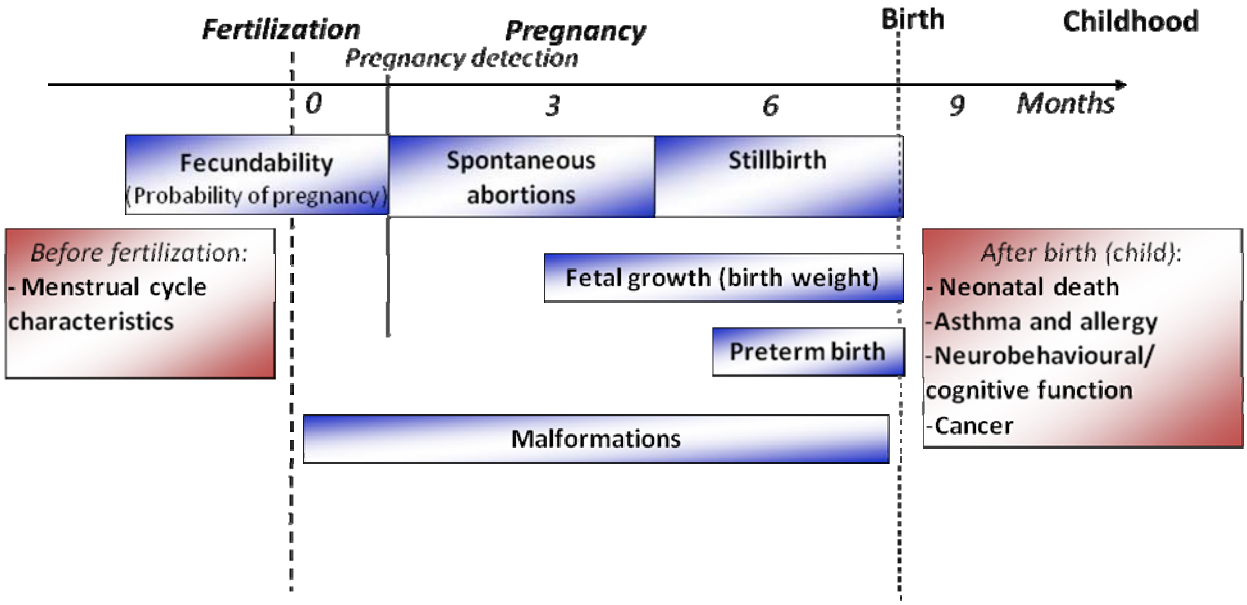
- to develop protocols for the evaluation of existing information, including protocols, tools, methods and publications, in terms of availability, quality and potential use;
- to set up a database(s) with the tools and methods that have been used to assess health outcomes;
- to discuss the feasibility to study environmental influences on specific health outcomes little or not considered so far in studies based on single cohorts, such as childhood cancer and congenital malformations;
- to make recommendations for potential further use of methods and tools in cohorts where they do not exist or where there has been insufficient use;
- where possible, it will harmonize health outcome information (create a minimum set: select the priorities, standardize methods, provide tools, create methods) for future environment and health analyses in the cohorts. The work will build on work that has already been conducted or is being conducted as part of ongoing EC projects such as GA2LEN, ESCAPE, HIWATE, HITEA, ENNAH and NEWGENERIS;
- to conduct a case-study on Persistent Organic Pollutants (POPs) and reproductive outcomes or children’s health.

1.3. Scope of the work package

1.3.1. Health outcomes covered

The scope of the work package is defined in terms of health outcomes considered. These span from the peri-conceptional period until childhood; they are outlined in Figure 1, and listed below, as well as in Table 2.

Figure 1: Schematic view of the health outcomes considered.



Pre- and peri-conceptional events: fecundability (time to pregnancy).

Pregnancy events and pregnancy outcomes: fetal losses (spontaneous abortions, stillbirth), preterm birth (gestational duration), congenital malformations, fetal growth (assessed by ultrasound or from measurements at birth).

Postnatal events in children: infantmortality (possibly restricted to perinatal mortality), asthma, allergy, reproductive health, neurobehavioural/cognitive function, childhood cancer, postnatal growth (BMI and related measures), obesity, puberty and metabolic disorders.

Unless otherwise specified, the age limit for the considered outcomes of child health is 18 years.

For the case study on POPs, the outcome will be chosen among fetal growth, gestational duration and sex-ratio.

1.3.2. Persistent Organic Pollutants (POPs) considered

The lipid adjusted serum concentration of CB-153 is taken as an indicator of organochlorine exposure level. The appropriateness of using CB-153 as an indicator of total PCB- exposure has been demonstrated in Swedish and Inuit populations [1,2].

1.4. Structure of the Work Package

The work will be divided in 6 families of health outcomes. For each type of health outcome, a working group (WG, see Table 1) will evaluate the existing information, including protocols, tools, methods and publications, in terms of availability, quality and potential use.

Table 1: Working groups (WG) within work package 3.

WG topic	WG leader	Participants	Specific outcomes
1. Reproductive outcomes	Rémy Slama	Jens Peter Bonde Gunnar Toft Sylvaine Cordier Frank Pierik Michael Wilhelm Anne Marie Nybo Andersen Greet Schoeters Constantine Vardavas Stephanie Vandentorren Merete Eggesbo Kinga Polanska Manon Van Eijsden Ferran Ballester	Time to pregnancy (fecundity), Fetal loss (abortions, stillbirth) Fetal growth Gestational duration (preterm birth) Congenital anomalies
2. Allergy, asthma and respiratory health	Thomas Keil	Joachim Heinrich John Henderson Constantine Vardavas Cynthia Hohmann Claudia Galassi	Asthma Wheezing Allergic rhinitis Eczema Allergic sensitization Lung function
3. Neurobehavioral/cognitive function	Jordi Sunyer	Sylvaine Cordier Henning Tiemeier Kinga Polanska Cynthia Hohmann Manon Van Eijsden Viaene, Mineke Joan Forns	Neurodevelopment Neurobehavior Autism spectrum disorders
4. Childhood cancer	Manolis Kogevinas	Milena Maule	Specific childhood cancers Biomarkers of cancer risk
5. Case study on Persistent organic pollutants (POPs)	Jens Peter Bonde, Gunnar Toft	Jens Peter Bonde Gunnar Toft Remy Slama Michael Wilhelm Greet Schoeters Vicky Patelarou Stephanie Vandentorren Kiviranta Hannu Merete Eggesbo	Birth weight, gestational duration
6. Child growth, metabolic and endocrine disorders	Marie-Aline Charles	Greet Shoeters Martine Vrijheid Sylvaine Cordier	Statural growth, obesity and fat distribution, puberty

1.5. Responsibilities of WG-leaders and WG-members

We are aiming for small groups who actively pursue information within a larger group who will discuss and report on the material. The groups are open for senior investigators but also to e.g., PhD and post doc researchers. Each working group will be lead by a WG-leader, who will:

- provide scientific leadership and co-ordination of the working group;
- monitor, and report on progress of the work within the working group;

- provide early identification of, and trouble-shoot, any delays or problems in the work of the working group;
- act as a focal point for contact between the working group members, and with the work package leader.

The WG-leader should draft protocols and contact each WG-member to discuss the protocol and the responsibilities and assignments for each member. WG-members are responsible for performance of tasks assigned by the WG-leader within the allotted time period. WG-members are expected to actively participate in the preparation of protocols and manuscripts.
WG-members can chose between an active involvement or a more passive involvement. Active involvement includes both a) reviewing drafts of protocols and reports, and b) writing of specific sections of the reports (tasks to be distributed among active members). Please note that all basic review work (PubMed searches, finding of references, contacting cohorts, etc) will be done at the institute of the WG-leader, but that expert opinions are needed for the evaluations and recommendations. More passive involvement includes commenting only on (near) final drafts of reports.

2. Outline of the approach that will be used for all health outcomes

This outline generally applies to working groups 1 to 4 and 6. The approach used in the case study on POPs is given in section 4. Issues specific to each working groups and additional questions are listed in section 3. A proposed format working group reports is shown in annex I.

2.1. Main steps

For each health outcome, we will:

a. Define the health outcome and identify diagnostic criteria.
b. Identify the sources of measurement error in outcome assessment.
c. Discuss and if possible group qualitatively each of the main approaches used to assess the outcome.
d. Identify the protocol of assessment of the outcome in the main ENRIECO cohorts.
e. Propose *homogeneous groups of cohorts* similar in terms of health outcome assessment.
f. Make *recommendations* in terms of standardization of methods to assess health outcomes, in terms of further analyses, statistical analyses, and future studies.

These steps are defined below.

2.2. Definition of the health outcomes

Each health outcome considered will be defined, and, if appropriate, its ICD (international classification of diseases) code given. If relevant, diagnostic guidelines will be listed and variations of diagnostic criteria in the recent years identified. A suggested list of basic information to be given for each outcome is listed Table 2. Additionally, key references can be listed.

Table 2: Proposed list of basic information to be listed for each health outcome.

	Outcome	**Main definition**	**ICD #**	**Alternative definitions (if relevant)**	**Existing guide-lines**	**Possible assessment tools**	**EU project covering this outcome**	**Usual range of value, prevalence (P) or incidence rate (I)**
Comment			According to ICD-10*				Focus on projects in environmental health.	May be used for power calculations or to identify "outlying" cohorts
Example	Small for gestational age	Birth weight<10^{th} centile of gestational age-specific birth weight	P05.1	Other centiles than 10^{th} sometimes used		Needs reference growth curves	ESCAPE (2008-), HiWate	Prevalence at birth should be close to 10% if the relevant reference curves are used.

* See http://apps.who.int/classifications/apps/icd/icd10online/.

2.3. Identification of main strengths and limitations in outcome assessment methods

For each health outcome considered, the main strengths and limitations of the methods used for outcome assessment will be identified and listed, as indicated in Table 3.

Whenever possible, we will identify if specific assessment methods have a potential to cause bias in exposure-response relationships.

Table 3: Proposed list of potential sources of measurement error in the assessment of each health outcome.

	Source of bias or error														
	Related to study design			Related to existence of various definitions of outcomes			Related to technique used to assess outcome			Inter-observer source of variability			Other sources of bias or error		
Health outcome	Description	I [a]	Ease [b]	Description	I [a]	Ease [b]	Description	I [a]	Ease [b]	Description	I [a]	Ease [b]	Description	I [a]	Ease [b]

[a] Usual importance of error or, if available, of any resulting bias in the exposure-response relationship (++: major; -- minor)
[b] Ease of identification of the source of measurement error.

2.4. Discussion and classification of each tool used to assess the considered health outcomes

Based on the main sources of errors identified for each tool used to assess the health outcome, we will:

-discuss the advantages and limitations of each of these assessment tools;

-propose a grouping of these tools that should result in homogeneous groups in terms of measurement error (see Table 4).

Table 4: Suggested presentation of the grouping of tools used to assess health outcomes. The example is given for the outcome "ultrasound-based assessment of fetal growth"

	Study design (e.g., timing of recruitment)	Inclusion or exclusion criteria	Technique used to assess health outcome	Other
Group 1 (to be labeled)	Recruitment during the 1st trimester of pregnancy. Limited number of maternity wards.	Should not be based on pregnancy outcome (e.g., birth weight)	Ultrasonography. Limited number of maternity wards and obstetricians implied in ultrasound measurements.	At least 3 ultrasound measurements available for 80% of the cohort. Head circumference and femoral length available
Group 2 (to be labeled)	Postnatal recruitment	Should not be based on pregnancy outcome (e.g., birth weight)	Ultrasonography.	At least 1 ultrasound measurements available for 80% of the cohort.
Group 3 (to be labeled)				

2.5. Identification of the protocol of assessment of the health outcomes in each cohort

Based on the work of WP1, a basic inventory of cohorts will be built.
This first stage will inform the preparation of a more detailed questionnaire. The detailed questionnaire will contain all items needed to build the final inventory.
Further information needed for the working groups will be collected separately from this inventory.

The cohort inclusion criteria (as defined by WP1 and ENRIECO core protocol) should be:

Study population:
Main population: European birth cohort studies and cohorts of pregnant women (where exposures and outcomes assessed have been evaluated) and also cohorts with ongoing exposure assessment. Mothers, children and adolescents will be included.
Other population for comparison purpose:

- Not limited to cohorts with start of enrolment during pregnancy or at birth, but also including cohorts with start of enrolment at later ages
- Other study designs (case-control and registry-based studies)
- Studies conducted out of Europe

This last part will be only based on existing review papers.

Study design:

- Observational studies including both longitudinal and cross-sectional study structure.
- Meta-analysis
- Systematic reviews

2.6. Grouping of cohorts

For each outcome, each cohort will be classified according as belonging to one of the groups listed in Table 4. This classification will allow identify groups of cohorts homogeneous in terms of tools used to assess the health outcome, and will also indicate the corresponding sample size; the information will then be structured e.g., as presented in Table 5.
In a further step, this information should be cross-tabulated with information from WP2 on exposures, which would allow identify which health outcome/exposure pairs can be studied with a reasonable statistical power using existing cohorts. This will also be done in coordination with WP4.

Table 5: Suggested presentation of the cohorts in homogeneous groups in terms of tools used to assess health outcomes (fictitious example).

	List of cohorts	Sample size[a]	Number of events[b]	Recruitment period
Group 1	Cohort A	10,000	1,100	1999-2003
	Cohort B	2,000	180	2001-2007
	Cohort C	60,000	5,000	1996-1999
	Total	*72,000*	*6,280*	*1996-2007*
Group 2	Cohort D	2,500	250	2004-2007
	Cohort E	800	80	1996-1999
	Total	*3,300*	*330*	*1996-2007*
Group 3				

[a] With available information on outcome.
[b] In the case of binary outcomes. For non-binary outcomes, a threshold value defining the outcome needs to be given.

2.7. Recommendations

Finally, we will formulate recommendations and conclusions concerning:

- The advantages and limitations of each tool used to assess health outcomes;
- *"new uses of existing cohorts":* Key health outcomes that can be studied by pooling existing European birth cohorts, suggesting strategies on how to pool most efficiently these cohorts;
- *needs for new studies:* Specific health outcomes whose sensitivity to environmental pollutants is unlikely to be efficiently characterized by existing European birth cohorts, indicating if relevant approaches could be used to fill in this knowledge gap;
- and possibly *analytical strategies* that could be used to analyze the influence of environmental factors on specific health outcomes (jointly with WP2).

3. Methodology: search strategy and assessment of quality

3.1. Search strategy

- Information about exposure assessments within European cohorts will mainly come from the full cohort inventory conducted by ENRIECO WP1.
- Publications of each ENRIECO birth cohort will come from direct contact with their members (papers in press or published) or by cohort websites. If more information is needed, cohorts will be contacted directly.
- Relevant publication will be identified in the electronic database PubMed and Scopus with the use of keywords and MESH terms.
- Hand search from the citations of the publications identified from the electronic search.
- Manual search of personal files will be performed to identify literature which was not found by the electronic search.
- Other web pages: CDC; WHO (Air quality guidelines for Europe); IPCS (International Programme on Chemical Safety-Environmental Health Criteria Monographs (EHCs)-Chemical Safety Information from Intergovernmental Organizations (INCHEM)); etc.
- Scientific papers which will be published in the following months which can be identified through personal contact will be included.

Information extraction:

- Two independent authors will check titles and abstracts identified from the searches. If it is clear that the study does not fulfill the inclusion criteria (European birth cohort study) or does not assess the outcomes of interest, the study will be excluded.
- The two authors will independently assess each study to determine whether it meets the pre-defined selection criteria, any differences will be resolved through discussion with the other working group members.

Data extraction:
One author will extract the information and data from the selected article and the other author will check the extraction. Any disagreement will be resolved through discussion with the other working group members.

The division of tasks between WG members will be decided (see *1.5.Responsabilities of WG-leaders and WG-members*), but it is clear that the WG leader will be responsible for conducting the searches.

3.2. Assessment of methodological quality

The quality assessment will include an evaluation of the following components for each included study:

- Clear definition of the type and timing of the health outcome assessment
- Clear description of the inclusion and exclusion criteria of the cohort
- Whether appropriate statistical analysis has been performed (longitudinal vs cross-sectional; confounder adjustment; etc.)
- Clear report on the cohort members who were lost of the follow-up and compare them with the cohorts who were followed-up
- Temporal relationship (relevant window of exposure; changes in exposure associated with disease, reverse causation)
- Possibility of reverse causation
  Additional aspects can be added to this list if necessary.

4. Issues specific to each type of health outcome

4.1. Reproductive outcomes

4.1.1. Issues related to study design

The design of birth cohorts may impede efficient study of environmental influences on "early" peri-conceptional events; this may in particular be the case for time to pregnancy (fecundability) and fetal loss. Indeed, most birth cohorts with a post-natal recruitment probably exclude most (if not all) early fetal losses, and a large proportion of stillbirths; this may also be the case for many of the cohorts with a recruitment during pregnancy. The working group will define criteria (e.g., in terms of timing of recruitment and inclusion criteria) that will allow identify cohorts in which these outcomes could be or have been studied. A question to be tackled is whether or not birth cohorts constitute a relevant design to study such outcomes.

In the case of fecundability, the problem lies in the fact that couples who remain childless are not considered in most birth cohorts. This exclusion is likely to entail a bias in the effect of environmental factors on fecundability estimated in studies excluding infertile couples [3].

For congenital malformations, issues related to the identification and/or inclusion of therapeutic abortions will be discussed.

4.1.2. Issues related to the diagnosis or measurement of the health outcome

For specific health outcomes, there may be a large inter-observer variability in the assessment of the outcome, which may entail large classification error and limit the validity of studies in which the health outcome has been assessed by a large number of physicians or technicians. As an example, a proportion of mild cases of cryptorchidism may not be diagnosed. The working group will identify such outcomes and define criteria that could allow identify homogeneous groups of cohorts in terms of standardization of diagnosis. Recommendations for the statistical analysis, that could allow identify the presence of measurement error in the assessment of the outcome, assess the amplitude of the resulting bias, or partly correct for it, could also be made.

For outcomes that can be assessed by questionnaires (e.g., time to pregnancy, fetal loss, birth weight), the working group will identify the key information to be collected and make recommendations for future studies in terms of questionnaires to be used.

For fetal growth, many outcome variables can be built using birth weight and gestational duration information (e.g., low birth weight, small-for gestational age, fetal growth restriction based on the fetal growth potential…). We will try to discuss the relevance of these in the context of environmental health, or point to already existing literature covering this issue.

4.1.3. Methodological issues

For some little studied outcomes, several options exist in terms of statistical analysis; this is in particular the case for ultrasound measurements of fetal biometry. These options will be reviewed and discussed.

4.1.4. Issues related to statistical power

Some relatively infrequent outcomes are possibly out of reach of pooled analyses of existing EU cohorts; this may in particular be the case for many congenital malformations, which might more efficiently be addressed using register data or a case-control design. Based on simple statistical power calculations, we will identify the main congenital malformations that could be studied based on existing cohorts.

4.1.5. Issues related to the identification of developmental windows of sensitivity to environmental pollutants

Identifying a window of heightened sensitivity to environmental pollutants (e.g., during pregnancy) may be hampered by limited sample size in studies based on a single cohort. Pooling cohorts may allow identify such sensitivity windows more efficiently. We will suggest approaches that may allow progress in this issue. If necessary, this issue will be discussed with other work packages.

4.1.6. Organizational issues

Coordination needed with working group on "occupation and birth outcomes" (WP4).

4.2. Asthma and allergy

4.2.1. Overview

Asthma and allergy are the most common chronic diseases in childhood and particularly in the industrialized world, with high and in some countries even further increasing prevalences.
Emanating from GA^{2}LEN birth cohorts with focus on asthma and allergy, this working group aims to evaluate the availability and quality (reliability, validity) of tools and methods used to assess these diseases.
Asthma and allergy can develop as early as in infancy and last from childhood throughout adolescence and adulthood. Heredity (family history, genetic markers) is seen as one important causal factor of asthma and allergy. The impact of its contribution to disease development, respectively interaction-effects with indoor and outdoor environmental exposures remains unclear.
Ongoing birth cohorts are a necessary source to clarify relevant environmental exposures as causal factors the development of asthma, allergic symptoms and allergic sensitization. Indoor exposures at home are particularly relevant during the first years of life. Later, outdoor or work-related exposures gain importance. For some rare event-assessments related to allergy, it might be useful to aim at combined analysis, strengthening statistical power. Therefore, and to compare outcomes from epidemiological studies from different (European) countries, asthma and allergy assessments need to be clearly and consistently conducted.

4.2.2. Nomenclature

The definition of health outcome and diagnostic criteria will be one of the working group's core tasks, as well as identifying sources of measurement error in outcome assessment.
Special attention will be paid to well-defined nomenclature of allergic diseases. For the main outcomes such as asthma, wheezing, allergic rhinitis, eczema and allergic sensitization, different definitions have been used throughout the years. A consensus was tried to reach with the Revision of the Nomenclature Review Committee of the World Allergy Organization, 2003 [4]. The definitions used in the European birth cohorts will be evaluated.

4.2.3. Diagnostic criteria

There is a great diversity among tools used to assess asthma, wheezing, allergic rhinitis, eczema and allergic sensitization. Most often information is interview-, respectively questionnaire-based and can be parent, doctor reported or a combination of both. Each identified approach will be discussed in its contribution to assess a reliable and valid outcome measure. An important differentiation has to be made between validated and unvalidated methods.

The main focus lays on the identification of valid core questions, which can be recommended for the use in ongoing and planned cohorts, aiming at a comparable and integrative approach in future research.

Objective outcome measures have been less frequently used in birth cohort studies. Varying information on allergic sensitization (skin prick tests and immunoglobulin-E-antibodies) and lung function tests are partly available in studies. Quantity and quality of the assessments will be reviewed and discussed, especially regarding added-value of objective compared to subjective measures.

4.2.4. Organizational issues

Coordination is needed with the working groups of Work Package 5 investigating the impact of dampness/mould and tobacco smoke exposure on asthma and wheezing outcomes from assessed from infancy to early adolescence.

4.3. Neurobehavioural/cognitive function

4.3.1. Overview

Neurodevelopment is the development of central nervous system during the life of an organism, which is a genetically driven process with several phases. Although neurodevelopment generally goes from prenatal life until adolescence, in some cases it could last until 20 years of life (i.e. prefrontal cortex). During the target period of this process, which goes from intrauterine life until 2 years of age, brain is extremely vulnerable to some environmental agents. Human brain grows and specializes according to a precise genetic program with modifications driven by environmental influences, both positive and negative [5].

Numerous neurodevelopmental disorders have been described, such as learning disabilities, sensory deficits, autism, attention deficit and hyperactive disease (ADHD), developmental delays, cerebral palsy, etc [6]. ADHD is a neurobehavioral developmental disorder that is characterized by a persistent pattern of impulsiveness and inattention, with or without a component of hyperactivity. The autism spectrum, also called autism spectrum disorders (ASD), is a spectrum of psychological conditions characterized by widespread abnormalities of social interactions and communication, as well as severely restricted interests and highly repetitive behavior. ADHD and autism have been the most studied neurodevelopmental disorders. It is worth noting that in US, one in every six children has a developmental disability and that in most cases these disabilities affect the nervous system [7].

The use of neuropsychological tests in environmental epidemiology research is suitable to detect alterations in cognitive development due to exposure to neurotoxicagents. Neuropsychological tests are standardized measuring devices designed to give quantitative information about cognitive functioning. There are two options in neuropsychological assessment: general intelligence-Intelligence Quotient (IQ) or specific cognitive domains. The first one is a score derived from one of several different standardized tests designed to assess general intelligence. The second consists in tests that assess specific cognitive domains, such as memory, language, performance abilities, attention or executive function.

These neuropsychological tests are applied by neuropsychologists. Usually, these tools are paper- and pencil-tests but, specific neuropsychological computerized tests also exist. Cognitive development can be also assessed by parents using self-reported questionnaires, which can evaluate children cognitive function, school achievements or neurobehavior. Parents can assess cognitive functioning answer but school achievements are another important issue to assess neurodevelopment.

There are many cohorts studies in Europe where neurodevelopment and its association with environmental exposures are assessed (ABCD, ALSPAC, BiB, Faroes Island, CONER, DNBC, DUISBURG, EDEN, ELFE, FLESH, Generation R, Generation XXI, GESP II, INMA, MoBa, NFBC 1986, NINFEA, PCB-Slovakia, PÉLAGIE, RHEA). Each cohort has used its own protocol of neurodevelopment assessment, resulting in a huge diversity of neuropsichological tools. Hence, there is an urgent need to perform a systematic review in order to identify the main neuropsychological tools used. In addition, there are many factors that determine the choice of neuropsychological protocol

(logistic, practical problems, budget, time required...). Therefore, the main objective of this work is to provide a general guideline for neurodevelopment assessment and to create a specific list of these determining factors in order to facilitate the choice of neuropsychological tools.

4.3.2. Plan of work

- Review of the European epidemiological studies that assess neurodevelopment restricted to birth cohorts studies.
    - Psychometric tests
    - Methodology
    - Resources
    - Logistic
- Review of the European neuropsychological studies that assess neurodevelopment (including case-controls studies):
    - Psychometric properties of each test (sensitivity and specificity)
- To elaborate a guideline of neurosychological tools to assess neurodevelopment in epidemiological cohort studies.

4.4. Childhood cancer

4.4.1. Overview

Childhood cancer is rare in Europe, with incidence rates ranging between 80 and 150 cases per million annually [8,9]. Increases in the incidence of childhood cancer in Europe, and specifically leukaemia have been recently reported [10,11]. Only few exogenous risk factors have been established for childhood cancers and most of these are infective agents [12], highlighting the link between communicable and non-communicable diseases. The evidence on gene–environment interactions is still very limited [13]. Several hypotheses are being investigated concerning non-genetic factors including pre-natal and post-natal exposure to pesticides, maternal and early infancy dietary factors, maternal folate acid intake and polymorphisms in genes controlling the enzyme methylenetetrahydrofolatereductase (MTHFR), paternal pre-conception occupational exposures and smoking, chromosomal translocations present at birth, the interplay of maternal or early postnatal immune system handling of common infections, determinants of high birth weight, parental age and specifically paternal age, exposure to electromagnetic fields and other factors [14]. A close coordination of all major cohorts is essential to evaluate rare outcomes such as childhood cancer [15].

Given the low incidence of childhood cancer, and the fact that cancer does not belong to the health outcomes initially in focus in most of the European birth cohorts (register-based studies or case-controls studies being the approaches most frequently used for this outcome in children), this outcome raises very specific questions. For this reason, the approach depicted in part 2 of this protocol may not be fully relevant to discuss issues relative to the study of environmental influences of childhood cancer incidence. Instead, this working group will focus on two main questions:

- is the incidence of specific childhood cancers high enough for this outcome to be studied efficiently in the existing European birth cohorts in relation to environmental exposures? The relevance of a meta-analytical (or pooled) approach including non-European cohorts such as discussed in the context of I4C, the International Childhood Cancer Cohort Consortium[15], which is focused mostly on leukaemia, will be studied;
- are there biomarkers related to cancer risk that could be assayed in biological samples available in birth cohorts, whose association with environmental exposures would provide a clue

concerning the possible influence of these exposures on cancer risk? This approach has been followed in a large FP6 funded European project [16].

4.4.2. Issues related to statistical power

Given the relatively low incidence of childhood cancers compared to most of the other health outcomes considered in this work package, a key issue is whether the influence of environmental factors on the incidence of childhood cancer can be studied with a satisfying statistical power by pooling all the existing European cohorts in which information on cancer occurrence can be collected. As an illustration, assuming a prevalence of exposure of 30%, the minimal sample size in order to detect an odds-ratio associated with exposure of 2 is about 80,000 subjects [15]. Power curves based on several hypotheses in terms of total sample size, age distribution and excess risk associated with exposures will be provided. The issue of statistical power is particularly important to fully understand how risk factors interact with each other (including gene-environment interactions) to determine child health and disease status.

4.4.3. Identification of biomarkers of elevated cancer risk

The working group will discuss the availability, validity and relevance of using biomarkers relevant to cancer risk as an outcome to inform the possible influence of environmental factors on cancer risk. Validated biomarkers of genotoxicity such as micronuclei in cord blood can be measured simultaneously with novel effect biomarkers based on transcriptomics and proteomics to study how environmental exposure can affect patterns of gene expression and protein production. In addition, interindividual differences in genotoxic responses can be evaluated genotypically and phenotypically, in relation to the level of DNA repair. Moreover, polymorphisms encoding for susceptibility can be investigated. The use of large registers predominantly in Nordic countries in combination with stored samples (blood spots) from all newborns can be examined and incorporated in research conducted within the large Nordic mother-child cohorts.

4.4.4. Organizational issues

Contacts will be established with I4C, the International Childhood Cancer Cohort Consortium, to which the working group leader belongs. Connections with the NewGeneris project will also be envisaged.

4.5. Child growth, obesity and puberty

4.5.1. Child growth

Assessment of a child's growth needs serial measurements of height, weight and head circumference to establish individual growth curve and to compute growth velocities. Diagnosis a growth disorders relies on the comparison with growth reference curves.

Issues related to study design

In longitudinal epidemiologic studies, the number of measurements may be too small to establish precise individual growth curves, which is most of a concern in the first years of life, characterized by the largest variations in growth velocities. Follow-up examinations may also be performed at different ages in different studies. Even within a study there are usually large variations around the planned age at measurement specified in the protocol.

When individual growth curves cannot be computed, comparison of the child measurements at a given age with reference curves allows computing the percentage of children above extreme values of percentiles. It may also allow the computation of Z-scores (or SD scores) to quantify the difference between the child's measurements and the expected average given the child's sex and age.

Methodological issues

The choice of a reference curve is a matter of debate in international studies, as different studies have in general used different country-specific reference curves. Since 2006, the results of the WHO Multicenter Growth Reference Study, which took place between 1997 and 2003 (http://www.who.int/childgrowth/mgrs/en/) has however provided international Growth Standards from birth to 5 years. More recently, the growth curve has been extended to 19 years by merging with the 1977 NCHS/WHO Growth reference curve, thus providing a reference for the 5 to 19 years age group.

Agreement on a common reference curve is a prerequisite for a pooled analysis of EU cohorts.

4.5.2. Obesity and fat distribution

Obesity is defined as an excess of body fat detrimental for health.

Methodological issues

There are issues pertaining both to the measurement of body fat and to the level at which it is detrimental for health.

The adipose tissue is spread within the body and its amount cannot be quantified directly in living individuals. However, several ways to estimate the amount of fat in an individual can be used in epidemiological studies. The most widely used is the body mass index (weight (kg) /height² (m), BMI) or the ponderal index (weight (kg) /height^3 (m)) at birth. Weight and height/length are available in most epidemiological studies. However, BMI or ponderal index are only indirect measures of fat mass, also influenced by fat free mass. The amount of subcutaneous fat can be estimated more directly by the thickness of skinfolds at different sites of the body. There is often good agreement between studies regarding the choice of the sites (tricipital and subscapularskinfolds are classical choices). However, skinfolds measurements suffer from a notoriously large interobserver variability. Bioimpedance analysis is another way of measuring fat mass used in large scale epidemiological studies, but specific equation and validation studies are lacking for children below 5 years. Because of cost and/or safety issues, CT scan and DEXA are rarely used in epidemiological studies in children.

As for weight and height, fat mass in absolute and relative amount changes with growth and development. Any definition of overweight and obesity has to be relative to age and gender. There is currently no definition of overweight or obesity in children based on its consequences on health. The definition proposed by the working group of the International Obesity Task Force (IOTF) in 2000 [17] relies on BMI percentiles that reach at 18 years the levels used for the definition of overweight and obesity in adults. Adult levels have been defined in relation to the risk of all cause mortality.

4.5.3. Fat distribution

In addition to the amount of fat mass, its distribution is also independently related to the health consequences. A central fat distribution, characterized by an excess of fat at the level of the trunk or abdomen compared to the limbs, is associated with a worse cardiovascular and metabolic profile.

Waist circumference is used in children as an index of abdominal fat and the ratio of waists/hip circumferences or trunk/peripheric skinfolds as indexes of central fat distribution.

Abdominal fat distribution is associated in children as in adults with higher blood pressure and metabolic disorders such as glucose intolerance, high triglyceride and low HDL-cholesterol concentration. This association is designated as a metabolic syndrome in adults.

Methodological issues

There is no definition of abdominal obesity or abnormal fat distribution in children but references curves for waist circumference including preschool ages are now available from different countries.

Several definitions of the metabolic syndrome have been proposed in adults and attempts to adapt the adult definitions to adolescents have been made. However, the issue is far from being settled.

4.5.4. Puberty

Pubertal development has been categorized in 5 stages by Tanner. Tanner stages are defined according to pubic and axillary's hairs development, breast and testes size in girls and boys respectively. Rating is done by a health professional. Questionnaires have been developed for self reporting of Tanner stages by the children but validation studies have given conflicting results. In girls, the age at menarche is a widely used index of pubertal maturation, easily recordable in epidemiologic studies. It occurs on average 2-2.5 years after the onset of puberty. In boys, age at voice breaking is also used but it is not a punctual event and can occur at various pubertal stages.

Sexual or gonadotrophic hormones are sometimes measured in epidemiologic studies; their measurement has a high cost, and an important issue relates to the need of repeated measures in time, due to their pulsatile or cyclic secretion.

5. Case study on POPs

5.1. Objective

The overall aim of the case study is to prove the ENRIECO concept by an examination of the feasibility using European mother-child cohorts to obtain additional insight into environmental effects on reproductive outcomes. The case study will discuss and illustrate the additional value of meta-analyses or pooled analyses across several European birth cohorts relative to stand-alone analyses.

The specific objective is to model exposure-response associations between biological markers of POP-exposure to selected adverse pregnancy outcomes in order to:

- Discuss causal inference
- Detail dose-response relations, if any
- Identify thresholds and no-effect levels, if any
- Identify vulnerable subgroups, if any
- Examine interactive effects of exposures and characteristics

5.2. Background

Persistent organic pollutants (POPs) are organic compounds that are highly resistant to environmental degradation with half-lives in the environment and in living organism in the range of several years. POPs bioaccumulate in fat tissues in the organism and biomagnify through the food chain from lower organisms to top predators including humans. An important class of POPs are organochlorines that include a number of anthropogenic compounds manufactured in large scale since 1930s. The most widespread organochlorines in the environment and in human tissues are polychlorinated biphenyls (PCB) and dichlorodiphenyltrichloroethane (DDT). The concentration of these compounds and several other organochlorines as chlordane, aldrin, dieldrin, hexachlorobenzene, toxaphene and dioxins are highly correlated in serum samples from the general human population and exposure to the most common PCB-congener (CB-153) has therefore been suggested as an indicator of overall exposure to persistent organochlorines[1,2,18]. The co-occurrence of these compounds in human samples makes it difficult to establish which compounds cause the observed effects. Moreover, one group of organochlorines, the dioxins, is more toxic than most PCB-congeners and has the same mechanisms of action as the co-planar PCB-congeners.

The production of PCBs and DDTs has been limited or completely banned since 1970s in most developed countries. The last PCB-production facility in Russia was shut down in 1993. In spite of this, organochlorines including PCBs are still being released into the environment from previously produced material or by combustion processes.

The concentration of PCBs human tissues has decreased since the ban of these compounds in most countries. During the past 10 years the decrease has levelled off. Compounds are still detected in blood and milk samples in the vast majority of humans all over the globe.

Concern about adverse reproductive effects of POPs including PCBs arises from experimental studies and accidental exposure of humans. Moreover, during the past few years several observational studies have addressed reproductive toxicity of POPs in exposed population and using hospital based case-referent studies. These studies indicate that high concentrations of persistent organochlorines may adversely affect semen quality and cause testicular cancer, induce menstrual cycle abnormalities and spontaneous abortions and cause delayed pregnancy, reduced birth weight, skewed sex ratio and

altered age of sexual development[19]. Most effects have been demonstrated at exposure levels above the present exposure level in European and North American populations.

An overview of epidemiological studies investigating effects of the persistent organochlorine on birth weight is given below (based on[19]).

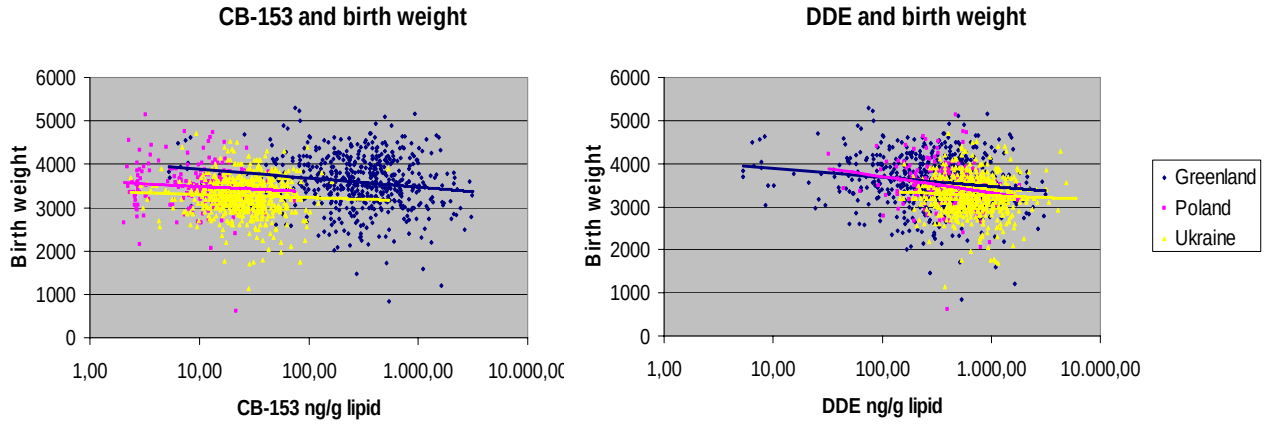
Table 6: Overview of epidemiological studies investigating effects of the POPs on birth weight.

Reference and Place	Exposure groups/ compounds	Mean, median or midrange estimated as maternal serum PCB or DDE[a]	Birth weight
[20] Michigan, USA	Fish eaters – PCBs	5.5 ng/g	↓
[21] New York State, USA	Working women exposed to PCB	21 ng/g	↓
[22] Wisconsin, USA	Fish eaters (PCBs)	2.8 ng/g	↑
[23] Taiwan	PCB, PCDF maternal exposure	-	↓
[24] Sweden	Fishermen's wives	-	↓
	East coast (high PCB) vs West coast (lower PCB)		
[25] Sweden	East coast fishermen's wives	-	
	High vs low fish consumption		↓
	Living in fishing village		↓
[26] The Netherlands	General population (PCBs)	1.6 ng/g	↓
[27] Sweden	East coast fishermen's wives	3.4 ng/g	
	CB-153 estimated in blood		
	>300 ng/g lipid in plasma		↓
[28] Rural Finland	General population PCDDs + PCDF		↓
	PCB	5.9 ng/g	→
[29] USA	p,p'-DDE increasing concentrations	25 ng/g	↓
[30] Faroe Islands	Fishing community (PCB)	2.2 ng/g	→
[31] India	General population (p,p'-DDE)	7.6 ng/g	↓
	HCHs		↓
	otherDDTs		→
[32] Ukraine	General population (DDE, PCB	16.4 ng/g DDE	→
		4.0 ng/g PCB	

[a] Values approximated by conversions – see Toft et al 2004 for details.
→no effect on birth weight
↓significant decrease in birth weight associated with exposure.
↑significant increase in birth weight

The studies indicate quite consistently that pregnant women exposed to relatively high concentrations of PCB or DDT are at increased risk of giving birth to children with low weight. Besides, studies of women with accidental exposure to high concentrations of PCBs in Taiwan and Japan and a large US study of women giving birth between 1959 and 1966 (when DDT was still being used) found a dose response relationship between DDT concentration in maternal serum on the one hand and low birth weight on the other hand. Children in the high exposure group (> 60 ng/g) weighed 150g less and were born about one week earlier than the children in the low exposure group (< 15ng/g). Preliminary findings on birth outcomes on a mother-child cohort from Greenland, Ukraine and Poland are consistent with these results (Figure 2).

Figure 2: Preliminary findings on the association between selected POPs and birth weight (mother-child cohort from Greenland, Ukraine and Poland).



However, at lower exposure level, findings are not entirely consistent (cf. Table 6). One reason why some studies may fail to demonstrate an association between PCB-exposure and birth weight, if such an effect really does exist, may be lack of adequate exposure contrast. All humans have measurable concentrations of POPs in their serum and a no-exposure group cannot be defined.

In summary, exposure to high concentrations of POPs may cause fetal toxicity as seen from accidental exposures, but the effects at lower concentrations are not as obvious. Therefore, a recent review concluded that "large scale-studies with a sufficient number of participants in well-defined groups with substantial exposure contrast are needed in order to fully elucidate the possible adverse effects of persistent organochlorines on human reproductive health" [19]. The ENRIECO framework provides the basis for such a study.

5.3. Study populations

According to preliminary information, there are eight ENRIECO mother-child cohorts where indicators of POP-exposure have been measured in maternal serum or breast milk. The characteristics of these cohorts are given below:

Table 7:ENRIECO Cohorts with biological POP data (including ARCRISK)

Cohort	Region	Years	Children	Birth-outcomes	Growth outcomes	Participation 18.8.09
C Faroes I	Faroes	1986-87	1022	BW?, GA?	CG?	?
C Faroes III	Faroes	1998-2000	547	BW, GA, CA	CG	?
Duisburg	Germany	2000-2002	232	BW, GA	CG	+
FLESH	Belgium	2002-2004	1196	BW, GA	CG, OB	+
HUMIS	Norway	2003-2008	6000	?	CG	+
INMA	Spain	1997-2007	3871	BW, GA, AGD	CG, OB, MS	?
Inuendo	Greenland, Poland, Ukraine	2002-2004	1350	BW, GA	CG, OB,	+
PCB Cohort	Slovakia	2001-2004	1139	?	?	+
RHEA	Greece	2007-2008	1500	BW, GA, SB, SA, US, AGD	CG,OB, MS, DIA	+
ARC-RISK	Norway/Russia		900	BW, GA	CG, OB	Expressed interest

BW= birthweight, GA= gestational age, CA = congenital abnormalities, AGD= anogenital distance, SB= stillbirth; SA=spontaneous abortions, US= ultrasound measurements; CG=childhood growth, OB= obesity, MS= metabolic syndrome, DIA= diabetes.

5.4. Exposure Assessment

The lipid adjusted serum concentration of CB-153 is taken as an indicator of organochlorine exposure level. The appropriateness of using CB-153 as an indicator of total PCB- exposure has been demonstrated in Swedish and Inuit populations [1,2]. In so far as several PCB congeners have been measured, it is essential to examine if the PCB-congener profiles are comparable across populations. If not, major categories of PCB-exposure profiles will need to be defined and analyses adapted accordingly. If available, the serum concentrations of n-3 fatty acids should also be included to characterise exposure profiles. Fish eaters may have high concentrations of POPs as well as of n-3 acids and adverse effects of POPs on birth weight might be counteracted of effects of n-3 fatty acids. The time in pregnancy when a serum sample is taken may systematically interfere with the concentration of POPs and therefore time in relation to gestational age must be accounted for in analyses. If POP measurements are not available in serum but in breast milk only (as may be the case in some cohort), it may be possible to estimate maternal serum concentration by extrapolation.

Serum concentrations of PCBs and the DDT-metabolite DDE are highly correlated in some populations as Inuits and Swedish fishermen-families [33], but not in other populations, depending on dietary habits and local contamination. If possible, separate analyses will be performed with respect to DDE.

5.5. Outcomes

The main outcomes to be examined are gestational duration and weight at birth in pregnancies that are carried to gestational week 22 or beyond. Only singleton pregnancies are included. The method used to estimate gestational age needs to be taken into account. When alternative methods have been used, priority is given to ultrasound measurements, first day of last menstrual period and others in that order. Sex ratio at birth is an outcome that may be considered as a fall back, if it turns out that the proposed case-study overlaps the OBELIX project too much.

5.6. Covariates

Potential confounding and/or interacting factors that should be accounted for in the analysis include maternal and paternal age, parity, pre-pregnancy height and body mass index, socio-economic status, tobacco smoking during pregnancy, intake of alcohol beverages during pregnancy, chronic disease. For some variables as socio-economic status that may be defined several ways there is a particular need to harmonise criteria across pregnancy cohorts.

5.7. Data analyses

The defining criteria and formats for exposure variables, outcome variables and covariates will be harmonised according to a uniform protocol and a protocol describing the analysis step by step is to be developed. The initial analysis is to be formed separately for each study cohort – either by the principal investigator and his/her team or by a small group of researchers assigned by the project group.

The birth weight as continuous and dichotomous outcome is modelled as a function of CB-153 and covariates using linear and logistic regression. Cut-offs defining dichotomized variables need to be agreed upon before analyses are carried out (2500 g, 3000 g, or gestational age and sex-specific cut-offs). Several options are available for treatment of confounders. If all covariates are included in initial full-models and eliminated according to change of estimate principles [34], different set of confounders will probably be included in analyses performed by centre. It may be decided to keep certain variables that are believed to be of particular importance in the models irrespective of change of estimates across all centres. Associations may be modelled by non-parametric methods. Formal analysis of exposure or response by trend analysis and analysis for thresholds are performed if appropriate.

Heterogeneity of estimates across the birth cohorts will be examined and tests for heterogeneity will be performed by standard methods. If appropriate, aggregated data will be analysed either by analysing summary statistics from each birth cohort (meta-analysis) or by stratified analysis of a pooled dataset including all observations from all cohorts. The latter is to be decided during the mid-term workshop.

Possible effect modifications by POP exposure profile, 3n-fatty acid serum concentrations, socio-economic status, smoking and possibly several other determinants will also be investigated.

5.8. Organization and time distribution

Jens Peter Bonde and Gunnar Toft will coordinate the work. Each cohort principal investigator assigns 1-2 researchers to join the case-study working group. Experts in meta-analyses are also assigned. The entire working group reviews the protocol and decides the analytical strategy. Each cohort team extracts and formats the set of key variables according to the uniform protocol. Data- analysis will be performed by cohort or by a smaller group assigned by the entire working group. The entire working group participates in a mid-term and a final workshop discussing the findings. The working group authors the ENRIECO report and scientific papers.

5.9. Work plan and time schedule

June – August 2009:	Drafting and reviewing detailed study protocol
September-December 2009:	Permissions, extraction of key variables and formatting of a data set according to uniform principles

January 2010:	Meeting for the entire working group with the objective to discuss and decide the analytic strategy in detail
February-April 2010:	Data analyses center-wise according to agreed strategy
May, 2010:	Group meeting in relation to the Amsterdam meeting with the objective to discuss results of separate analyses and how to perform the meta-analysis or pooled analysis
June- December 2010:	Analysis, reports and paper writing

5.10. Permissions and ethical issues

The principal investigators obtain the necessary permissions to analyse anonymous datasets according to the protocol. All personal identifiers are kept by the principal investigators according to national guidelines. Permission to analyse anonymous minimum data set at the international level is obtained, if necessary. No biological samples will cross the borders. Data analyses and presentation of papers should adhere to good epidemiological practice and the STROBE guidelines. Aggregated data sets with individual anonymous observations, if any, are to be deleted, when the data analysis is finished.

5.11. Publication

The entire working group authors an ENRIECO report describing the process of the collaboration and feasibility and logistic issues relating to the meta or pooled analysis. The entire working group authors the scientific papers with authorship according to the Vancouver Guidelines. All the working group participants are invited to contribute to publications.

6. Time frame and deliverables

The first month of the project corresponds to March 2009. Work package 3 starts in month 4 of the project. Table 8 summarizes the deliverables of the work package, while Table 9 summarizes the deliverables of the case study on POPs.

Table 8: Deliverables of work package 3 (excluding case study).

No.	Description	Due
	Constitution of the working groups (see Table 1)	06/2009
D4	Protocol for evaluation of health outcome information	09/2009
	Steps a., b., c. of current protocol (section 2, Table 2-Table 3)	04/2010
D17	Report, including a scientific paper ready for submission, with evaluation of health information and recommendations in European birth cohorts	12/2010

Table 9: Deliverables of work package 3 (case study on POPs).

No.	Description	Due
D4	Constitution of the working group (see Table 1). Drafting of detailed study protocol	09/2009
	Meeting for the entire working group with the objective to discuss and decide the analytic strategy in detail	01/2010
	Data analyses center-wise according to agreed strategy	01-04/2010
	Group meeting in relation to the Amsterdam meeting with the objective to discuss results of separate analyses and how to perform the meta-analysis or pooled analysis	05/2010
D18	Report, including a scientific paper ready for submission, for POPs related outcomes in European birth cohorts	12/2010

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8. Annex I

Proposed format working group reports

Drafted by Mark Nieuwenhuijsen

There are 26 working groups and 3 case studies. To get a manageable amount of paper work we need concise reports with the information that matters.

The working group members are leaders in their field and should make use of their expert knowledge to a large extent when writing the reports. The reports may be read by people that are not expert in the field, and this should be taken into account by providing some clarification where needed, and glossary and list of the meaning of abbreviations where needed.

The reports should not be exhaustive, but concise and to the point. They need to be informative regarding what has been done within the European cohorts and specifically what could be done within the European cohorts. The work will need to be placed in context with regards to work in countries outside Europe and studies using different designs, but this should be short and make use of reviews where possible. We should aim for a report for each working group of between 10 and 20 pages of text (font 12, 1.5 line spacing) (exclusive tables) with extra material going into annexes)

Outline:

Title working group

Researchers involved

Summary (1 page)

Back ground and context (2-4 pages): This section will need to give a short introduction of the topic and what the relevance is. It will put the work within the cohorts in context with work going on in other parts of the world and using other study designs.

Current work in the European birth cohorts (7-13 pages): This section will provide a review of what has been done or is currently going on with the European birth cohorts. It will include at least one table of which cohorts under take the activity, and furthermore a description of the various approaches and methods that are being used, and provide some evaluation of the strength and limitations. Include also if the work is part of a European project. This section should not be exhaustive, and where possible should generalise and/or summarise activities and findings rather than provide great detail. Great detail should only be mentioned where it is particularly important, or in annexes. Make use of tables as much as possible.

Recommendations (1-3): This will recommendations of what could be done more on the topic in the European cohorts, either as individual cohorts or by pooling cohorts. The recommendations should be appropriate for birth cohorts and feasible. The recommendations will need to be presented in bullet point style. The recommendation section will to a large extent depend on expert judgement.

References

Tables

Annexes