ENRIECO

Work package 2

Evaluation of existing environmental exposure information, methods and tools, including assurance of quality and interoperability, and data access, analysis and validation, and make recommendations

Protocol

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1. Introduction

1.1. Background and aims of the work package

Many European pregnancy and birth cohorts are studying environment-health relationships, but often sample sizes are too small to lead to conclusive results on their own in particular if health outcomes and exposures with low prevalence are studied. Sometimes inconsistent or opposite results are reported. Environmental exposure assessment often is the weakest part in the studies as a result of lack of funding and expertise, and could be improved. Nevertheless, these cohorts often contain high quality data in many areas such as outcomes and possible confounders and have a team of highly experienced researchers working on them with great expertise and commitment.

The overall aim of this work package is to evaluate existing environmental exposure information, including protocols, methods tools and protocols of the cohorts and to make recommendations for further analyses. Based on these evaluations, it will be possible to explore whether differences in exposure assessment may explain part of the heterogeneity of the exposure-health relationships reported from the studies. Furthermore, it will facilitate collaborative projects between cohorts to enhance statistical power.

The specific aims of the work package are

1. to develop protocols for the evaluation of existing information, including protocols, tools, methods and publications, in terms of availability, quality and potential use;
2. to set up a database(s) with the tools and methods that have been used. Specific effort will be made to collect relevant information on the nature of the biobanks constituted, including timing of collection and nature of biological samples, sampling protocol, mode of storage, amount available and analytes already assessed;
3. 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, and for further laboratory and statistical analyses of existing environmental information and samples;
4. where possible, it will harmonize environmental exposures (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.

A case study will be conducted to explore in more depth how to obtain and combine environmental exposures. The case study will focus on occupational exposures of expecting women during pregnancy for immediate outcomes such as birth weight and pre-term delivery, and events in later life (Case study leader: Sylvaine Cordier, INSERM Rennes). Occupational

exposures were chosen because there is already substantial amount of work on e.g. water contaminants (HIWATE), air pollution (ESCAPE), noise (ENNAH), Allergens (GA2LEN, HITEA), and because there are no European efforts in this area yet, while relatively high exposure levels may occur. Occupational exposures include exposures such metals, solvents, pesticides, and dust, but because of the specific exposure patterns they are different from everyday exposures. As part of the work, an evaluation will be conducted of available methods to identify and quantify these exposures such as self reports, expert judgement and job exposure matrices (JEMs). Job coding systems will be reviewed for use in this work (e.g. ISCO 1988, ISCO 2000). Cohorts with information on paternal and maternal occupation will be evaluated and assessed for potential use in any analyses of occupational exposure, and recommendations will be made for potential use of any of the exposure assessment methods. As where some cohorts may have only collected on maternal job title and industry, others may have in addition specific information on tasks performed and specific exposures, and careful consideration is required for the use of the information. Furthermore, cross validation may be possible between existing JEMs, new expert judgement and self reported specific exposures to improve existing information.

1.2. Objectives of work package

The two main objectives of this work package are

1. To give an overview of how exposure to environmental pollutants were/are been assessed in European pregnancy and birth cohort studies. This first objective will be divided in:
    a. Describe exposure assessments used by European birth cohorts
    b. Compare methods for exposure assessment
    c. Discuss strengths and limitations of different assessment methods
2. 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, and for further laboratory and statistical analyses of existing environmental information and samples.

Whereas objective 1 obviously focuses on European pregnancy and birth cohort studies, information form other studies should be included for objective 2. In the following, the protocol for the evaluation of environmental exposure information is described. For their reviews, working groups should make use of other European collaborative projects e.g. ESCAPE, HIWATE, HITEA, and NEWGENERIS).

1.3. Working groups

The work will be divided in a number of exposure themes. For each exposure theme, a small working group (WG) will evaluate the existing information, including protocols, tools,

methods and publications, in terms of availability, quality and potential use. Table 1.1 gives an overview of the working groups.

1.4. 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 students. 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.

1.5. Which cohorts will be included in ENRIECO?

Inclusion criteria will be flexible. The main focus will be on cohorts that

1. collect(ed) data on at least one environmental exposure topic (Table 1.2)
2. start enrolment during pregnancy or at birth (or during first year of life if data on birth outcomes is collected from medical records)
3. have at least one follow-up point after birth
4. include at least 200-300 mother-child pairs.

Table 1.1 Working groups (WGs) within work package 2

Topic	WG leader	Participants	Email
Air pollution	Ulrike Gehring u.gehring@uu.nl	Frank Pierik Vicky Patelarou Kinga Polanska Ferran Ballester Ann Colles	Frank.pierik@tno.nl patelarou@edu.med.uoc.gr kinga@imp.lodz.pl Ballester_fer@gva.es ann.colles@vito.be
Water contamination	Mark Nieuwenhuijsen mnieuwenhuijsen@creal.cat	Sylvaine Cordier Vicky Patelarou	sylvaine.cordier@univ-rennes1.fr patelarou@edu.med.uoc.gr
Allergens & biological organisms	Joachim Heinrich joachim.heinrich@helmotz-muenchen.de	Ulrike Gehring Chih-Mei Chen Constantine Vardavas	u.gehring@uu.nl chih-mei.chen@helmoltz-muenchen.de vardavas@edu.med.uoc.gr
Heavy metals	Jordi Sunyer jsunyer@creal.cat	Ferran Ballester Kinga Polanska	Ballester_fer@gva.es kinga@imp.lodz.pl
Pesticides	Sylvaine Cordier sylvaine.cordier@univ-rennes1.fr	Frank Pierik Cecile Chevrier Stephanie Vandentorren	Frank.pierik@tno.nl cecile.chevrier@rennes.inserm.fr stephanie.vandentorren@ined.fr
Emerging Exposures (phthalates, BPA, PFCs, brominated flame retardants)	Martine Vrijheid mvrijheid@creal.cat	Maribel Casas Elly Den Hond Jorn Olsen Frank Pierik Marieta Fernardez Gunnar Toft	mcasas@creal.cat EllyDenHond@vito.be jo@ucla.edu Frank.pierik@tno.nl marieta@urg.es gunntoft@rm.dk
Radiations: EMF/UV/ionising	Martine Vrijheid mvrijheid@creal.cat	Mark Nieuwenhuijsen Elisabeth Cardis	mnieuwenhuijsen@creal.cat ecardis@creal.cat
Smoking and ETS	Magnus Wickman magnus.wickman@ki.se	Constantine Vardavas John Henderson Sofia Correia	vardavas@edu.med.uoc.gr a.j.henderson@bris.ac.uk scorreia@med.up.pt

Table 1.1 (continued).

Topic	WG leader		
Noise	Thomas Keil thomas.keil@charite.de	Cynthia Hohmann Maria Pia Fantini Lorenza Luciano Henk Miedema	cynthia.hohmann@charite.de mariapia@fantini.gmail.com lorenza.luciano@libero.it henk.miedema@tno.nl)
Persistent organic pollutants (POPs)	Jens Peter Bonde jpb@bbh.regionh.dk	Gunnar Toft Remy Slama Michael Wilhelm Greet Schoeters Vicky Patelarou Stephanie Vandentorren Kiviranta Hannu Merete Eggesbo	gunntoft@rm.dk remy.slama@ujf-grenoble.fr Wilhelm@hygiene.rub.de greet.schoeters@vito.be patelarou@edu.med.uoc.gr stephanie.vandentorren@ined.fr hannu.kiviranta@thl.fi merete.eggesbo@fhi.no
Occupation	Sylvaine Cordier sylvaine.cordier@univ-rennes1.fr	Jens Peter Bonde Claudia Snijder Vicky Patelarou Kiviranta Hannu Merete Eggesbo Manon Van Eijsden Alex Burdorf Martine Vrijheid	jpb@bbh.regionh.dk c.snijder@erasmusmc.nl patelarou@edu.med.uoc.gr hannu.kiviranta@thl.fi merete.eggesbo@fhi.no mveijsden@ggd.amsterdam.nl a.burdorf@erasmusmc.nl mvrijheid@creal.cat

Cohorts that do not fit these criteria entirely can be included on request, but data collection will be passive rather than active. Table 2 gives an overview of the cohorts that will be included.

Table 1.2 Cohorts included in the ENRIECO project.

Country	**Cohort**	**Recruitment**	**n subjects**
Denmark	Danish National Birth Cohort		100,000
…			

2. Concept for evaluation of environmental exposure information

The methods and structure will be very similar for all reviews and follow the proposal below. In some cases, variations and extensions of this proposal will be needed. These will be described in the working-group specific sections of the protocol.

2.1. Proposed format for working group reports

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:

A. Title working group

B. Researchers involved

C. 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 such as cross-sectional studies.

D. 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 describing:

(a) Description of the current available data of European birth cohorts (cohorts contributing to exposure topic; pollutant(s) assessed; timing of exposure assessment; number of participants, etc.).

(b) Details on protocol; comparison/evaluation of assessment methods among them and with other study designs and other studies conducted out of Europe.

(c) Evaluation of the strengths and limitations of different exposure assessments (data gaps in the literature; possible confounders not considered; inadequate methodology; small sample size; etc.)

This information could be summarized in a table as follows:

Example Summary table of air pollution exposure assessment in the cohorts.

Cohort	**Pollutant**	**Type of assessment**	**Timing**	**Participants with exposure info**
XYZ	NO_2	Land-use regression	Pregnancy (3 months)	xxx
XYZ	PM_{10}	Nearest Monitor	At birth	

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.

(d) Comparability of exposure assessment/protocols between studies?

- For a special type of exposure assessment: comparability of protocols. In case of differences in protocols: Do we believe they matter?
- Availability of validation studies exploring these differences?
- Comparability of different types of exposure assessment?
- Availability of validation studies comparing different types of exposure assessment? (e.g. personal monitoring vs. stationary measurements); measurements vs. questionnaires,…)
- Is exposure assessment comparable enough for a subset of studies to allow pooled/combined analyses?

Most of the information needed for this part of the review will be available from the web inventory questionnaire (see Data collection for details and Appendix 1).

If the number of pollutants is large, we may decide to focus on a limited set of pollutants of which we think that they are of particular importance/interest. These could be more traditional pollutants as well as emerging pollutants. Alternatively, we may decide to split a working group into sub-groups. Potential overlap between working groups (e.g. between "emerging pollutants" and "POPs") were identified and discussed with the respective WG-leaders.

E. Recommendations (1-3): This will give recommendations for future research in European birth cohorts, either as individual cohorts or by pooling cohorts, and for exposure assessment methods. It will also include recommendations for potential further use of methods and tools in cohorts where they do not exist or where there has been insufficient use. 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.

This section may differ between working groups depending on the specific needs that will be identified by the working groups. The following issues could be included:

- If someone wants to study the health effects of exposure to X and has not assessed exposure X, yet:
    - Which of the approaches that are currently used do we think is best and would we like to recommend for use in health effects studies
    - If the recommended approach is not possible (time/money), is there a second best we would like to recommend? Which approaches are more suitable for smaller cohorts (like time-intense, costly approaches), which are suitable for large cohorts.
    - If I cannot ask more than 2 or 3 questions about exposure to X, which are the questions I should ask?
    - Are there further developments of the currently used exposure assessments that could be the focus of future projects?
    - Are there validation studies that we would like to recommend to implement in future studies?
- Long-term validity: In many studies exposure to air pollution was probably assessed once i.e. at a single point in time. If we want to link air pollution exposure to different health outcomes like pregnancy outcomes, asthma and allergies etc. we need some information about the long(er)-term validity of a single exposure estimate.
    - Have repeated measurements been performed to investigate the long-term validity of their exposure estimates?
    - Are there any methods available to account for long-term changes in air pollution levels (e.g. use of data from air quality monitoring networks)

- Aspects relevant to exposure assessment:
    - Exposure changes for subjects who move house during the follow-up. Can these subjects be identified (e.g. for sensitivity analyses)? Is a complete address history available for the study participants? Is it possible to use information on address history in exposure assessment? How?
    - Time-activity pattern: The participants may spend considerable amounts of time at places other than home (daycare, school; parents: work), where they experience exposure to air pollution. Is information available on time-activity pattern? Are daycare/school/work addresses of the participants known? Can they be included in the exposure assessment?
    - Within and between home variability of exposure: Having a large error variance reduces the ability to detect a significant association between exposure and disease. Information available on within/between home variability ratios? Correlation between different samples taken in the same home? If correlation is moderate/low, is there a location within the home that we think is of major relevance?
- Lessons learned from the cohorts.
- Knowledge about new techniques
- Gaps of knowledge
- Determinants of exposure
- Important confounders (very briefly, indicate the most important ones)
- Biological samples: nature of biological samples; storage of samples; analyses available

This list is by no means complete and not all issues are relevant for all exposure topics.

F. References

G. Tables

2.2. Data collection

A basic inventory of cohorts that collect environmental exposure data has been built by searching websites and publications, and communicating with existing EC studies (such as GA2LEN (Keil et al. 2006a; Keil et al. 2006b), ESCAPE, HIWATE, HITEA and NEWGENERIS) and distributed to all workshop participants before the first workshop. The basic inventory gives some indication of which exposure has been/will be assessed in the cohorts and can serve as a starting point for our reviews. Please note: information may be incomplete and some information may be incorrect.

Cohort websites and publications identified by PubMed searches and manual searches within references of publications identified by electronic searches of cohort websites and Pubmed will provide additional information.

A more detailed questionnaire was made for the final full inventory. The final version of the questionnaires (Appendix 1) has been distributed to all workshop participants in July 2009. A great part of the information that is needed for the reviews, will be available from this full inventory. However, it will take some time before the information from the full inventory questionnaires will be available.

WGs will need to determine if and what extra information is needed. They can then discuss with WP1 to decide who will collect this extra information. In some cases it may be preferable for the WGs themselves to contact the cohorts for specific extra information, but we want to avoid that cohorts are contacted by many different people for pieces of information.

For the evaluation of available assessment methods, a search for the respective exposures will be done in PubMed. Where available, existing review articles will be used. 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. could serve as sources of information.

Another option may be to contact experts for unpublished studies or dissertations.

2.3. Extraction of information

Study selection:

1. 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 (birth cohort study) or does not assess the outcomes of interest, the study will be excluded.

2. 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 review team.

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 review team.

2.4. 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 exposure assessment
- 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; single-pollutant vs multi-pollutant models; confounder adjustment)
- 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.

3. Description of working-groups

3.1. Outdoor air pollution

3.1.1. Background

Exposure to ambient air pollution has been associated with childhood asthma and allergy; (Brauer et al. 2007; Gladen et al. 1999; Glynn et al. 2000; McConnell et al. 2002; Morgenstern et al. 2008; Nordling et al. 2008; Ryan et al. 2007) and pregnancy outcomes such as intrauterine growth retardation, low birth weight, prematurity, and congenital malformations (Glinianaia et al. 2004; Lacasana et al. 2005; Maisonet et al. 2004; Sram et al. 2005; Stillerman et al. 2008). Recently , there is emerging evidence for an impact of ambient air pollution on the cognitive development of children (Calderon-Garciduenas et al. 2008; Perera et al. 2006; Perera et al. 2009; Suglia et al. 2008) .

Exposure assessment for epidemiological studies of long-term effects of ambient air pollution on pregnancy and childhood health outcomes is a difficult challenge. The first studies relied on between-city comparisons. In the past decade, various studies have indicated the importance of spatial variability in concentration within urban areas as an important determinant of exposure for important pollutants such as NO_2 and black smoke. Personal or stationary monitoring alone will generally not be feasible, as the study populations of epidemiological studies generally comprise several hundreds to thousands of subjects, living or attending school/daycare at different places. An additional complication is that that only long-term (i.e. annual) average concentrations are useful for these studies, so that multiple daily or weekly samples have to be collected. In large parts of Europe, ambient air quality monitoring networks are operated and provide substantial information on the temporal variability in air pollution concentrations. However, the density of the monitoring networks is usually insufficient to reflect the spatial contrasts in air pollution concentrations within urban areas. This may lead to considerable exposure misclassification, especially in relation to pollution from local sources such as traffic. During the last decade, the use of Geographic Information System (GIS)-based methods for air pollution exposure assessment became more and more popular to take into account the within-city variability of air pollution concentrations. These include the use of exposure indicator variables (e.g. traffic intensity at the residential address or distance to a major road), interpolation methods (e.g. kriging, inverse distance weighing), dispersion modelling and land-use regression modelling. An additional complication in studies on air pollution and pregnancy outcomes is that a more detailed temporal resolution is required. It is very common in these studies to express exposures per trimester or month of pregnancy. Only recently, exposure modelling using measurement data and GIS-data were introduced in studies on air pollution and pregnancy outcomes.

3.1.2. Objectives

We will describe here in more detail how exposure to ambient air pollution is assessed in the participating pregnancy and birth cohorts. There are recent review papers on air pollution exposure assessment (Hoek et al. 2008; Jerrett et al. 2005). The purpose of the present review is to complement these reviews rather than to replicate them.

3.1.3. Points to consider in evaluation of exposure information

- Details on protocol
  - exposure modelling
    - Type of model (dispersion, land-use regression, ...)
    - Number of measurement sites, number of measurements per site
  - Air monitoring network
    - Number of monitoring sites used
    - Description of site type
  - Indicator variables
    - Definition/source
  - Questionnaire
    - Exact questions asked
- Comparability of exposure assessment between cohorts
  - Same type of exposure assessment, different protocols: do we believe difference matter?
  - Comparability of different types of assessment (here it might be useful to include data from studies other than the birth cohort studies, since comparison studies are probably scarce)
- Considerations of validity
  - Long-term validity (again, data is probably limited and therefore, data from other studies should be included as well)
- Strengths and limitations of different types of exposure assessments
- Other aspects relevant to exposure assessment
  - Change of residential address
  - time-activity pattern
  - important confounders

3.2. Water contamination

3.2.1. Background

Water contaminants such as disinfection by-products (DBPs), metals, pesticides, nitrates and others have been associated with increased risks of bladder, rectal, and/or colon cancers and adverse pregnancy outcomes (Arbuckle et al. 2002). One of the most researched relationships recently is that of chlorination DBPs and birth outcomes, but the relationship still appears to be inconclusive and inconsistent (Nieuwenhuijsen et al. 2000). Currently a large European project is ongoing to investigate the potential pregnancy outcomes associated with long-term exposure to low levels of disinfectants (such as chlorine) and DBPs called HIWATE (www.hiwate.org). Heavy metals, pesticides and nitrates have been also investigated but to a smaller extent (Ljung et al. 2009; Villanueva et al. 2005; Windham and Fenster 2008). Others such as endocrine disrupting substances have attracted some interested but have not been investigated because they are difficult to measure in water (Smith and Steinmaus 2009).

Assessment of exposure is one of the most difficult and so far the weakest aspects of the epidemiological studies conducted to date. Where it possible to relate contaminants levels in the water with adverse health outcomes, it is better to have also information on personal behavioral information such as ingestion rate of tap water, and for volatile and skin absorbent substances such as trihalomethanes (THMs), information on showering, bathing and swimming to improve the exposure assessment. Furthermore, for example, most monitoring of DBP levels has been limited to total THMs in drinking water, which are generally the most prevalent and are routinely measured, but sometimes they may not be the most important from a health point of view (Arbuckle et al. 2002). Furthermore, there are very real difficulties in making any accurate assessment of DBP exposure because of the variation in concentrations of DBPs in different parts of the distribution system, at different times of the year (Nieuwenhuijsen et al. 2000).

The limited ability to measure of epidemiologic studies to accurately assess exposure to drinking water contaminants has likely caused some of the inconsistencies among studies. Clearly there is a need for better characterization of exposure and the studies to date have used several approaches to overcome the difficulties with varying success. A combination of measurement and modelling could potentially improve the assessment of exposure.

In Europe there are some birth cohort studies that have evaluated or are planning to assess the effects of water contaminants and health outcomes in children (table 1). Combination of this valuable information should bring a good resource to study environmental exposure response relationship. Previously, it should be recommended to do a systematic review in order to compare and evaluate the different exposure assessments and make recommendations for future studies.

Table 3.1. ENRIECO cohorts where water contaminants were assessed or will be assessed (table will be completed when the inventory questionnaire of WP1 will be finished)

Birth cohort	Country	Water contaminants
BiB	UK	THMs, HAAs
INMA	Spain	THMs
KANC	Lithuania	THMs
NFBC 1986	Finland	?
PÉLAGIE	France	THMs, HANs, HAAs, HAKs
RHEA	Greece	THMs

3.2.2. Objectives

The aim of this systematic review is to evaluate how exposure to drinking water contaminants is assessed in the participating European birth cohorts.

- Describe exposure assessments used by European birth cohorts
- Put this information in context with other study designs (case-controls, etc.) and other studies conducted out of Europe
- Compare methods for exposure assessment: type of assessment; ecological/individual monitoring and modelling; personal biomonitoring; water contaminants assessed; sampling procedure; laboratory protocol (sample preparation, standard solutions, instrumentation and conditions); etc.
- Evaluation of variables considered/possible confounders
- Discuss strengths and limitations of different assessment methods (data gaps in the literature; possible confounders not considered; inadequate methodology; small sample size; etc.)
- Give recommendations for further research in European birth cohorts and for the use of methods and tools in cohorts planning exposure assessments

3.2.3. Points to consider in evaluation of exposure information

- Water contaminants: DBPs, pesticides, metals, endocrine disrupting substances, others
- Sampling procedure
- Laboratory protocol (sample preparation, standard solutions, instrumentation and conditions)
- Type of assessment:
    - Routine monitoring water concentration data from water companies or government
    - Modelling of contaminants
    - Newly collected water concentration data (measurements)
    - Questionnaire:

        - information on tap/bottled water ingestion
        - information on coffee, tea and other tap water based beverage ingestion
        - information on swimming habits
        - information on showering/bathing habits
    - Personal biomonitoring
- Evaluation of variables considered/possible confounders

3.3. Allergens and biological organisms

3.3.1. Background and objectives

Infants and children are vulnerable to environmental exposures. Exposure to different stimuli during childhood may lead to under development or chronic diseases. Most of the allergen and biological organisms are ubiquitous, too high or insufficient amount of exposures may lead to adverse health effect such as allergic diseases. In recent years, researches focused on the health effect of allergy and biological organisms have been carried out. However, it is fundamental to perform accurate exposure assessments to correctly evaluate the exposure-response relationship. For example, health effect of allergen exposure has been profoundly studied as the prevalence of allergic diseases has been rapidly increasing. The assessments of allergen exposure, however, are discrepant. Some studies measure allergen level from settled house dust samples from different location of the homes or public places such as schools, some measured air born allergen level, while some studies used surrogates such as cat ownership for the amount of cat allergen exposure. As a result, the discrepant exposure assessment leads to contradictory observations of the exposure-response relationships. Furthermore, the timing of the exposure to allergen and biological organisms is crucial, especially during the perinatal phase when the organ systems of the foetus undergo maturation and formulate reaction mechanisms to these environmental stimuli. Exposure to the same dosages of allergen or biological organisms at different trimester of the pregnancy or during the early years of life may have different influences on different health outcomes. Therefore, more detailed temporal resolution of the exposure assessment is required.

3.3.2. Objectives

The aim of this evaluation is to describe in details the methods of assessments of exposures to allergen or biological organisms from European birth cohort studies.

3.3.3. Points to consider in evaluation of exposure assessment methods

<u>Points to consider in evaluation of exposure assessment methods</u>

- Is the exposure information based on questionnaire data or measurements of the samples?

- Sampled materials (settled house dust samples, air samples,…)
- Sampling location (Public area, home, mattress, floor….)
- Sampling period (repeated measurement over a period of time?, timing of the exposure,…..)
- Sampling device (vacuum cleaner used, filter used, passive sampling dish, wipe test……)
- Post processing of the sample (storage, transportation, sieving,…..)
- Extraction of the bio organisms
- Assay used for the quantifying the bio organisms

3.4. Heavy metals

3.4.1. Background

Metals present in the environment have the potential to induce health effects, especially in fetus and in the yearly years of life. In order to associate correctly metal exposure and health outcomes is necessary to carry out an appropriate sampling collection and treatment as well as the use of sensitive analytical techniques. Besides, there is a need to standardized protocols since quality assurance is crucial to obtain comparable results.

Contaminated water, soil and food, air pollution and smoking habits are the main sources of metal exposures (table 1). The presence of chemicals in the environment can be determined by measurements of their concentrations in the environmental matrices such as air, soil, water or food. However, adverse effects in humans are not necessary related with the metal concentration in the environment. Hence, human biomonitoring provides a more correct estimate of the total dose absorbed and therefore its potential health effects. Most recent studies use biomonitoring as the tool to measure metal exposure but information of this data can be also provided by questionnaire, dietary exposure, occupational exposure, tap water consumption, etc. Whatever it is the assessment tool used it is necessary to take into consideration that there are many host factors (age, gender, genetic), metals interactions, environmental conditions (pH, temperature, salinity) as well as measurement tools and methodologies that influence the effects of metals. Metals speciation and bioavailability, which are frequently interlinked, have to be also considered.

Sometimes, due to the expensive cost of some of these measurements few samples are analyzed and consequently it is difficult to derive conclusive results. In Europe there are some studies that have evaluated or are planning to assess the effects of metal exposure and health outcomes in children (table 2). Combination of this valuable information should bring a good resource to study environmental exposure response relationship. Previously, it should be recommended to do a systematic review in order to compare and evaluate the different metal exposure assessments and make recommendations for future studies.

Table 3.2. Main uses, exposure sources and samples of some metals (adapted from (Wigle 2003) and (Esteban and Castano 2009).

Metal	Uses	Exposure sources	Biological samples
Lead (Pb)	Gasoline; paint; plumbing; industrial (storage batteries, batteries, solders, metals alloys, plastics, leaded glass, ceramic glass); contaminated drinking water; soil/dust	Contaminated water; inhalation of industrial; traffic smoke	Blood (Pb-B) or plasma (Pb-P); cord blood; urine; breast milk; hair (environmental and occupational exposure); saliva (recent exposure); nail (smokers); deciduous teeth and other bones (long-term exposure); meconium; faeces; placenta
Mercury (Hg)	Cathodes; extraction of gold; dental amalgam; thermometers; barometers; mercury vapor lamps; electrical switches	Dental amalgam (elemental mercury); food specially fish, seafood and sea mammals (methylmercury)	Hair (long-term exposure); blood (recent exposure); cord blood (fetal exposure during late gestation); nail; bile; faeces; urine; breast milk
Arsenic (As)	Rocks; soil; water; air; plants; animals	Food; drinking water; soil	Urine (recent and ongoing exposure); blood; hair; nail
Cadmium (Cd)	Batteries; pigments; metal coatings; plastics; metal alloys	Inhalation of cigarette smoke; workplace; food	Blood; urine; hair; nail; breast milk; saliva; meconium; faeces; cord blood; placenta
Manganese (Mn)	Steel production; dry-cell batteries; matches; fireworks; glazes; varnishes; ceramics; nutritional supplements	Food; air; water	Blood; urine (recent exposures)

Table 3.3. ENRIECO cohorts where metals were assessed or will be assessed (table will be completed when the inventory questionnaire of WP1 will be finished)

Birth cohort	Country	Metals assessed	Type of assessment	Samples
ABCD	Netherlands	Planned		
ALSPAC	UK	Planned		
C. Faroes I and II	Faroes Islands	Hg, Pb, Se		
Duisburg	Germany	Hg, Pb, Se, Cd		
EDEN	France	Hg, Pb, Se, Cd, Mn		
ELFE	France	Hg, Pb		
FLESH	Belgium	Pb, Cd		
INMA	Spain	Hg, As, Pb, Cd, Cr, Mn, V	Biological sampling	Urine, cord blood, hair
INUENDO	Denmark	Hg, Pb, Cd	Biological sampling	Total blood
KANC	Lithuania	Planned		
LUKAS	Finland	Hg, Pb, Se, As		
PÉLAGIE	France	Hg		
PMC	Poland	Hg, Pb, Cd, Se	Biological sampling	Blood, cord blood, hair
RHEA	Greece	Hg, Pb, Se, As, Cd, Mn		

[1]Hg: Mercury; Pb: Lead; Se: Selenium; Cd: Cadmium; As: Arsenic; Mn: Manganese

3.4.2. Objectives

The aim of this systematic review is to evaluate the different metal exposure assessments conducted in European birth cohorts.

3.4.3. Points to consider in evaluation of exposure assessment methods

- Metals assessed; speciation
- Instrument used: sample preparation, standards, detection limit, sensitivity & specificity, interferences, units, etc.
- Type of assessment:
    - Biological sampling (spot sample, etc.): hair, urine, blood, nails, etc.
    - Participants: mother, child, father
    - Environmental sampling: water, air, etc.
    - Questionnaires
    - Occupational exposure
    - Dietary exposure
    - Tap water consumption
- Possible confounders: subject variables (age, gender, ethnic, socioeconomic status); environmental variables (pH, temperature, season); tester variables (reliability of the examiners, motivation, level of fatigue, systematic errors); situational variables (physical location of testing, test procedures), etc.

3.4.4. Recommendations

It may have to be considered: the best sample for each metal (correlation with others, speciation correlation, short or long metal exposure information, interactions with other metals, etc.); standardized biological limit values to compare studies; metals that should be further investigated in Europe; other metal exposures; interaction with metals and other environmental exposures (PCBs, air pollution, etc.); bioavailability considered; etc

3.5. Pesticides

3.5.1. Background

Pesticide exposure has been usually assessed in relation to its use in agriculture or other occupations. However, use of pesticides at home (on plants, domestic animals…), in cities or industries (for cleaning roads, parks, industrial sites…) is widespread. Pesticide residues have been found in different compartments of our environment, and therefore contaminate our water resources, ambient air, food and indoor environment. Exposure of pregnant women and their children is of particular concern because little is known about the potential developmental hazards of such exposures.

The first evidence for an increased risks for adverse pregnancy outcomes came from studies assessing occupational exposures, usually considered at higher levels than environmental exposures (Hanke and Jurewicz 2004). More recently, studies have focused on environmental exposures and have provided results varying with methods of exposure assessment and pregnancy outcomes. These studies have investigated water contamination by pesticides, dietary intake of pesticide residues, or residence proximity of the mother to agricultural crops in association with intrauterine growth (Levario-Carrillo et al. 2004; Longnecker et al. 2001; Munger et al. 1997), birth weight (Rodenbeck et al. 2000; Xiang et al. 2000), premature births (Longnecker et al. 2001; Xiang et al. 2000), stillbirths (Bell et al. 2001; Xiang et al. 2000) and congenital anomalies (Carbone et al. 2006; Meyer et al. 2006; Schreinemachers 2003; Xiang et al. 2000). The last results came from three American cohorts which had planned to collect biological samples of the mother and/or the child. They have therefore assessed the exposure to organophosphorous pesticides from urinary biomarkers assuming that these levels of exposure reflected mainly the exposure to domestic use of pesticides and to agricultural activities. They however reported inconsistent associations between these biomarker levels and birth weight, birth length, gestational duration and head circumference (Berkowitz et al. 2003; Berkowitz et al. 2004; Eskenazi et al. 2004; Fenster et al. 2006; Perera et al. 2003; Whyatt et al. 2004). A limiting factor in most of these studies has been crude exposure assessment. Use of ecological exposure estimates results in exposure misclassification. The retrospective nature of many of the studies is likely to introduce errors in exposure assessment. Only few of theses studies have provided combined information on individual and ecological levels. Finally, the multiple sources, the multiple contaminants (mixtures) and the low levels of environmental exposure are the main challenges in assessing the environmental exposure to pesticides.

3.6. Emerging exposures (Bisphenol A, Phthalates, Polyfluorinated Compounds and Brominated Flame Retardants)

3.6.1. Background (incomplete)

During the last years, new concerns have arisen about environmental exposure to industrial chemical substances because of their widespread production and use, potential for toxicity in animals and humans, and, for some, their persistence and bioaccumulation in the environment. Bisphenol A (BPA) and phthalates are plasticizers which are very used for a variety of applications such as baby feeding bottles, food-cans, infant toys, etc. (table 3.4) (Dekant and Volkel 2008; Shea 2003). Brominated Flame Retardants (BFRs) and Poly-Fluorinated Compounds (PFCs) are used for electrical equipment, textiles as well as in

numerous other industrial and consumer applications (Birnbaum and Staskal 2004)[1]. BPA, phthalates, BFRs and PFCs have been linked to endocrine, including estrogenic, effects. Besides, some experimental studies in animals have also described a carcinogenic effect (Birnbaum and Staskal 2004; Joensen et al. 2009; Wigle 2003) (table 3.4).

At this time, most studies of the health effects of these "new" environmental exposures have been conducted in animals and their applicability to humans remains incompletely characterized and controversial (Wigle 2003). In some cases, assessments have used data obtained from environmental media or food; information from biomonitoring should provide more exact information as compared to such indirect assessment (Dekant and Volkel 2008). However, as we are dealing with chemicals of emerging concern, biomonitoring techniques and methods are not always fully standardised and comparisons and interpretation of results may still be problematic.

Recently, epidemiological studies conducted in Europe have shown that the estimated average daily intake of BPA and phthalates as well as the frequency of consumption of canned foods (BPA indicator) are lower than EFSA Tolerable Daily Intake's (Mariscal-Arcas et al. 2009; Ye et al. 2008; Ye et al. 2009)[1]. The effects of low-level exposure to phthalates, BFRs, PFCs and BPA especially in sensitive population, including pregnant and lactating women, premature infants and children, remain unknown however. For these reasons a number of European birth cohort studies have assessed or are planning to assess the effects of these exposures and their health outcomes in children (table 3.5).

However, as these are exposures of emerging concern, there are still many questions surrounding the validity of different measurements and exposure assessment methods. Review, evaluation and comparison of existing data are important prerequisites for the setting of recommendations for future research at the European level.

[1]Polyfluorinated compounds - a new class of global pollutants in the coastal environment. The Coastal Portal (on line) http://www.coastalwiki.org/coastalwiki/Polyfluorinated_compounds-a_new_class_of_global_pollutants_in_the_coastal_environment (consulted 21 August 2009)

Table 3.4. Main uses, exposure sources and samples of bisphenol A, phthalates, brominated flame retardants and poly-fluorinated compounds (to be completed).

Biomarker	Matrix	Uses	Exposure sources	Potential toxic effect	Health effects studied
Bisphenol A	Blood (serum and red blood cells), cord blood and bile (of fish), breast milk, urine	Epoxy resin and polycarbonate plastics	Food cans, bottle caps, water supply pipes, breast feeding	Hormone disruptor-estrogenic activity	Abnormality of reproductive organs, advance female puberty, change behaviour, brain sexual differentiation, increase in prostate size
Phthalates (DEHP, DINP)[2]	Food, indoor air, urine	Plastics (PVC), solvents, lubricating oils, fixatives, detergents, cosmetics, wood finishes	Food, outdoor and indoor air, soils, sediments, toys, medical devices, breast milk	Teratogenic, developmental and reproductive toxicant (estrogenic & anti-androgenic endocrine disruptor), animal carcinogen	Shorter pregnancy duration, preterm birth, intrauterine & postnatal death, malformations, decrease fertility, degeneration of seminiferous tubules, shorter anogenital distance, premature breast development, decrease intrauterine & postnatal growth, neural tube defects
Brominated Flame Retardants (TBBPA, HBCD and Deca-BDE)[1]	Air, soil, sediment, breast milk, serum	Different polymers used in computers, electronics and electrical equipment, televisions, textiles, foam furniture, etc.	Air, soil, food, textiles	Endocrine disruptor (thyroid disruptor; estrogenic effect), animal carcinogen	Thyroid hormone effects, neurobehavioral alterations, early onset of puberty, decrease in ventral prostate, increase prostatal size, decrease epididymal weight, deficits in learning and memory
Polyfluorinated compounds	Soil, water, air, biota, food, blood, breast milk	Carpets (surface treatment), textiles, leather, paper, plymer production, fire-fighting foams, cosmetics, cleaning agents		Endocrine disruptor	Male reproduction

[1]TBBPA: tetrabromobisphenol A; HBCD: hexabromocyclododecane; Deca-BDE: decabromodiphenyl ether. [2]DEHP: diethylhexyl phthalate; DINP: diisononyl phthalate

Table 3.5. ENRIECO European birth cohorts where BPA, Phthalates (Pht), BFRs, and PFCs have been or will be (table will be completed when the inventory questionnaire of WP1 will be finished)

Birth cohort	Country	Exposure assessed	Type of assessment	Sample
Generation R	Netherlands	BPA, Pht	Biological sampling	Urine
INMA	Spain	BPA, Pht, BFRs	Biological sampling & Questionnaire	Urine
INUENDO	Denmark	BPA, Pht	Biological sampling	Serum
Danish National Birth Cohort	Denmark	PFCs	Biological sampling	Serum?
MoBa	Norway	BPA, Pht	Biological sampling	Urine
RHEA	Greece	Pht	Biological sampling	Urine

3.6.2. Objectives

The aim is to evaluate the assessments of exposure to chemicals of emerging concern (bisphenol A, phthalates, polyfluorinated compounds and brominated flame retardants) conducted in European birth cohorts and to set recommendation for future studies.

3.6.3. Points to consider in evaluation of exposure assessment methods

- Type of assessment: biological/environmental sample; etc.
- Sampling procedure: sample preparation; detection limit; sensitivity & specificity; standards; units; etc.

3.7. Radiations (non-ionising, UV, ionizing)

3.7.1. Background (incomplete)

The spectrum of electromagnetic radiation extends from static electric and magnetic fields, through radiofrequency and infrared radiation, to UV and ultimately ionising radiations including X-rays. Various forms of electromagnetic radiation are very different. Ionising radiations - gamma rays given off by radioactive materials, cosmic rays and X-rays – carry enough energy to break bonds between molecules. Non-ionizing radiations include those radiations and fields, e.g. electromagnetic fields and ultraviolet (UV) radiation, which do not have enough energy to cause ionization in tissues, but which may have adverse health consequences in other ways.

Ionizing radiations and birth cohorts. The main health effects of concern in relation to ionizing radiation have traditionally been rare outcomes such as cancers, and outcomes in late adulthood, such as cardiovascular disease. Pregnancy outcomes, congenital anomalies and other, have also been of interest. Exposure to ionizing radiation in the general population is

widespread, but exposure is generally to extremely low doses and studies have therefore tended to focus on populations with above-baseline exposures (e.g. of occupationally, residentially, or medically exposed persons). In children, the main exposures of concern are those from medical radiation sources. The growing use of diagnostic X-rays and of high-dose techniques (CT, interventional procedures) has led to increasing concerns because a) children may be more sensitive to health effects of radiation than adults, b) children tend to receive higher doses to specific organs from these procedures because of their smaller body size, and c) children have a longer life span to express any radiation-related health effect. Studies of cohorts of children exposed to CT scans are ongoing or planned in a number of European countries. However, the combination of rare outcomes and small populations with high exposures means that prospective birth cohort studies in Europe have not been particularly suitable for the study of health effects of ionizing radiation exposure either during pregnancy or childhood. Possible links between exposed cohorts and birth cohorts need further evaluation.

UV radiation and birth cohorts

Solar UV radiation has been associated with harmful effects such as skin cancer, cataracts, and immune suppression and benefits such vitamin D production (Lucas et al. 2006). It is thought that UVR exposure in early childhood may be important in the development of some of these harmful effects, while of course vitamin D production is essential for bone health. There is relative little on the exposure to UVR in children while they may receive considerable exposure to UVR because of their outdoor activities such as outdoor school breaks, sports, and longer holidays than they an adult population. A good indication of children potential UV dose is the latitude where they live, the latitude where they go on holiday (e.g. Southern Europe), the amount of time they spend outdoors during the year (specifically during the summer months), the amount of cloth they wear while outdoors, and if they use sun glasses, use of sun cream, and skin type.

Points to consider:

- latitude where they live
- latitude where they go on holiday
- the amount of time they spend outdoors during the year (e.g. going to and coming back from school, school breaks, sports, other activities), specifically during the summer months, but also possibility other months
- amount of cloth they wear while outdoors (cover shoulders, sun glasses, hat, shorts or less)
- use of sun cream
- skin type (e.g. white, brown, black from Fitzgerald scale).

Non-ionizing radiations and birth cohorts. Again, the main health effects of concern include mainly rare outcomes (childhood cancers) which make the birth cohort design unsuitable. Pregnancy outcomes (spontaneous abortions, malformations, low birth weight, and congenital diseases) have been studied in relation to different EMF sources (computer screens, electric blankets, etc), but few studies have used birth cohort designs. The WHO has identified exposure to RF fields from mobile phones in young people as a research priority and for outcomes other than childhood brain cancers, in particular neurobehavioural outcomes, older birth cohorts have the possibility of playing an important role. The Danish National Birth Cohort study has recently published results relating pre and postnatal use of mobile phones to neurobehavioural outcomes in children (Divan et al 2008).

As the assessment of radiation exposures in birth cohorts is rare and not well developed (Table 1), this WG will focus on setting recommendations of which exposures could be usefully measured within the birth cohort design, and, where appropriate, how exposure assessments could be conducted.

Table 3.6. ENRIECO European birth cohorts where radiation exposures have been or will be assessed (*from preliminary inventory - table will be completed when the inventory questionnaire of WP1 will be finished)*

Birth cohort	Country	Exposure assessed	Type of assessment
INMA	Spain	Mobile phones use during pregnancy	questionnaire
Danish National Birth Cohort	Denmark	Pre and post natal mobile phone use	questionnaire
ALSPAC	UK	X-rays	Questionnaire

3.7.2. Objectives

The aim is to evaluate the assessments of exposure to different types of radiation exposures conducted in European birth cohorts and to set recommendation for future studies.

3.8. Smoking and Second Hand Tobacco Smoke Exposure

3.8.1. Background

The evidence for health hazards associated with exposure to environmental tobacco smoke (ETS) has been extensively reviewed. Children have been identified to be particularly sensitive: ETS exposure is associated with an increased risk of lower respiratory tract infections; increased prevalence of fluid in the middle ear, symptoms of upper respiratory tract irritation; reduction in lung function; new cases of asthma, and additional episodes and increased severity of symptoms in children with asthma. Recently, it has been shown that

maternal tobacco smoke, in particular when the child is born increases the risk of allergic sensitisation (Keil et al. 2009).

In epidemiological studies, exposure to ETS is most frequently assessed by questionnaire reports, (Jaakkola and Jaakkola 1997; Nieuwenhuijsen et al. 2000) less often by measurements of biomarkers, such as urinary nicotine and its metabolite, cotinine, in body fluids (The Surgeon General 2004; US Environmental Protection Agency 1992) and rarely by passive monitors (Eisner et al. 2001; Marbury et al. 1993; O'Connor et al. 1995) All these methods have assets and drawbacks and cover somewhat different aspects of exposure. Questionnaires represent an inexpensive method to assess long term exposures as well as short term exposures experienced by study participants at different locations.

However, using questionnaires may result in misclassification from recall bias and response bias due to awareness of the hypothesis or parents' feelings of guilt for smoking in the presence of their children. Passive monitors can be used for stationary or personal monitoring of short term exposures. While stationary monitoring provides a measure of exposure in one specific environment (for example, an individual's home), personal monitoring provides an integrated measure of exposure across a number of environments, but does not provide information on exposure in individual environments.

Validation with indoor air nicotine measurements across several studies with preschool and school children demonstrated that parental questionnaires of smoking habits gave good estimates of passive smoking exposure (Brunekreef et al. 2000; Gehring et al. 2006; Nieuwenhuijsen et al. 2000). Questionnaires seem to provide sufficiently accurate qualitative information on tobacco smoke exposure; however, quantitative information needs to be interpreted with more caution.

3.8.2. Objectives

We will describe here in more detail how exposure to second hand tobacco smoke (SHS) has been assessed in the participating cohorts.

3.8.3. Points to consider when evaluating exposure information

- Cotinine levels
  - Type of method
  - Number of measurements and timing of theses
- Questionnaire
  - Exact questions asked

3.8.4. Recommendations

- If someone wants to study the health effects of exposure to SHS and has not assessed exposure to SHS, yet, which of the approaches that are currently used do we think is best and would we like to recommend for use in health effects studies
- Are there further developments of the currently used exposure assessments that could be the focus of future projects, such as tobacco-specific *N*-nitrosamines in urin?

3.9. Noise

3.9.1. Background

Chronic noise exposure is one of the most common environmental pollutants for the European population. Environmental/community noise refers to noise from domestic neighborhood and traffic sources, noise due to constructions and to industries. While exposure to occupational noise is restricted to isolated population groups, community noise is omnipresent and scarcely avoidable.

The most difficult challenge of road traffic noise assessment is to disentangle the health impact of exhaust fumes versus noise, as often both occur simultaneously. Noise is hypothesized to make an independent contribution to immune-mediated diseases, for which stress acts as a co-factor. Sleep disturbance, sympathetical and endocrinological stress responses are assumed to be mediators in the causal pathway between noise and health outcomes. Known physical correlates are an increased heart rate, blood pressure and stress hormone release.

Differences in noise assessment are essential and may account for a great amount of outcome variability.

Several studies focus on traffic density, asking for truck and motorcar traffic. Other chronic noise sources (domestic, airport or train noise) and differentiations between day- and night-time exposures are inconsistently assessed. This may lead to considerable exposure misclassification.

Another crucial consideration is the discrimination between objective noise measurements (for instance, by specific catalogues for workplace noise, by traffic noise maps) versus subjective assessments of noise exposure by annoyance and disturbance scales. In many studies, noise sensitivity, which is considered to be a personality trait, remains neglected so far. Thus, there is first evidence that noise sensitivity may act as one of the most essential confounders for noise exposure and its association with health effects. Other potential confounders, as socio-economic status, smoking, environmental tobacco smoke or time span living in the present dwelling are also irregularly integrated in former investigations.

Children and adolescents might constitute an important vulnerable group to chronic stressors as community noise, as well as expectant mothers.

Ongoing birth cohorts have the ideal study design to examine different chronic noise exposures and their relation to cardiovascular (e.g. blood pressure), immunological (e.g. asthma) and mental disorders. It will require a closer look to the type of objective and subjective exposure assessments, used in different studies, to evaluate results properly.

3.9.2. Objectives

It will be described if and how chronic noise exposure is assessed in published studies and European birth cohorts. One focus is the distinction between objective and subjective measures. It will be evaluated how often each method is used and if methods are used in combination, making the validation of different instruments possible.

Recommendations of the minimum required measurements will be made for potential further use of different assessment methods.

3.9.3. Methods

Inclusion criteria

Study Type:

- Observational study (longitudinal and cross-sectional)
- Meta-analysis
- Systematic review

Exposure:

- Chronic noise exposure (objectively and subjectively assessed)
- Noise annoyance

Each will be taken into consideration for all types of chronic community noise, at school (for children and adolescents) and at work (for expectant mothers).

Method of noise exposure assessment:

- Objective assessments
- Parent/child reported noise exposure
- Parent/child reported noise annoyance

Exclusion criteria:

- Laboratory noise experiments/studies (no assessment of chronic noise exposure)
- Other noise sources (e.g. noise of neonatal intensive care units)

Points to consider in evaluation of exposure information

Summaries will contain details on study protocols, as information on indicator variables, detailed variables definition in questionnaires and exposure modeling.

Comparability of studies will be discussed, regarding similar assessment types, as well as comparability between obviously different types of assessment and how they were validated if applicable.

3.10. Persistent organic pollutants

3.10.1. 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 (Gladen et al. 1999; Glynn et al. 2000).

Assessment of human exposure to persistent organic pollutants has been performed in several European cohorts as a basis for epidemiological studies. Although estimation of exposures based on food intake was used as method for determination of exposure in some of the earlier epidemiological studies, recent studies have exclusively used direct measurement of the chemical compounds in biological samples from humans, with HPLC methods.

Several of the studies participate in interlaboratory calibration programmes and thus the measured concentration in different studies should be comparable across studies.

3.10.2. Objectives

We will describe here in more detail how exposure persistent organic pollutants is assessed in the participating cohorts.

There are recent review papers on persistent organic pollutiant exposure assessment, e.g.

- Fromme H, Tittlemier SA, Völkel W, Wilhelm M, Twardella D. Perfluorinated compounds--exposure assessment for the general population in Western countries. Int J Hyg Environ Health. 2009 May;212(3):239-70.
- Non-invasive matrices in human biomonitoring: a review. Esteban M, Castaño A. Environ Int. 2009 Feb;35(2):438-49. Epub 2008 Oct 31. Review.

The purpose of the present review is to complement these reviews rather than to replicate them.

3.10.3. Methods

Inclusion criteria

- All European pregnancy and birth cohorts in which exposure to persistent organic pollutants is assessed (including cohorts with ongoing exposure assessment). The following list of exposures will be included:
  - chlordane
  - DDT and metabolites
  - dieldrin and endrin
  - Heptachlor
  - Hexachlorobenzene
  - Mirex
  - Polychlorinated biphenyls
  - Polychlorinated dibenzo-p-dioxins
  - Polychlorinated dibenzo furans
  - Toxaphene
  - Brominated flame retardants
  - Flourinated compounds
  - Organometallic compunds (TBT)

Exclusion criteria

- None

Points to consider when evaluating exposure information

- Details on protocol
  - Methods for exposure assessment
  - Types of biosamples used
- Considerations of validity
  - Is spot measurement representing long-term exposures ?
  - How precise is individual measures of POPs

3.11. Occupation

3.11.1. Background

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.

Occupational exposures are more or less precisely defined by 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, 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.

In addition to difficulties in exposure assessment, 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 especially for rare outcomes. Use of existing birth cohorts to improve knowledge on these issues is therefore particularly relevant.

3.11.2. Methods

Task 1: *Description of methods for occupations/occupational exposures assessment in the participating cohorts (collected according to questionnaire included in WP1)*

Table 3.7: Description of data collected relative to parental occupational history in Enrieco cohorts

Cohort	Source of information	Timing of assessment	Coding used	**M**other or **F**ather/ Period covered	N participants with info recorded/coded
ex.PELAGIE	Self report mother	Pregnancy (3 months)	ILO 1968 +ISIC 1971	M: periconceptual, early pregnancy; F: periconceptual, early pregnancy;	3421/3421 3421/3421
PELAGIE	Self report mother	2 years after pregnancy	ILO 1968 +ISIC 1971	M: late pregnancy	1506
XYZ					

Table 3.8: Description of data collected relative to parental occupational exposures in Enrieco cohorts

Cohort	Source/ Timing*	Agents considered	Type of assessment	**M**other or **F**ather/ Period covered	N participants with info recorded/coded
ex PELAGIE		Solvents	-checklist -occupation +JEM	M: periconceptual, early pregnancy;	3421/3421
XYZ					

* if different from first table

Task 2: *Selection of priority occupations and occupational exposures for further work*

During the kick-off meeting in Barcelona a number of occupations and occupational exposures were listed as deserving special consideration:

Occupations: health-care workers, hairdressers, cleaners, day care workers, cooks, flight attendants, agricultural workers, drivers, electricians, biomedical research workers…

Occupational exposures: solvents, endocrine disrupters (including pesticides, cosmetics…), physical exposures (noise, heat, work load, night shift), psychological stress….

These preliminary lists will be completed and discussed between partners and also in association with the review on health effects conducted in WP4. Numbers of subjects of the participating cohorts belonging to each category will be counted.

Task 3: *Inventory of existing questionnaires and JEMs available in Europe, of validation studies for these tools and assessment of their applicability to Enrieco cohorts*

Available JEMs, task-specific questionnaires and validation studies will be identified. Their potential use in Enrieco cohorts will be assessed and the extra-work needed to apply these JEMs to Enrieco cohorts will be estimated.

Task 4: *Identification of national or European surveys describing the specificity of occupational exposures in some priority occupations*

Surveys (very often unpublished reports) describing exposure profiles of similar occupations in different European countries will be retrieved and the validity of grouping similar occupations across cohorts will be assessed.

Task 5: *Building of a protocol for creating a common data base for a selected number of occupations/occupational exposures for future analyses*

Following previous inventories of: available Enrieco data, occupational exposure assessment tools and national surveys, a protocol for grouping a number of Enrieco cohorts and building a common data base on occupation will be prepared.

Task 6: *Recommendations for data collection and coding for occupations and for a selected number of occupational exposures*;

In parallel, strengths and weaknesses of existing methods for occupational exposure assessment will be discussed and recommendations for future data collection including built-in validation procedures will be drafted.

Task 7: *Reporting*

4. Deliverables and time schedule

Work package 2 started in month 4 of the project (June 2009). Table xx summarizes the deliverables of the work package as described in the Description of work.

Table 4.1 Deliverables of work package 2.

No.	Description	Due
D3	Protocol for evaluation of environmental exposure information	Month 6 (Aug 2009)
D4	Report, including a scientific paper ready for submission, with evaluation of environmental information and recommendations	Month 21 (Nov 2010)
D5	Report, including a scientific paper ready for submission, of methods and approaches of evaluating occupational exposures in European birth cohorts	Month 21 (Nov 2010)

A more detailed time schedule for the work within work package 2 is presented below:

Time schedule:

- September 2009: draft protocol sent to WP leader and WG members. Final version by end of September.
- January-February 2010: draft evaluations and discussions between WG participants (5-10 pages)
- April 2010: final comments from all WG participants on the draft report
- May 2010: (2nd ENRIECO meeting) discussion of the draft report with results and recommendations
- After 2nd ENRIECO meeting (until Oct/Nov 2010): finalization of reports and writing of scientific papers.

5. References

Arbuckle TE, Hrudey SE, Krasner SW, Nuckols JR, Richardson SD, Singer P et al. 2002. Assessing exposure in epidemiologic studies to disinfection by-products in drinking water: report from an international workshop. Environ.Health Perspect. 110 Suppl 1:53-60.

Bell EM, Hertz-Picciotto I, Beaumont JJ. 2001. Case-cohort analysis of agricultural pesticide applications near maternal residence and selected causes of fetal death. Am.J.Epidemiol. 154:702-710.

Berkowitz GS, Obel J, Deych E, Lapinski R, Godbold J, Liu Z et al. 2003. Exposure to indoor pesticides during pregnancy in a multiethnic, urban cohort. Environ.Health Perspect. 111:79-84.

Berkowitz GS, Wetmur JG, Birman-Deych E, Obel J, Lapinski RH, Godbold JH et al. 2004. In utero pesticide exposure, maternal paraoxonase activity, and head circumference. Environ.Health Perspect. 112:388-391.

Birnbaum LS, Staskal DF. 2004. Brominated flame retardants: cause for concern? Environ.Health Perspect. 112:9-17.

Brauer M, Hoek G, Smit HA, de Jongste JC, Gerritsen J, Postma DS et al. 2007. Air pollution and development of asthma, allergy and infections in a birth cohort. Eur Respir J 29:879-888.

Brunekreef B, Leaderer BP, van Strien R, Oldenwening M, Smit HA, Koopman L et al. 2000. Using nicotine measurements and parental reports to assess indoor air: the PIAMA birth cohort study. Prevention and Incidence of Asthma and Mite Allergy. Epidemiology 11:350-352.

Calderon-Garciduenas L, Mora-Tiscareno A, Ontiveros E, Gomez-Garza G, Barragan-Mejia G, Broadway J et al. 2008. Air pollution, cognitive deficits and brain abnormalities: a pilot study with children and dogs. Brain Cogn 68:117-127.

Carbone P, Giordano F, Nori F, Mantovani A, Taruscio D, Lauria L et al. 2006. Cryptorchidism and hypospadias in the Sicilian district of Ragusa and the use of pesticides. Reprod.Toxicol. 22:8-12.

Dekant W, Volkel W. 2008. Human exposure to bisphenol A by biomonitoring: methods, results and assessment of environmental exposures. Toxicol.Appl.Pharmacol. 228:114-134.

Eisner MD, Katz PP, Yelin EH, Hammond SK, Blanc PD. 2001. Measurement of environmental tobacco smoke exposure among adults with asthma. Environ Health Perspect 109:809-814.

Eskenazi B, Harley K, Bradman A, Weltzien E, Jewell NP, Barr DB et al. 2004. Association of in utero organophosphate pesticide exposure and fetal growth and length of gestation in an agricultural population. Environ.Health Perspect. 112:1116-1124.

Esteban M, Castano A. 2009. Non-invasive matrices in human biomonitoring: a review. Environ.Int. 35:438-449.

Fenster L, Eskenazi B, Anderson M, Bradman A, Harley K, Hernandez H et al. 2006. Association of in utero organochlorine pesticide exposure and fetal growth and length of gestation in an agricultural population. Environ.Health Perspect. 114:597-602.

Gehring U, Leaderer BP, Heinrich J, Oldenwening M, Giovannangelo ME, Nordling E et al. 2006. Comparison of parental reports of smoking and residential air nicotine concentrations in children. Occup Environ Med

Gladen BC, Longnecker MP, Schecter AJ. 1999. Correlations among polychlorinated biphenyls, dioxins, and furans in humans. Am.J.Ind.Med. 35:15-20.

Glinianaia SV, Rankin J, Bell R, Pless-Mulloli T, Howel D. 2004. Particulate air pollution and fetal health: a systematic review of the epidemiologic evidence. Epidemiology 15:36-45.

Glynn AW, Wolk A, Aune M, Atuma S, Zettermark S, Maehle-Schmid M et al. 2000. Serum concentrations of organochlorines in men: a search for markers of exposure. Sci.Total Environ. 263:197-208.

Hanke W, Jurewicz J. 2004. The risk of adverse reproductive and developmental disorders due to occupational pesticide exposure: an overview of current epidemiological evidence. Int.J.Occup.Med.Environ.Health 17:223-243.

Hoek G, Beelen R, de Hoogh C, Vienneau D, Gulliver J, Briggs D. 2008. A review of land-use regression models to assess spatial variation of outdoor air polution. Atmos Environ

Jaakkola MS, Jaakkola JJ. 1997. Assessment of exposure to environmental tobacco smoke. Eur Respir J 10:2384-2397.

Jerrett M, Arain A, Kanaroglou P, Beckerman B, Potoglou D, Sahsuvaroglu T et al. 2005. A review and evaluation of intraurban air pollution exposure models. J Expo Anal Environ Epidemiol 15:185-204.

Joensen UN, Bossi R, Leffers H, Jensen AA, Skakkebaek NE, Jorgensen N. 2009. Do perfluoroalkyl compounds impair human semen quality? Environ.Health Perspect. 117:923-927.

Keil T, Kulig M, Simpson A, Custovic A, Wickman M, Kull I et al. 2006a. European birth cohort studies on asthma and atopic diseases: I. Comparison of study designs -- a GALEN initiative. Allergy 61:221-228.

Keil T, Kulig M, Simpson A, Custovic A, Wickman M, Kull I et al. 2006b. European birth cohort studies on asthma and atopic diseases: II. Comparison of outcomes and exposures--a GA2LEN initiative. Allergy 61:1104-1111.

Keil T, Lau S, Roll S, Gruber C, Nickel R, Niggemann B et al. 2009. Maternal smoking increases risk of allergic sensitization and wheezing only in children with allergic predisposition: longitudinal analysis from birth to 10 years. Allergy 64:445-451.

Lacasana M, Esplugues A, Ballester F. 2005. Exposure to ambient air pollution and prenatal and early childhood health effects. Eur J Epidemiol 20:183-199.

Levario-Carrillo M, Amato D, Ostrosky-Wegman P, Gonzalez-Horta C, Corona Y, Sanin LH. 2004. Relation between pesticide exposure and intrauterine growth retardation. Chemosphere 55:1421-1427.

Ljung KS, Kippler MJ, Goessler W, Grander GM, Nermell BM, Vahter ME. 2009. Maternal and early life exposure to manganese in rural Bangladesh. Environ.Sci.Technol. 43:2595-2601.

Longnecker MP, Klebanoff MA, Zhou H, Brock JW. 2001. Association between maternal serum concentration of the DDT metabolite DDE and preterm and small-for-gestational-age babies at birth. Lancet 358:110-114.

Lucas R, McMichael T, Smith W, Armstrong B. Solar Ultraviolet Radiation: Global burden of disease from solar ultraviolet radiation. 2006. Geneva, World Health Organization Public Health and the Environment.

Maisonet M, Correa A, Misra D, Jaakkola JJ. 2004. A review of the literature on the effects of ambient air pollution on fetal growth. Environ Res 95:106-115.

Marbury MC, Hammond SK, Haley NJ. 1993. Measuring exposure to environmental tobacco smoke in studies of acute health effects. Am J Epidemiol 137:1089-1097.

Mariscal-Arcas M, Rivas A, Granada A, Monteagudo C, Murcia MA, Olea-Serrano F. 2009. Dietary exposure assessment of pregnant women to bisphenol-A from cans and microwave containers in Southern Spain. Food Chem.Toxicol. 47:506-510.

McConnell R, Berhane K, Gilliland F, London SJ, Islam T, Gauderman WJ et al. 2002. Asthma in exercising children exposed to ozone: a cohort study. Lancet 359:386-391.

Meyer KJ, Reif JS, Veeramachaneni DN, Luben TJ, Mosley BS, Nuckols JR. 2006. Agricultural pesticide use and hypospadias in eastern Arkansas. Environ.Health Perspect. 114:1589-1595.

Morgenstern V, Zutavern A, Cyrys J, Brockow I, Koletzko S, Kramer U et al. 2008. Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. AM J RESPIR CRIT CARE MED 177:1331-1337.

Munger R, Isacson P, Hu S, Burns T, Hanson J, Lynch CF et al. 1997. Intrauterine growth retardation in Iowa communities with herbicide-contaminated drinking water supplies. Environ.Health Perspect. 105:308-314.

Nieuwenhuijsen MJ, Toledano MB, Eaton NE, Fawell J, Elliott P. 2000. Chlorination disinfection byproducts in water and their association with adverse reproductive outcomes: a review. Occup.Environ.Med. 57:73-85.

Nordling E, Berglind N, Melen E, Emenius G, Hallberg J, Nyberg F et al. 2008. Traffic-related air pollution and childhood respiratory symptoms, function and allergies. Epidemiology 19:401-408.

O'Connor TZ, Holford TR, Leaderer BP, Hammond SK, Bracken MB. 1995. Measurement of exposure to environmental tobacco smoke in pregnant women. Am J Epidemiol 142:1315-1321.

Perera FP, Li Z, Whyatt R, Hoepner L, Wang S, Camann D et al. 2009. Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. Pediatrics 124:e195-e202.

Perera FP, Rauh V, Tsai WY, Kinney P, Camann D, Barr D et al. 2003. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. Environ Health Perspect 111:201-205.

Perera FP, Rauh V, Whyatt RM, Tsai WY, Tang D, Diaz D et al. 2006. Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. Environ Health Perspect 114:1287-1292.

Rodenbeck SE, Sanderson LM, Rene A. 2000. Maternal exposure to trichloroethylene in drinking water and birth-weight outcomes. Arch.Environ.Health 55:188-194.

Ryan PH, LeMasters GK, Biswas P, Levin L, Hu S, Lindsey M et al. 2007. A comparison of proximity and land use regression traffic exposure models and wheezing in infants. Environ Health Perspect 115:278-284.

Schreinemachers DM. 2003. Birth malformations and other adverse perinatal outcomes in four U.S. Wheat-producing states. Environ.Health Perspect. 111:1259-1264.

Shea KM. 2003. Pediatric exposure and potential toxicity of phthalate plasticizers. Pediatrics 111:1467-1474.

Smith AH, Steinmaus CM. 2009. Health effects of arsenic and chromium in drinking water: recent human findings. Annu.Rev.Public Health 30:107-122.

Sram RJ, Binkova B, Dejmek J, Bobak M. 2005. Ambient air pollution and pregnancy outcomes: a review of the literature. Environ Health Perspect 113:375-382.

Stillerman KP, Mattison DR, Giudice LC, Woodruff TJ. 2008. Environmental exposures and adverse pregnancy outcomes: a review of the science. Reprod Sci 15:631-650.

Suglia SF, Gryparis A, Wright RO, Schwartz J, Wright RJ. 2008. Association of black carbon with cognition among children in a prospective birth cohort study. Am J Epidemiol 167:280-286.

The Surgeon General. The health consequences of smoking. 2004. Washington, DC, Dept. of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health.

US Environmental Protection Agency. Respiratory health effects of passive smoking: lung cancer and other disorders. EPA/600/6-90/006F.1992. Washington, DC, US Environmental Protection Agency.

Villanueva CM, Durand G, Coutte MB, Chevrier C, Cordier S. 2005. Atrazine in municipal drinking water and risk of low birth weight, preterm delivery, and small-for-gestational-age status. Occup.Environ.Med. 62:400-405.

Whyatt RM, Rauh V, Barr DB, Camann DE, Andrews HF, Garfinkel R et al. 2004. Prenatal insecticide exposures and birth weight and length among an urban minority cohort. Environ Health Perspect 112:1125-1132.

Wigle,DT, 2003, Metals-Lead & Metals-Mercury, Arsenic, Cadmium, and Manganese, in DT Wigle (ed), Child Health and the Environment: Oxford University Press, USA, p. 71-135.

Windham G, Fenster L. 2008. Environmental contaminants and pregnancy outcomes. Fertil.Steril. 89:e111-e116.

Xiang H, Nuckols JR, Stallones L. 2000. A geographic information assessment of birth weight and crop production patterns around mother's residence. Environ.Res. 82:160-167.

Ye X, Pierik FH, Angerer J, Meltzer HM, Jaddoe VW, Tiemeier H et al. 2009. Levels of metabolites of organophosphate pesticides, phthalates, and bisphenol A in pooled urine specimens from pregnant women participating in the Norwegian Mother and Child Cohort Study (MoBa). Int.J.Hyg.Environ.Health 212:481-491.

Ye X, Pierik FH, Hauser R, Duty S, Angerer J, Park MM et al. 2008. Urinary metabolite concentrations of organophosphorous pesticides, bisphenol A, and phthalates among pregnant women in Rotterdam, the Netherlands: the Generation R study. Environ.Res. 108:260-267.