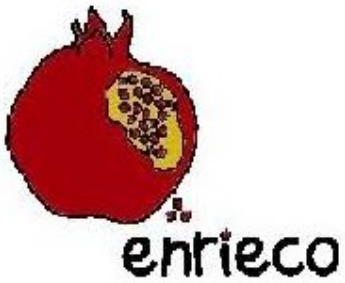
ENRIECO



Work Package 4

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

Protocol

prepared by Chih-Mei Chen

Draft version 1

November 12, 2009

Contents

1 Background and Context

1.1 Rationale and Objective

The associations between environmental hazards and adverse health outcomes have been investigated by epidemiological studies. For foetus and infants who are especially vulnerable to the exposure to environmental risk factors that disrupt the developmental processes, birth cohort studies were conducted to exam the causal link between exposures and responses. However, different studies often report contradictory observations.

Many factors may influence the exposure-response associations observed in birth cohort studies. Most frequently discussed are the different methods employed for the assessment of the environmental exposure and health outcomes. For example, the health effects of exposures to ambient air pollution have been intensively studied, and the level of exposure may be defined based on the measurements from personal monitoring, model led exposure using the information of stationary monitors, or questionnaire or interview based self-assessed exposure. On the other hand, the assessments of the health outcomes may be based on physician diagnoses, reported symptoms in the questionnaires or interviews, or medication use. Therefore, here is a need to systematically address the discrepancies of the methodology between the studies and how they are linked to inconsistent observed exposure-response relationships.

In addition, in many cases, the studies have limited statistical power to study rare health outcomes or exposures with a low prevalence. Therefore, many important exposure-response associations are not yet well explored. The main objective of this

work package is to systematically collect information from the existing exposure response data including the methods and tools that were used from European birth cohort studies, evaluate the information, and identify knowledge gaps. The secondary objectives are:

- Perform a systematic review on peer reviewed (published or impressed) exposure-response relationships of major environmental hazards on different health outcomes in European birth cohort studies.
- Evaluation of the availability, quality, and the potential use of the published information
- Evaluation of the appropriate adjustment of confounding factors, potential bias, and the possibility of chance findings.
- Identify strengths and limitations
- Make recommendations to harmonize future research on exposure-response associations by identifying the appropriate exposure assessment, health outcome definition, and statistical tools, in order to achieve future meta or polled analysis. The reviews will identify areas where only limited knowledge is available and proposals for further use of the environmental exposure, response data will be made.

1.2 Working groups

A total number of eleven exposure response relationships will be evaluated. Each theme will be lead by one working group.

Table 1.1: Working Groups for Evaluation of Exposure Response Relationship

Theme	WG Leader	WG Members
Air pollution and Birth Outcomes	Manolis Kogevinas kogevinas@creal.cat	Ulrike Gehring Frank Pierik Anne Marie Nybo Remy Slama Kinga Polanska Ferran Ballester Koppen Gudrun
Air Pollution and Allergy and Asthma	Bert Brunekreef b.brunekreef@iras.uu.nl	Joachim Heinrich Ulrike Gehring John Henderson Maties Torrent
Allergens/Biological Organism and Allergy and Asthma	Joachim Heinrich joachim.heinrich@helmotz-muenchen.de	Chih-Mei Chen Christina Tischer Ulrike Gehring Maties Torrent Constantine Vardavas
Pesticides and Birth Outcomes	Sylvaine Cordier sylvaine.cordier@univ-rennes1.fr	Cecile Chevrier Frank Pierik Jens Peter Bonde Stephanie Vandentorren
Second Hand Smoking and Birth Outcomes	Constantine Vardavas vardavas@edu.med.uoc.gr	Kinga Polanska Francesa Bravi
Water contaminants and Birth Outcomes	Mark Nieuwenhuijsen	

Table 1.1: Working Groups for Evaluation of Exposure Response Relationship

Theme	WG Leader	WG Members
	mnieuwenhuijsen@creal.cat	
Metals and Birth Outcomes	Jordi Sunyer jsunyer@creal.cat	Maribel Casas Kinga Polanska Ferran Ballester Constantine Vardavas
Metals and Neurobehavioural/Cognitive	Jordi Sunyer jsunyer@creal.cat	Maribel Casas Constantine Vardavas
POPs and Birth Outcomes	Jens Peter Bonde jpb@bbh.regionh.dk	Gunnar Toft Sylvaine Cordier Pal Weihe Stephanie Vandentorren Ferran Ballester
POPs and Neurobehavioural/Cognitive Function	Jordi Sunyer	Sylvaine Cordier
	jsunyer@creal.cat	Joan Forns
Noise, Birth Outcomes, Asthma/Allergy, and Cardiovascular Outcomes	Thomas Keil thomas.keil@charite.de	Cynthia Hohmann Frank Pierik Cynthia Hohmann Maria Pia Fantini Lorenza Luciano
Occupation and Birth Outcomes	Martine Vrijheid mvrijheid@creal.cat	Jens Peter Bonde Sylvaine Cordier Remy Slama Frank Pierik MP Fantini

Table 1.1: Working Groups for Evaluation of Exposure Response Relationship

Theme	WG Leader	WG Members
		Lorenza Luciano Kinga Polanska Anne Marie Nybo Andersen

1.3 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.

1.4 Structure of the review

1. Background and context
2. Current work in the European birth cohorts:

    - Summary of study characteristics and key results in tables which will include information of authors, country and data collection period, size of the cohort included, type and age of exposure assessment, health outcome endpoint, confounders, and key results

- Comparison/evaluation of assessment methods

3. Recommendations for future research in European birth cohorts:

- Methods and tools for future exposure and health outcome assessment (combination with WP 2 and 3)
- Methods and tools for future statistical analysis of exposure-response relationships
- Methods for future pooled or meta- analysis of existing exposure-response relationship assessed in cohort studies
- Data collection and analysis of those exposure-response relationships which are not sufficiently investigated in current literature

1.5 Inclusion criteria

1.5.1 Study population

Main population: European birth cohort studies (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.

1.5.2 Study design:

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

- Systematic reviews

1.5.3 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 webpages: 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.

1.5.4 Information extraction

Study selection:

- 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, but it is clear that the WG leader will be responsible for conducting the searches.

1.6 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 multipollutant 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.

1.7 Time schedule

- January-February 2010: draft systematic review (5-10 pages)

- April 2010: comments from WG participants
- May 2010: (2nd ENRIECO meeting) discussion of the results and recommendations

2 Air Pollution and Birth Outcomes

2.1 Background

There is extensive evidence that short-term increases in ambient air pollution result in increased mortality and morbidity in adults and children, and that even low-level long term exposure is associated with several adverse health effects. Pregnant women and children are a subgroup of the population who could be vulnerable to the effects of air pollution, particularly traffic-related. Numerous studies published in the last decade have reported that adverse effects of traffic-related air pollution already manifest during the prenatal period by increasing the risk of intrauterine growth restriction, low birth weight, and preterm birth [1, 2]. Although results from these studies show considerable evidence for some birth outcomes, they are still inconclusive in identifying the most harmful pollutants and the most susceptible periods within gestation. Synthesis of the findings has been difficult for various reasons, including differences in study design, air exposure assessment, adjustment for confounding, and definition of birth outcomes [3]. In a meeting report on air-pollution and reproductive outcomes it was highlighted that research in this field needs input from toxicology, exposure assessment, and clinical research, especially to aid in the identification and exposure assessment of fetotoxic agents in ambient air, in the development of early markers of adverse reproductive outcomes, and of relevant biological pathways [2].

Table 2.1. ENRIECO cohorts where air pollution and birth outcomes were assessed or will be assessed (table in progress)

Birth cohort	Country	Air pollution[1]	Birth outcomes[2]
ABCD	Netherlands	PM_{10}, PM_{25}, NO_x	BW, GA, SB, CA
ALSPAC	UK	Yes	BW, GA, SB, CA
APREG	Hungary	PAHs, NO_2, PM_{10}	BW, GA, SA
BAMSE	Sweden	NO_2, PM_{10}, NO_x, PM_{25}	BW, GA
BiB	UK	NO_2, NO_x	BW, GA, US
DNBC	Denmark	Yes	BW, GA, SB, SA, CA
EDEN	France	NO_2, PM_{10}	BW, GA, US
FLESH	France	NO_2, PM_{10}, O_3	BW, GA
Generation R	Netherlands	PM_{10}, PM_{25}, NO_2	BW, GA
GESP II	Italy	NO_2, PM_{10}, NO_x, PM_{25}, O_3	BW, GA, SB, CA
INMA	Spain	PAHs, O_3, VOCs, NO_2	BW, GA, US, AGD
KANC	Lithuania	NO_2, PM_{25}, NO_x	BW, GA, US
LISA	Germany	PM_{25}, NO_2, PM_{10}	BW, GA
MoBa	Norway	PM_{10}, PM_{25}, NO_x	BW, GA, SB, SA, US, CA
PIAMA	Netherlands	PM_{25}, NO_2	BW, GA
RHEA	Greece	PM_{10}, PM_{25}, NO_x	BW, GA, SB, SA, US, AGD

[1] NO_2: nitrogen dioxide; NO_x: nitrogen oxides; PM_{10}: particulate matter <10 µg in diameter; PM_{25}: particulate matter <2.5 µg in diameter; O_3: ozone; PAHs: Polycyclic Aromatic Hydrocarbons; VOCs: Volatile Organic Compounds.
[2] BW: birth weight; GA: gestational age; SB: stillbirth; CA: congenital anomalies; US: ultrasound measurement; AGD: anogenital distance; SA: spontaneous abortion.

To advance in this emerging and fast-growing field, some key methodological issues have been highlighted. Because most of studies have linked birth outcomes and covariates from birth certificate records with routinely measured air pollutants (cross-sectional design), prospective cohorts studies are needed to obtain high-quality individual data on outcomes, covariates, and exposure estimates [3]. The ENRIECO framework brings together over 30 birth/mother-child cohorts and most of them evaluate air pollution and birth outcomes (table 2.1). Therefore, ENRIECO provides the basis for improving our understanding of the effects of air pollution on human pregnancy outcomes.

2.2 Aim

The aim of this systematic review is to evaluate the association between air pollution and birth outcomes in European birth cohorts.

2.3 Objectives

- Describe currently available data published by European birth cohorts.

Systematic review of published literature.

- Put this information in context with other study designs and other studies conducted out of Europe (mainly using existing reviews).
- Identify strengths and limitations
- Set recommendations for future research in European birth cohorts, in close collaboration with WP2.

2.4 Methods

Exposure:

- Dispersion modeling
- Land-use regression modeling (LUR)
- Routine air monitoring network measurements (e.g. nearest monitor; interpolation)
- Exposure indicator variables (e.g. traffic density; proximity to traffic/industry from geographic information system)
- Questionnaires (e.g. self-reported traffic densities; proximity to traffic or industrial sources; wood smoke exposure)
- Individual measurements (e.g. personal monitoring; stationary measurements outside/inside participants' homes)

Health outcomes:

- Time to pregnancy
- Congenital anomalies
- Spontaneous abortions (until 21 weeks of amenorrhea)
- Stillbirths (after 22 weeks of amenorrhea)
- Prematurity and gestational duration (Gestational duration, Gestational age, preterm delivery, very preterm delivery)
- Birth weight and foetal growth (Low birth weight, term low birth weight, small for gestational age, foetal growth restriction)

3

Air Pollution, Allergy and Asthma

3.1 Background

Numerous studies from Europe and elsewhere suggest that current levels of air pollution can exacerbate existing asthma [4, 5]. For example, asthmatics experience more symptoms and attacks, thus require more health care services as daily ambient levels of pollution increase. The role of exposure to ambient air pollution in the development of childhood asthma, allergy, and related symptoms, however, remains less clear [6, 7, 8] due in part to the limited number of prospective birth cohort studies addressing this problem.

The prevalence of respiratory symptoms changes rapidly during childhood and only a minority of children with reports of symptoms in early childhood develop asthma at school-age [9, 10]. It is therefore important to study incidence of asthma over a sufficiently long period of time in relation to air pollution exposure. This can be done in the context of prospective birth cohort studies.

3.2 Objectives

The objective of this paper is to systematically review results from prospective cohort studies on the association between air pollution exposure and asthma and allergies in children. We will discuss limitations and new developments.

3.3 Methods

3.3.1 Inclusion criteria

Exposure

Exposure to outdoor air pollution from traffic and other sources (e.g. industrial or wood-burning) and limitation to some key pollutants (e.g. NOx/NO2, PM, soot and ozone). Types of exposure assessment: dispersion modeling, land-use regression modeling, routine air monitoring network measurements, exposure indicator variables, individual measurements

Health outcomes:

- Asthma and related symptoms
- Use of asthma medication
- Allergic sensitization (assessed by measurements of specific IgE or skin prick-test)
- Lung function
- Hay fever and related symptoms

3.3.2 Exclusion criteria

- Short-term effect studies
- Studies on indoor air pollution
- Studies with questionnaire-based exposure assessment

4

Biological Organism and Allergy and Asthma

4.1 Background

Exposure to visible mould and mould components in indoor environment and its effect on allergic diseases in children is being widely discussed in the recent years. Several studies have investigated the associations and the results were not conclusive.

Some studies have shown that visible mould in homes increases the risk of doctor diagnosed asthma and wheezing in children [11, 12, 13, 14, 15]. A US birth cohort concluded that one year old children from asthmatic and allergic mothers who were exposed to high levels of Penicillium in the first 4 months of life are at significant higher risk for wheeze and persistent cough [16]. Another study in the U.S. showed that early exposure to fungal spores such as Cladosporium or Aspergillus at 3 months of age seems to contribute to the development of doctor diagnosed allergic rhinitis in 5 years-old children [17]. Elevated concentrations of current indoor mould spore exposure during winter seem to play a role in increasing the risk for allergic respiratory symptoms and allergic sensitization against inhalant allergens in German school children [18].

Some studies used the measured bio-components of mould, such as (1,3)-ß-D-glucan and Extracellular Polysacchardies (EPS), in the indoor dust or air samples as a surrogate of mode exposure [19, 20, 21, 22, 23]. Recent birth cohort studies showed that exposure to high levels of (1,3)-ß-D-glucan decreases the risk of developing wheezing symptoms in children whose parents have atopy [24, 23, 20]. Similar observation was reported in another study that elevated levels of (1,3)- ß-D-glucan and EPS exposure from mattress dust is associated with a lower prevalence

of allergic sensitization in 2-4 years-old children [22]. However, the mechanism of this inverse effect is not yet clear. It may be also due to the fact that (1,3)-ß-D-glucan does not derive exclusively from mould spores or from only one mould genera[23]. The other sources are for example plant materials, such as pollen, and cellulose and soil bacteria. Therefore, the protective effects may result from exposures to other microbial components and the (1,3)-ß-D-glucan may be seen as an independent measure of biological active exposure [24].

Different ways of assessing mould exposure can be one of the reasons for the conflicting study results. Dales et al. reported that there is only weak correlation between visible mould and levels of viable indoor fungi in the settled house dust samples [25]. For that reason, the comparability of questionnaire based exposure assessment to studies based on house dust sampling is questionable. Furthermore, early exposure to mould or mould components compared with the exposure later in life may have different impact on allergic health outcomes. Especially since the immune response of newborns is dominated by Th2 cells and a shift to Th1-mediated immune response happens during early childhood. Finally, asthmatic symptoms in the first year of life are often seen as a transient phenomenon and therefore it is crucial to look especially on persistent effects later in children's life.

As there are apparently conflicting study results with mould exposure assessment were conducted using several different methods, we think there's a strong need for a systematic review on the association between mould exposure and allergic outcomes in birth cohort studies. Birth cohort studies are seen as the most suitable study population because the longitudinal design can better assign the direction of causality. As the early exposure is known, birth cohort studies can best describe the associations during this crucial period of time after birth without any additional noise. Therefore we it is essential to conduct the systematic review based exclusively on available European birth cohort studies.

4.2 Objectives

This review is aimed to assess the effect of exposure to indoor mould on the development and exacerbate asthma and allergy.

4.3 Methods

Exposure

- Visible mould in the domestic area
- Number of mould counts
- Measured specific bio-markers of mould species such as EPS and (1?3)ß-D-glucan
- Agents released during the life cycle of mould

Method of mould exposure assessment:

- Visible mould assessed by the inspector
- Subjective assessment of mould exposure
- Culturable fungi spores
- Enzyme immunoassay (EIA) for mould markers

Health outcomes:

- Allergic sensitization assessed by skin prick test and elevated serum IgE against
- Specific allergens
- Physician diagnosed asthma
- Using asthma medication
- Physician diagnosed allergic rhinitis
- Physician diagnosed eczema
- Asthma symptoms-persistent wheezing or chest tightness or attacks of breathlessness following activity or at rest' or coughing without having a cold
- Eczema symptoms-itchy rush skin outside the diaper area with flexural nature
- Symptom of rhinitis-itchy, blocked, or running nose without having a cold

5 Pesticides and Birth Outcomes

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, etc.), in cities or industries (for cleaning roads, parks, industrial sites, etc.) 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 [26]. 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 [27, 28, 29], birth weight [30, 31], premature births [28], stillbirths [32] and congenital anomalies [33, 34, 35, 36]. 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 [37, 38, 39, 40, 41, 42].

5.2 Methods

5.2.1 Inclusion criteria

Exposure:

- Agricultural activities and residence proximity (with or without GIS)
- Drinking water contamination by pesticides
- Air pesticide measurements
- Domestic use of pesticides
- Biomonitoring
- Diet contamination

Health outcomes:

- Spontaneous abortions/still births
- Congenital malformations, including anomalies of the male reproductive system
- Low birth weight (<2500 g), small for gestational age (< 10th or 5th percentile for standard population at given gestational week and sex) and intrauterine growth restriction (taking into account additionally the maternal anthropometric parameters)
- Intrauterine growth parameters: birth weight, birth length, head circumference, gestational age
- Sex ratio

5.2.2 Exclusion criteria

None

6 Second-Hand Smoke and Birth Outcomes

6.1 Background

Secondhand smoke (SHS) is a potent mixture of approximately 4.000 chemicals, including known carcinogens such as polycyclic aromatic hydrocarbons (PAH), tobacco-specific nitrosamines, as well as other toxic and irritating compounds, including carbon monoxide, benzene, nicotine and respirable particulate matter [43]. Secondhand smoke itself, is comprised of mainstream smoke and side stream smoke. The first is exhaled from the active smoker and the later is produced by a smouldering cigarette and has been found to be even more toxic [44, 45].

Exposure to SHS is associated with numerous adverse health effects including cancer, cardiovascular disease, respiratory outcomes, infections and the predisposition to the development of asthma [45]. While the relationship between exposure to SHS during childhood, adolescence or adulthood is of interest to both researchers and public health advocates, it is also of significant interest to investigate into the role of prenatal exposure to SHS on reproductive outcomes, including low birth weight (LBW), small for gestational age (SGA), fetal growth restriction (FGR) and preterm delivery (PD). According to the 2006 US Surgeon Generals report on the health effects of involuntary exposure to second hand smoke, the existing data on SHS in birth cohorts is inadequate to infer the presence or absence of a relationship between maternal exposure to SHS and pregnancy outcome (namely spontaneous abortion, preterm delivery and perinatal death) [45]. However more recent studies have indicated that exposure to SHS is related to a minute reduction in birth outcomes. Specifically, among the EU

millennium cohort, exposure to domestic SHS lowered infants adjusted birth weights by 36 gr with this effect indicating a dose response relationship; however exposure to SHS also caused non statistical increases in the adjusted risks of low birth weight and premature birth [46]. Similarly to the above Danish women exposed to SHS in both the home and in public places were more likely to give birth to lighter children, with a dose response relationship identified for those exposed daily to SHS [47]. Bi parietal diameter has also been found to be affected by early gestational exposure to SHS, with serum cotinine concentrations in the mother found to negatively associated with bi parietal distances in the unborn child [48].

Exposure to SHS and preterm delivery is a topic in which mixed findings are commonly reported. While other studies have indicated positive associations between exposure to SHS and preterm delivery, others have not and the data remains as stated above, insufficient to infer a relationship between the two [45, 49, 50].

While a number of studies have investigated into exposure to SHS and preg-nancy outcome, few have used biomarkers to quantify exact exposure, a fact which should be taken into account when comparing published evidence [51, 52]. Furthermore, it is of significant interest to study the effect of maternal exposure to SHS during pregnancy on infant somatometrics having taken into account other possible confounding factors that could have an effect on fetal growth potential (such as maternal height, pre-pregnancy body mass index (BMI), parity, ethnicity, and fetal sex) which could allow to better differentiate between infants who are small because their in utero growth has been restricted and infants who are small, but have reached their individual growth potential [53].

As there are different study results with SHS exposure assessment conducted using several different methods, we think there is a strong need for a systematic review on the association between exposure to SHS and birth outcomes in birth cohort studies.

6.2 Objectives

This review is aimed to assess the effect of exposure to secondhand smoke during pregnancy on birth/pregnancy outcomes.

6.3 Secondary Objectives:

To assess the prevalence and level of exposure to SHS of pregnant women in Europe.

6.4 Methods

Exposure

- Self reported exposure at home from spouse, family, friends
- Self reported exposure at work (for those that work during pregnancy)
- Self reported exposure to SHS in public places (depending on country specific smoke free legislations)
- Self reported exposure to SHS from other sources were available (visits, cars, etc.)
- Tobacco specific biomarkers identified in maternal urine or serum (i.e cotinine, the main metabolite of nicotine). The use of other biomarkers (i.e NNAL) will also be assessed.

Method of mould exposure assessment:

- Self reported variables
- Nationwide, regional smoke free legislations
- GC-MS for the determination of urinary/serum cotinine levels

Birth or Pregnancy outcomes:

- Low birth weight (maybe also Very low birth weight and Term low birth weight for sure)
- Fetal growth restriction for length (not sure)
- Fetal growth restriction for head circumference (not sure)
- Fetal growth restriction for birth weight (this is most common definition, I am not sure we can perform an analysis based on FlGR, FGR_hc not relevant studies)
- Preterm delivery (maybe also very preterm delivery)
- Spontaneous abortion
- Infant somatometrics as continuous variables (infant weight, length, head circumference at birth)

- Small for gestational age (based on infant weigth, not enough studies assessing SGA based on other somatometrics)

6.4.1 Exclusion criteria:

Non EU cohorts (they will investigated into as a separate section).

7 Water and Birth Outcomes

7.1 Background

Disinfection by-products (DBPs), metals, pesticides, nitrates and endocrine disrupting substances are well recognized water contaminants. Disinfection by products (DBPs) are produced when the disinfectant chlorine reacts with organic matter. Some DBPs and other contaminants present in water such as metals, pesticides and nitrates are known to be fetotoxic, teratogenic and carcinogenic[54]. Until recently, few toxicological and epidemiological studies have been conducted studying the effects of DBPs on reproductive health outcomes. The most adverse reproductive outcomes studied have been low birth weight, preterm delivery, spontaneous abortion, stillbirth, and birth defects such as central nervous system. However, the relationship between them still appears to be inconclusive and inconsistent [55]. Currently a large EU project is ongoing to examine the effects of DBPs on reproductive outcomes called HIWATE (www.hiwate.org). On the other hand, some epidemiological evidence suggests an association between prenatal exposure to drinking-water with elevated nitrate concentrations and incidence of congenital anomalies. Heavy metals and pesticides have also been investigated but to a smaller extent [56, 57]. Others such as endocrine disrupting substances have attracted some interested but have been poorly investigated because they are difficult to measure in water [58].

The major limitation factor in these studies has been crude exposure assessment, since ecological water estimates as an exposure index may result in exposure

misclassification. However, a study carried out in Italy was the only one which measured personal levels of DBPs showing a weak association with increase in the risk of small gestational age [59]. Furthermore, most monitoring of DBP levels has been limited to total trihalomethanes (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 [60].

Little research on DBPs in relation to adverse birth outcomes has been conducted in Europe; however, there are some studies that have evaluated or are planning to assess those effects in health children (table 7.1). 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 DBPs exposure assessments and make recommendations for future studies.

Table 7.1: ENRIECO cohorts where water contaminants were assessed or will be assessed (table in progress)

Birth cohort	Country	Water contaminants	Birth outcomes[1]
BiB	UK	THMs, HAAs	BW, GA, US
INMA	Spain	THMs	BW, GA, US, AGD
KANC	Lithuania	THMs	BW, GA, US
NFBC 1986	Finland	?	BW, GA, SB, CA
PÉLAGIE	France	THMs, HANs, HAAs, HAKs	BW, GA, US, CA
RHEA	Greece	THMs	BW, GA, SB, SA, US, AGD

[1]BW: birth weight; GA: gestational age; SB: stillbirth; CA: congenital anomalies; US: ultrasound measurement; AGD: anogenital distance; SA: spontaneous abortion.

7.2 Objectives

The aim of this systematic review is to evaluate the association between water contaminants and birth outcomes in European birth cohorts.

- Compare methods and tools to evaluate exposure assessment (this objective will be more developed in WP2, WG: Water contaminants)
- Compare methods and tools to evaluate outcome assessment (this objective will be more developed in WP3, WG: Birth outcomes)
- Describe exposure response relationships in the European birth cohorts for water contaminants
- Put this information in context with other study designs (case-controls, etc.) and other studies conducted out of Europe
- Evaluation of variables considered/possible confouders

- 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

7.3 Methods

Exposure

- Water contaminants: DBPs, pesticides, metals, endocrine disrupting substances, others
- Types of exposure assessment:
  - Routine monitoring water concentration data from water companies or government
  - 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

Health outcomes:

- Use of a contraceptive method at the start of a pregnancy
- Time to pregnancy
- Infertility treatment before the index pregnancy
- Likelihood of conception
- Congenital anomalies
- Specific anomalies of the male reproductive system
- Spontaneous abortions (until 21 weeks of amenorrhea)
- Stillbirths (after 22 weeks of amenorrhea)
- Medical termination of pregnancy
- Birth weight

- Gestational Duration
- Premature Rupture of Membranes
- Onset of labour (spontaneous, induced, caesarean section before onset, ...)
- Mode of delivery (spontaneous vaginal birth, operative vaginal birth, caesarean section)
- Ultrasound measurements
- Doppler measurements (of uterine, umbilical, fetal cervical arteries, or other)

8

Metals and Birth Outcomes

8.1 Background

Environmental exposure to metals may affect the correct development of fetus and infant who are more vulnerable to their toxic effects than adults. Several epidemiological studies have found association of metal exposure with adverse birth outcomes (table 6.1). Although lead has been the most studied heavy metal there is still limited evidence of association between a prenatal lead exposure and birth effects [61, 54]. Methylmercury is extremely neurotoxic for fetus and the developing infant [62, 63] but the studies conducted in its effects and adverse pregnancy outcomes are not conclusive [64, 65]. On the other hand, there has been little epidemiologic research on the potential role of arsenic, cadmium and manganese as much as other metals in adverse health outcomes.

Table 1**.** Association between metal environmental exposure and birth outcomes (adapted from Wigle, 2003, 2007 and 2008)

Metal	**Preterm delivery**	**Low birth weight**	**Spontaneous abortion**	**Stillbirth**	**Fetal death**	**Decrease fecundity**	**Birth defects**
Lead	x	x	x	x	x	x	x
Mercury	x		x	x			x
Arsenic	x	x	x	x	x		x
Cadmium	x	x		x			
Manganese		x					x

Table 2. ENRIECO cohorts where metals and birth outcomes were assessed or will be assessed (table will be completed when the inventory questionnaire of WP1 will be finished)

Birth cohort	Country	Metals assessed[1]		Birth outcomes[2]
		Done	Planned	
ABCD	Netherlands		x	BW, GA, SB, CA
C. Faroes I and II	Faroes Islands	Hg, Pb, Se		BW, GA, CA
Duisburg	Germany	Hg, Pb, Se, Cd		BW, GA
FLESH	Belgium	Pb, Cd		BW, GA
INMA	Spain	Hg, Pb	As, Pb, Cd, Cr, Mn, V	BW, GA, US, AGD
INUENDO	Denmark		Hg, Pb, Cd	BW, GA, SB
PMC	Poland	Hg, Pb, Cd		BW, GA, SB, SA, US, CA
RHEA	Greece	Hg, Pb, Se, As, Cd, Mn		BW, GA, SB, SA, US, AGD

[1]Hg: Mercury; Pb: Lead; Se: Selenium; Cd: Cadmium; As: Arsenic; Mn: Manganese
[2]BW: birth weight; GA: gestational age; SB: stillbirth; CA: congenital anomalies; US: ultrasound measurement; AGD: anogenital distance; SA: spontaneous abortion.

In Europe, few studies have been done in this area and sometimes there is a lack of conclusive results [66, 67, 68, 69]. Besides, these studies are difficult to compare due to different biological samples and methods used. Therefore, it would be recommended to conduct a systematic review on the association between metal exposure and birth outcomes.

Birth cohorts included in ENRIECO project where metals and birth outcomes are assessed or will be assessed are shown in table 6.2. Although cohort studies are the more suitable population design to associate cause and effect, cross-sectional studies should be recommended to be included. The systematic review will focus on European birth cohort studies and recommendations will be done comparing these studies with other surveys carried out in other countries.

8.2 Objectives

The aim of this systematic review is to evaluate the association between metals and birth outcomes in European birth cohorts.

- Description of the current available data of European birth cohorts
- Put this information in context with other study designs and other studies conducted out of Europe
- Comparison of methods and tools to evaluate exposure assessment: sample used for each metal; detection limit; metal form measured; etc. (this

objective will be more developed in WP2, WG: Metals)

- Comparison of methods and tools to evaluate outcome assessment (this objective will be more developed in WP3, WG: Birth outcomes)
- Comparison of variables considered: subject variables (age, gender, ethnic, socioeconomic status); tester variables (reliability of the examiners, motivation, level of fatigue, systematic errors); situational variables (physical location of testing, test procedures), etc.
- Agreement of results and conclusions
- Identification of lacks: data gaps in the literature; possible confounders not considered; inadequate methodology; small sample size; etc.
- Set recommendations for future research in European birth cohorts: metals/outcomes that should be further investigated; standardization of exposure/outcome assessment methods; interaction with metals and other environmental exposures (PCBs, air pollution, etc.); etc.

8.3 Methods

8.3.1 Inclusion criteria

Exposure

- Metals assessed; form measured and detection limit
- Instrument used
- Type of assessment:
  - Biological sampling: hair, urine, blood, nails, etc.
  - Participants: mother, child, father
  - Environmental sampling: water, air, etc.
  - Questionnaires
  - Occupational exposure
  - Dietary exposure
  - Tap water consumption

Health outcomes:

- Use of a contraceptive method at the start of a pregnancy
- Time to pregnancy
- Infertility treatment before the index pregnancy

- Likelihood of conception
- Congenital anomalies
- Specific anomalies of the male reproductive system
- Spontaneous abortions (until 21 weeks of amenorrhea)
- Stillbirths (after 22 weeks of amenorrhea)
- Medical termination of pregnancy
- Birth weight
- Gestational Duration
- Premature Rupture of Membranes
- Onset of labour (spontaneous, induced, caesarean section before onset, ...)
- Mode of delivery (spontaneous vaginal birth, operative vaginal birth, caesarean section)
- Ultrasound measurements
- Doppler measurements (of uterine, umbilical, fetal cervical arteries, or other)

9

Metals and Neurobehavior

9.1 Background

Neurotoxicity is generally defined as a structural change or a functional alteration of the nervous system, resulting from exposure to a chemical, biological, or physical agent [70].

The development of the brain has a target period, which, approximately, goes from the intrauterine life up to 2 years of age, and which is extremely sensitive to several environmental determinants [71, 72]. The developing brain and organ systems of infants and children as well as their immature metabolism make them more vulnerable to environmental toxins.

There are several environmental exposures including socio-environmental characteristics that could influence child development. The most widely neurotoxicants studied are metals (lead, mercury, and manganese), pesticides, polychlorinated biphenyls, and polybrominated diphenyl ethers.

Numerous studies have confirmed that methylmercury compounds cause developmental disorders [71]. The primary sources of information on such effects in humans came from accidental exposure incidents in Japan and Iraq. In both cases, a range of developmental effects was noted in children exposed in utero or at young age.

Exposure to lead during eurodevelopment has significant effects on neurobehavioral and cognitive development. For example, some studies have found impairments in attention, hyperactivity, and learning disorders [73, 74]. These

neurological and intellectual effects have been documented in a variety of cases in which exposure took place either in the intrauterine environment or during early childhood. Epidemiological studies have associated chronic developmental Pb exposure with impairments in cognitive function and behavioral maturation in young children [75].

Possible combined adverse effects on cognitive development caused by arsenic and manganese exposures was suggested by metal concentrations in hair in children living near a hazardous waste site [76]. Although evidence for subclinical neurodevelopmental toxicity of arsenic is less well established than for lead and methylmercury, the data are consistent and fit with the high-exposure findings from Japan.

Neurodevelopment is mostly studied by neuropschology using several different methods (psychometric tests or self-reported questionnaires) at different stages of child development and taking into account several determinants factors (confounders and effect modifiers). For that, we consider necessary to apply a systematic review on the association between metals exposure and neurodevelopment outcomes in birth cohort studies. Birth cohort studies are seen as the most suitable study population because the longitudinal design can better assign the direction of causality. These studies can disentangle the potential consequences of low-dose exposures (both pre or postnatal) and offer a opportunity to identify critical periods of exposure and to clarify, if the observed effects are reversible or not. Therefore we it is essential to conduct the systematic review based exclusively on available European birth cohort studies.

9.2 Objectives

This review is aimed to assess the effect of exposure to metals on the child neurodevelopment and exacerbate cognitive delays or behavioral disorders.

9.3 Methods

9.3.1 Inclusion criteria

Exposure

- Routes: transplacental in fetus, via breast milk in nursing infants, hand-tomouth in early childhood and diet.
- Analyses of: blood, hair, nails, urine ,or breast milk
- Indirect methods (diet questionnaire)

Neurodevelopment outcomes:

All outcomes will be obtained from neuropsychological assessment (tests administered by psychologists or self-reported questionnaires):

- Cognitive functions (executive function, perceptual-performance, attention, language...)
- Psychomotor Development
- Attention deficit and hyperactivity disease (ADHD)
- Learning disabilities
- Autism Spectrum Disorders (ASD)
- Behavioral disorders
- Mental health

10 Persistent Organic Pollutants and Birth Outcomes

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 dichlorodiphenyl-trichloroethane (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 [77, 78]. The co occurrence of these compounds in human samples makes it difficult to establish which compounds that 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, organochlorine compounds 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 leveled 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, observational studies have addressed the effects of POPs. These studies indicate that high concentrations of persistent organochlorines may adversely cause spontaneous abortions and delayed pregnancy, reduced birth weight and induce skewed sex ratio and altered age of puberty onset [79]. Most effects have been demonstrated at exposure levels above the present exposure level in European and North American populations. However, it is not clear whether low level of POP exposure as found in the present day European populations may affect birth outcomes.

By reviewing the available results from existing European birth cohorts we might be able to get a more clear picture on whether low level POP exposure are related to adverse birth outcomes.

10.2 Objectives

This review is aimed to assess the effect of exposure to POPs during pregnancy on the occurrence of adverse birth in the offspring.

10.3 Methods

10.3.1 Inclusion criteria

Exposure

- 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)

Health outcomes:

- Spontaneous abortions/still births
- Birth weight
- Birth length
- Gestational age
- Low birth weight (<2500 g)
- Small for gestational age (<10th percentile for standard population at given gestational week)
- Congenital malformations (hypospadias, cryptorchidism, cleft lip/cleft palate.)
- Sex ratio
- Clear report on the cohort members who were lost of the follow-up and compare them with the cohorts who were followed-up
- Possibility of reverse causation

11

Persistent Organic Pollutants and Neurodevelopment

11.1 Background

Persistent organic pollutants (POPs) are persistent, ubiquitous toxicants that bioaccumulate in terrestrial and aquatic food chains. Organochlorines (OCs), an important class of POPs, include polychlorinated biphenyls (PCB) and dichlorodiphenyltrichloroethane (DDT) which are highly widespread in the environment and in human tissues. Newborns are exposed to PCBs and other POPs across the placenta and through breast feeding. Experimental animal studies have indicated that PCBs are neurotoxic but the neurological effects of these compounds on children are not clear [80]. Studies of women with accidental exposure to high concentrations of POPs in the Yusho and Yu-cheng poisoning epidemics in Japan and Taiwan, respectively, found a strong evidence relationship with different neuropsychologic effects such as delayed pscychomotor development and cognitive and auditory deficits during infancy [81, 82]. However, effects at lower concentrations are not as obvious.

A systematic review which include a total of 29 publications revealed that during the first months of life, a decrease in motor skills was observed in four of the five studies that investigated psychomotor development; the same review showed that at 4 years of age, an effect on the cognitive areas was observed in four of the five studies that evaluated it. This systematic review concluded that there was a

Table 11.1: ENRIECO cohorts where POPs and Neurodevelopment were assessed or will be assessed (table in progress)

Birth cohort	Country	POPs assessed	Neurodevelopment
Faroes Island I and III	Faroes Island	OCs	CF, ND
Duisburg	Germany	OCs, Dioxins	CF, ND
FLESH	Belgium	OCs, Dioxins	CF, ND, BD
INMA	Spain	OCs, PBDEs	CF, ND, BD, AUT
INUENDO	Denmark	OCs, Dioxins	
PCB Cohort	Slovakia	OCs, Dioxins	ND
PÉLAGIE	France	FC	ND
RHEA	Greece	OCs, Dioxins	ND

subtle adverse effect of low prenatal PCBs exposure on child neurodevelopment [80]. A recently meta-analysis which compared low prenatal POP exposure and neuropsychological development also indicated these low evidence of association and suggested that these effects may be resolved with time as POP exposure continues to decrease (revised in [83]).

Differences in study design and lack of homogeneous quantitative exposure data have led to difficulties in comparing epidemiological studies and inconclusive results. Large scale-studies are needed to elucidate the possible adverse effects of POPs on child health. ENRIECO provides an opportunity to evaluate and compare existing studies (see table 11.1).

11.2 Objectives

The aim of this systematic review is to evaluate the effect of exposure to POPs on the child neurodevelopment in the participating European birth cohorts.

- Description of the current available data of European birth cohorts
- Put this information in context with other study designs and other studies conducted out of Europe
- Evaluation of variables considered/possible confounders
- Discuss strengths and limitations of different assessment methods
- Give recommendations for further research in European birth cohorts in collaboration with other POP focused working groups in WP2 and WP4.

11.3 Methods

11.3.1 Inclusion criteria

Exposure:

- POPs: aldrin, chlordane, DDT and metabolites (DDE), dieldrin and endrin, heptachlor, hexachlorobenzene (HCB), mirex, polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzo furans (PCDFs), toxaphene, brominated flame retardants, flourinated compounds (PFCs), organometallic compounds (TBT), hexachlorocyclohexane (HCH); polybrominated diphenyl ethers (PBDE); perfluorinated organic compounds (PFCs), etc.
- Biological sample: Breast milk, whole blood, serum, cord blood, etc.
- Fatty acids measured in the blood samples

Health Outcomes:

- Outcomes assessed in children: neuropsychological assessment (e.g. developmental tests for executive function, memory, language, IQ), behavior (ADHD symptoms, etc), autism symptoms, school achievements/performance, etc.
- Outcomes assessed in parents: IQ, mental health, stress, attachment
- Test: Dubowitz, Bayley scales of infant development (BSID), Griffiths Mental Development scales, McCarthy scales of children's abilities (MSCA), Wechsler Preschool and Primary scale of Intelligence (WPPSI), etc.

12

Noise, Birth Outcomes, Asthma/Allergy, and Cardiovascular Outcomes

12.1 Background

Noise exposure is one of the most common environmental pollutants for the European population. Environmental/community noise refers to noise from domestic neighbourhood, traffic sources, constructions and industries. While exposure to occupational noise is restricted to isolated population groups, community noise is omnipresent and scarcely avoidable. WHO estimates that about 40% of EU inhabitants are exposed to traffic noise exceeding sound pressure levels of 55 dB(A) (decibel A filter) during day time. From those, 20% are confronted with noise louder than 65 dB(A). During the night, 30% of the population suffer from community noise with over 55 dB(A). This data is alarming, as the recommended sound pressure level for undisturbed sleep should not exceed 30 dB(A)[60]. Unsurprisingly, 10% of the population reports severe noise related sleep disturbance[61]. Children and adolescents might constitute an important vulnerable group to stressors as community noise, as well as expectant mothers.

The health impact of high traffic volume is presumably mediated by exhaust fumes and noise. Exhaust fumes were associated with an elevated risk of bronchitis with an OR=1.3 per 10µg PM10 [62]. Thus, noise as potential stressor 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 path- way between noise and health outcomes.

Differences in the exposure assessment are essential and may account for some of the outcome differences. Several studies focused on traffic density, asking for truck and motorcar traffic [67, 65]. Other chronic noise sources (domestic, airport or train noise) and differentiations between day and night time exposures were inconsistently assessed. Another crucial consideration is the discrimination between objective noise measurements (for instance, catalogue for workplace noise, noise maps) versus subjective feelings of noise annoyance [69, 66] and noise sensitivity, considered to be a personality trait [70].

In regard to health outcomes, three German cross-sectional studies reported a dose-dependent increase in prevalence for wheezing and allergic rhinitis in association with traffic density among adolescents aged 12 to 15 years. The living duration in the habitation was an important control variable and only youths living in the same dwelling five years and longer had higher prevalence odds ratios [65]. Intense traffic noise exposure was also associated with higher prevalence of chronic respiratory and dermatological diseases in 5 to 12 year old German children [66]. Behrens et al. (2004) reported elevated risks for wheezing and rhinitis in 13-14-year old adolescents, who were constantly exposed to truck traffic noise [67].

Noise exposure in the workplace of expectant mothers was in trend associated with intrauterine growth retardation [71] and preterm labor after controlling for long standing and lifting [72]. However, the association between occupational noise and infants' birth weights was inconsistent [73, 74].

Possible confounders, such as noise sensitivity, socio-economic status, smoking, environmental tobacco smoke or time span living in the present dwelling were irregularly integrated in studies.

Reasons for differences in study outcomes could be congruent with those named above. It will require a closer look to the type of exposure and outcome assessment, used in different studies in order to evaluate results properly. Although noise exposure might have severe negative health impacts, there are only few investigations on chronic noise in children, adolescents and expectant mothers. To

our knowledge, no systematic reviews have been conducted focusing on these potentially vulnerable population subgroups.

12.2 Objectives

This review will evaluate the impact of chronic noise on immune-mediated diseases (asthma and allergy) and cardiovascular health outcomes in children and adolescents.

12.2.1 Secondary objectives

The impact of chronic noise during pregnancy on birth outcomes (height, weight, preterm birth) will be reviewed.

12.3 Methods

12.3.1 Inclusion criteria

Exposure

- Chronic noise exposure (objectively and subjectively assessed)
- Noise annoyance each will be taken into consideration for all types of community noise, at school (for children and adolescents) and at work (for expectant mothers).

Method of noise exposure assessment

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

Health outcomes

- General stress response:
  - Cortisol levels, blood pressure, hypertension, heart rate
- Allergic diseases (for children and adolescents):
  - Physician diagnosed asthma
  - Asthma symptoms-wheezing or chest tightness/attacks of

breathlessness during or after physical activity or at rest, coughing without having a cold using asthma medication

- Physician diagnosed allergic rhinitis
- Symptom of rhinitis-itchy, blocked, or running nose without having a cold
- Physician diagnosed eczema
- Eczema symptoms-itchy rush skin outside the diaper area with flexural nature
- Allergic sensitization assessed by skin prick test and elevated serum IgE against specific allergens

- Pregnancy outcomes (for expectant mothers):
  - Fetal weight, height, head circumference, preterm labor, small for gestational age

12.3.2 Exclusion criteria

- Laboratory noise experiments/studies
- Other noise sources (e.g. noise of neonatal intensive care units)

12.3.3 Search strategy

Electronic searches

Terms for Exposure Assessment

'Noise'[Mesh]

Terms for Outcome Assessment-Children and Adolescents

('Stress, Physiological'[Mesh] OR ('cortisol'[All Fields]) OR 'Blood Pressure'[Mesh] OR 'Hypertension'[Mesh] OR 'Heart Rate'[Mesh] OR 'Immune System'[Mesh] OR 'Immune System Phenomena'[Mesh] OR 'Immune System Diseases'[Mesh] OR 'Immune System Processes'[Mesh] OR 'Allergy and Immunology'[Mesh] OR 'Hypersensitivity'[Mesh] OR 'Eczema'[Mesh] OR 'Dermatitis, Atopic'[Mesh] OR 'Dermatitis'[Mesh] OR 'Rhinitis, Allergic, Seasonal'[Mesh] OR 'Asthma'[Mesh] OR] OR 'Skin Tests'[Mesh] OR 'Respiratory Function Tests'[Mesh] OR 'Im- munoglobulin E'[Mesh] OR 'Rhinitis'[Mesh])

Terms for Limitations-Children and Adolescents

('humans'[MeSH Terms] AND ('infant'[MeSH Terms] OR ('infant'[MeSH Terms] OR 'child'[MeSH Terms] OR 'adolescent'[MeSH Terms]) OR 'infant'[MeSH

Terms:noexp] OR 'child, preschool'[MeSH Terms] OR 'child'[MeSH Terms:noexp] OR 'adoles- cent'[MeSH Terms])

Terms for Outcome Assessment-Foetuses and Infants

('Pregnancy'[Mesh] OR 'Fetal Weight'[Mesh] OR 'Birth Weight'[Mesh] OR 'Body Height'[Mesh] OR 'Embryonic and Fetal Development'[Mesh]) OR 'Gestational Age'[Mesh])

Terms for Limitations- Foetuses and Infants

'humans'[MeSH Terms]

Searching from other sources

Hand search will be performed by screening all references of the identified publications and from personal files when known literature is not found by the electronic search strategy.

12.3.4 Assessment of methodological quality

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

(a) Study design

–birth cohort study, cohort study, case control study, cross sectional

–meta-analysis, systematic review, narrative review

(b) Clear definition of the type and time of exposure assessment

–objectively vs. subjectively

–how often, how long

(c) Clear definition of the type and time of health outcomes assessment

–objectively vs. subjectively

–how often, how long

(d) Clear description of the inclusion and exclusion criteria of the study population

–yes/no criteria

(e) Performance of appropriate statistical analysis

–yes/no criteria

(f) Clear report of drop-out analysis

–yes/no criteria

(g) Consideration of possible confounders

–yes/no criteria

13

Occupation and Birth Outcomes

13.1 Background

Today women constitute nearly 50% of workforce in many countries and most are in their reproductive years. The proportion of pregnant women who work during pregnancy is increasing as more women move into previously male dominated occupations. Women are employed in occupations with exposure to chemical agents, pesticides, ionizing radiation, physical agents, noise, infectious agents, ergonomic factors and stress [99]. This way, pregnant women may be exposed to a variety of risk factors at work that may affect the outcome of a pregnancy, such as spontaneous abortion, congenital anomaly, stillbirth, preterm birth, and low birth weight. Several reviews have summarized the epidemiological evidence on associations between maternal occupational exposure and adverse pregnancy outcomes. They showed evidence that several chemical agents, physical factors and physical load were associated with low birth weight, preterm birth and spontaneous abortion but that results are inconsistent across studies [100]. In addition, exposure during pregnancy may lead to congenital malformations and neurobehavioral disorders at young age [101, 100]. At present, knowledge on the potential reproductive toxicity of common occupational exposures is limited and in many cases only suggestive [87].

The population-based birth cohort design has been little used in the study of occupational exposures and adverse pregnancy outcomes because of the often rare exposures and rare outcomes involved. However, this study designs important strengths in that it circumvents a main problem in other study designs (mainly

case-control studies), i.e. recall bias, and because of its longitudinal design which is most suitable to establish the direction of causality. For example, the French Pelagie cohort provides evidence of an association between exposure to solvents during pregnancy and the risk of major malformations such as oral cleft, urinary malformations and male genital malformation s[102] and the relation between laboratory work and pregnancy outcomes has been examined in the Danish National Birth Cohort [103]. Few birth cohorts have enough statistical power to examine the effects of occupational exposures and adverse birth outcomes in detail, and therefore pooling of data across European cohorts may be valuable. However, maternal work circumstances and therefore, exposures, may also differ greatly from country to country. An evaluation of published data on occupational exposures and adverse pregnancy outcomes is an important first step in establishing needs for future research within the European birth cohorts.

13.2 Aim

The aim of this systematic review is to evaluate the association between maternal and perhaps paternal occupational exposures and birth outcomes in European birth cohorts.

13.3 Objectives

- Describe currently available data published by European birth cohorts. Systematic review of published literature.
- Put this information in context with other study designs and other studies conducted out of Europe (using existing reviews).
- Identify strengths and limitations
- Set recommendations for future research in European birth cohorts, in close collaboration with the WP2 case study on occupational exposures.

13.4 Methods

13.4.1 Inclusion criteria

Exposures

- •other's occupation: job title, type of industry, specific exposures (chemical and physical)
- Father's occupation: job title, type of industry, specific exposures (chemical and physical)
- Type of assessment:
  - Self reports/ questionnaires
  - Job Exposure Matrixes (JEM)
  - Expert Judgement
  - Environmental monitoring, personal monitoring, biomonitoring

Health outcomes:

- Time to pregnancy
- Congenital anomalies, including anomalies of the male reproductive system
- Spontaneous abortions (until 21 weeks of amenorrhea)
- Stillbirths (after 22 weeks of amenorrhea)
- Medical termination of pregnancy
- Birth weight
- Gestational Duration
- Premature Rupture of Membranes
- Ultrasound measurements
- Doppler measurements (of uterine, umbilical, fetal cervical arteries, or other)

13.4.2 Search strategy

Searches will include:

- PubMed database using combinations of the following words: 'maternal occupation', 'paternal occupation', 'pregnancy outcomes', 'birth outcomes', congenital anomalies', 'birth weight', etc.
- Cohort websites
- References of publications identified by electronic search
- Web-based cohort inventory of European birth cohorts (ENRIECO WP1)

Bibliography

[1] S. V. Glinianaia, J. Rankin, R. Bell, T. Pless-Mulloli, and D. Howel. Particulate air pollution and fetal health: a systematic review of the epidemiologic evidence. *Epidemiology*, 15(1):36–45, 2004.

[2] R. Slama, L. Darrow, J. Parker, T. J. Woodruff, M. Strickland, M. Nieuwenhuijsen, S. Glinianaia, K. J. Hoggatt, S. Kannan, F. Hurley, J. Kalinka, R. Sram, M. Brauer, M. Wilhelm, J. Heinrich, and B. Ritz. Meeting report: atmospheric pollution and human reproduction. *Environ Health Perspect*,

116(6):791–8, 2008.

[3] T. J. Woodruff, J. D. Parker, L. A. Darrow, R. Slama, M. L. Bell, H. Choi, S. Glinianaia, K. J. Hoggatt, C. J. Karr, D. T. Lobdell, and M. Wilhelm. Methodological issues in studies of air pollution and reproductive health. *Environ Res*, 109(3):311–20, 2009.

[4] L. Trasande and G. D. Thurston. The role of air pollution in asthma and other pediatric morbidities. *J Allergy Clin Immunol*, 115(4):689–99, 2005.

[5] J. A. Sarnat and F. Holguin. Asthma and air quality. *Curr Opin Pulm Med*, 13(1):63–6, 2007.

[6] B. Brunekreef and J. Sunyer. Asthma, rhinitis and air pollution: is traffic to blame? *Eur Respir J*, 21(6):913–5, 2003.

[7] J. Heinrich and H. E. Wichmann. Traffic related pollutants in Europe and their effect on allergic disease. *Curr Opin Allergy Clin Immunol*, 4(5):341–8, 2004.

[8] M. I. Gilmour, M. S. Jaakkola, S. J. London, A. E. Nel, and C. A. Rogers. How exposure to environmental tobacco smoke, outdoor air pollutants, and increased pollen burdens influences the incidence of asthma. *Environ Health Perspect*, 114(4):627–33, 2006.

[9] F. D. Martinez, A. L. Wright, L. M. Taussig, C. J. Holberg, M. Halonen, and W. J. Morgan. Asthma and wheezing in the first six years of life. The group health medical associates. *N Engl J Med*, 332(3):133–8, 1995.

[10] R. J. Kurukulaaratchy, S. Matthews, and S. H. Arshad. Defining childhood atopic phenotypes to investigate the association of atopic sensitization with allergic disease. *Al lergy*, 60(10):1280–6, 2005.

[11] T. Antova, S. Pattenden, B. Brunekreef, J. Heinrich, P. Rudnai, F. Forastiere, H. Luttmann-Gibson, L. Grize, B. Katsnelson, H. Mosham- mer, B. Nikiforov, H. Slachtova, K. Slotova, R. Zlotkowska, and T. Fletcher. Exposure to indoor mould and children's respiratory health in the paty study. *J Epidemiol Community Health*, 62(8):708–14, 2008.

[12] J. Pekkanen, A. Hyvarinen, U. Haverinen-Shaughnessy, M. Korppi, T. Putus, and A. Nevalainen. Moisture damage and childhood asthma: a population-based incident case-control study. *Eur Respir J*, 29(3):509–15, 2007.

[13] J. J. Jaakkola, B. F. Hwang, and N. Jaakkola. Home dampness and molds, parental atopy, and asthma in childhood: a six-year population-based cohort study. *Enviro Health Perspect*, 113(3):357–61, 2005.

[14] Institute of Medicine. IOM. Damp indoor spaces and health. Technical report, Institute of Medicine, 2004.

[15] G. Emenius, M. Svartengren, J. Korsgaard, L. Nordvall, G. Pershagen, and M. Wickman. Indoor exposures and recurrent wheezing in infants: a study in the bamse cohort. *Acta Paediatr*, 93(7):899–905, 2004.

[16] J. F. Gent, P. Ren, K. Belanger, E. Triche, M. B. Bracken, T. R. Holford, and B. P. Leaderer. Levels of household mold associated with respiratory symptoms in the first year of life in a cohort at risk for asthma. *Environ Health Perspect*, 110(12):A781–6, 2002.

[17] P. C. Stark, J. C. Celedon, G. L. Chew, L. M. Ryan, H. A. Burge, M. L. Muilenberg, and D. R. Gold. Fungal levels in the home and allergic rhinitis by 5 years of age. Environ Health Perspect, 113(10):1405–9, 2005.

[18] B. Jacob, B. Ritz, U. Gehring, A. Koch, W. Bischof, H. E. Wichmann, and J. Heinrich. Indoor exposure to molds and allergic sensitization. Environ Health

Perspect, 110(7):647–53, 2002.

[19] J. Douwes, B. van der Sluis, G. Doekes, F. van Leusden, L. Wijnands, R. van Strien, A. Verhoeff, and B. Brunekreef. Fungal extracellular polysaccharides in house dust as a marker for exposure to fungi: relations with culturable fungi, reported home dampness, and respiratory symptoms. *J Al lergy Clin Immunol*, 103(3 Pt 1):494–500, 1999.

[20] J. Douwes, R. van Strien, G. Doekes, J. Smit, M. Kerkhof, J. Gerritsen, D. Postma, J. de Jongste, N. Travier, and B. Brunekreef. Does early indoor microbial exposure reduce the risk of asthma? the prevention and incidence of asthma and mite allergy birth cohort study. J Al lergy Clin Immunol, 117(5):1067–73, 2006.

[21] J. Douwes, A. Zuidhof, G. Doekes, S. C. van der Zee, I. Wouters, M. H. Boezen, and B. Brunekreef. (1–>3)-beta-d-glucan and endotoxin in house dust and peak flow variability in children. Am J Respir Crit Care Med, 162(4 Pt1):1348–54, 2000.

[22] U. Gehring, J. Heinrich, G. Hoek, M. Giovannangelo, E. Nordling, T. Bellander, J. Gerritsen, J. C. de Jongste, H. A. Smit, H. E. Wichmann, M. Wickman, and B. Brunekreef. Bacteria and mould components in house dust and children's allergic sensitisation. *Eur Respir J*, 29(6):1144–53, 2007.

[23] Y. Y. Iossifova, T. Reponen, D. I. Bernstein, L. Levin, H. Kalra, P. Campo, M. Villareal, J. Lockey, G. K. Hershey, and G. LeMasters. House dust (1-3)-beta-d-glucan and wheezing in infants. *Al lergy*, 62(5):504–13, 2007.

[24] Y. Y. Iossifova, T. Reponen, P. H. Ryan, L. Levin, D. I. Bernstein, J. E. Lockey, G. K. Hershey, M. Villareal, and G. LeMasters. Mold exposure during infancy as a predictor of potential asthma development. Ann Al lergy Asthma Immunol, 102(2):131–7, 2009.

[25] R. E. Dales, D. Miller, and E. McMullen. Indoor air quality and health: validity and determinants of reported home dampness and moulds. *Int J Epidemiol*, 26(1):120–5, 1997.

[26] W. Hanke and J. Jurewicz. 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(2):223–43, 2004.

[27] R. Munger, P. Isacson, S. Hu, T. Burns, J. Hanson, C. F. Lynch, K. Cherryholmes, P. Van Dorpe, and Jr. Hausler, W. J. Intrauterine growth retardation in

Iowa communities with herbicide-contaminated drinking water supplies. *Environ Health Perspect*, 105(3):308–14, 1997.

[28] M. P. Longnecker, M. A. Klebanoff, H. Zhou, and J. W. Brock. Association between maternal serum concentration of the DDT metabolite DDE and preterm and small-for-gestational-age babies at birth. *Lancet*, 358(9276):110–4, 2001.

[29] M. Levario-Carrillo, D. Amato, P. Ostrosky-Wegman, C. Gonzalez-Horta, Y. Corona, and L. H. Sanin. Relation between pesticide exposure and intrauterine growth retardation. *Chemosphere*, 55(10):1421–7, 2004.

[30] S. E. Rodenbeck, L. M. Sanderson, and A. Rene. Maternal exposure to trichloroethylene in drinking water and birth-weight outcomes. *Arch Environ Health*, 55(3):188–94, 2000.

[31] H. Xiang, J. R. Nuckols, and L. Stallones. A geographic information assessment of birth weight and crop production patterns around mother's residence. *Environ Res*, 82(2):160–7, 2000.

[32] E. M. Bell, I. Hertz-Picciotto, and J. J. Beaumont. Case-cohort analysis of agricultural pesticide applications near maternal residence and selected causes of fetal death. *Am J Epidemiol*, 154(8):702–10, 2001.

[33] D. M. Schreinemachers. Birth malformations and other adverse perinatal outcomes in four U.S. wheat-producing states. *Environ Health Perspect*, 111(9):1259–64, 2003.

[34] K. J. Meyer, J. S. Reif, D. N. Veeramachaneni, T. J. Luben, B. S. Mosley, and J. R. Nuckols. Agricultural pesticide use and hypospadias in eastern arkansas. *Environ Health Perspect*, 114(10):1589–95, 2006.

[35] P. Carbone, F. Giordano, F. Nori, A. Mantovani, D. Taruscio, L. Lauria, and I. Figa-Talamanca. Cryptorchidism and hypospadias in the sicilian district of ragusa and the use of pesticides. *Reprod Toxicol*, 22(1):8–12, 2006.

[36] R. P. Rull, B. Ritz, and G. M. Shaw. Neural tube defects and maternal residential proximity to agricultural pesticide applications. *Am J Epidemiol*, 163(8):743–53, 2006.

[37] G. S. Berkowitz, J. Obel, E. Deych, R. Lapinski, J. Godbold, Z. Liu, P. J. Landrigan, and M. S. Wolff. Exposure to indoor pesticides during pregnancy in a multiethnic, urban cohort. *Environ Health Perspect*, 111(1):79–84, 2003.

[38] G. S. Berkowitz, J. G. Wetmur, E. Birman-Deych, J. Obel, R. H. Lapinski, J. H. Godbold, I. R. Holzman, and M. S. Wolff. In utero pesticide exposure, maternal

paraoxonase activity, and head circumference. *Environ Health Perspect*, 112(3):388–91, 2004.

[39] F. P. Perera, V. Rauh, W. Y. Tsai, P. Kinney, D. Camann, D. Barr, T. Bernert, R. Garfinkel, Y. H. Tu, D. Diaz, J. Dietrich, and R. M. Whyatt. Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population. *Environ Health Perspect*, 111(2):201–5, 2003.

[40] R. M. Whyatt, V. Rauh, D. B. Barr, D. E. Camann, H. F. Andrews, R. Garfinkel, L. A. Hoepner, D. Diaz, J. Dietrich, A. Reyes, D. Tang, P. L. Kinney, and F. P. Perera. Prenatal insecticide exposures and birth weight and length among an urban minority cohort. *Environ Health Per- spect*, 112(10):1125–32, 2004.

[41] B. Eskenazi, K. Harley, A. Bradman, E. Weltzien, N. P. Jewell, D. B. Barr, C. E. Furlong, and N. T. Holland. Association of in utero organophos- phate pesticide exposure and fetal growth and length of gestation in an agricultural population. *Environ Health Perspect*, 112(10):1116–24, 2004.

[42] L. Fenster, B. Eskenazi, M. Anderson, A. Bradman, K. Harley, H. Hernandez, A. Hubbard, and D. B. Barr. Association of in utero organochlorine pesticide exposure and fetal growth and length of gestation in an agricultural population. *Environ Health Perspect*, 114(4):597–602, 2006.

[43] International Agency for Research on Cancer. IARC. *Monographs on the Evaluation of the carcinogenic risks to humans: Tobacco smoking*, volume 38. International Agency for Research on Cancer, Lyon, 1986.

[44] S. Schick and S. Glantz. Philipmorris toxicological experiments with fresh sidestream smoke: more toxic than mainstream smoke. *Tob Control*, 14(6):396–404, 2005.

[45] US Department of Health Services and Human. The health consequences of involuntary exposure to tobacco smoke: A report of the surgeon general. Technical report, US Department of Health and Human services, Center for Disease Control and Prevention, Coordinating Center of Health promotion, National Center for Chronic Disease Prevention and Health Promotion. Office on Smoking and Health, 2006.

[46] C. Ward, S. Lewis, and T. Coleman. Prevalence of maternal smoking and environmental tobacco smoke exposure during pregnancy and impact on birth weight: retrospective study using millennium cohort. *BMC Public Health*, 7:81, 2007.

[47] H. K. Hegaard, H. Kjaergaard, L. F. Moller, H. Wachmann, and B. Ottesen.

The effect of environmental tobacco smoke during pregnancy on birth weight. *Acta Obstet Gynecol Scand*, 85(6):675–81, 2006.

[48] W. Hanke, W. Sobala, and J. Kalinka. Environmental tobacco smoke exposure among pregnant women: impact on fetal biometry at 20-24 weeks of gestation and newborn child's birth weight. *Int Arch Occup Environ Health*, 77(1):47–52, 2004.

[49] L. George, F. Granath, A. L. Johansson, G. Anneren, and S. Cnattingius. Environmental tobacco smoke and risk of spontaneous abortion. *Epidemi- ology*, 17(5):500–5, 2006.

[50] M. Kharrazi, G. N. DeLorenze, F. L. Kaufman, B. Eskenazi, Jr. Bernert, J. T., S. Graham, M. Pearl, and J. Pirkle. Environmental tobacco smoke and pregnancy outcome. *Epidemiology*, 15(6):660–70, 2004.

[51] J. Barnoya and S. A. Glantz. Cardiovascular effects of smoke: nearly as large as smoking. *Circulation*, 111(20):2684–98, 2005.

[52] A. Chatzimicael, A. Tsalkidis, D. Cassimos, S. Gardikis, D. Spathopoulos, G. A. Tripsianis, K. Kambouri, V. Aivazis, G. Vaos, and D. Bouros. Effect of passive smoking on lung function and respiratory infection. *Indian J Pediatr*, 75(4):335–40, 2008.

[53] J. Gardosi, A. Chang, B. Kalyan, D. Sahota, and E. M. Symonds. Cus- tomised antenatal growth charts. *Lancet*, 339(8788):283–7, 1992.

[54] D. T. Wigle, T. E. Arbuckle, M. Walker, M. G. Wade, S. Liu, and D. Krewski. Environmental hazards: evidence for effects on child health. *J Toxicol Environ Health B Crit Rev*, 10(1-2):3–39, 2007.

[55] M. J. Nieuwenhuijsen, M. B. Toledano, N. E. Eaton, J. Fawell, and P. Elliott. Chlorination disinfection byproducts in water and their association with adverse reproductive outcomes: a review. *Occup Environ Med*, 57(2):73–85, 2000.

[56] C. M. Villanueva, G. Durand, M. B. Coutte, C. Chevrier, and S. Cordier. Atrazine in municipal drinking water and risk of low birth weight, preterm delivery, and small-for-gestational-age status. *Occup Environ Med*, 62(6):400–5, 2005.

[57] G. Windham and L. Fenster. Environmental contaminants and pregnancy outcomes. *Fertil Steril*, 89(2 Suppl):e111–6; discussion e117, 2008.

[58] P. C. Huang, P. L. Kuo, Y. Y. Chou, S. J. Lin, and C. C. Lee. Association between prenatal exposure to phthalates and the health of newborns. *Environ Int*, 35(1):14–20, 2009.

[59] G. Aggazzotti, E. Righi, G. Fantuzzi, B. Biasotti, G. Ravera, S. Kanitz, F. Barbone, G. Sansebastiano, M. A. Battaglia, V. Leoni, L. Fabiani, M. Triassi, and S. Sciacca. Chlorination by-products (cbps) in drinking water and adverse pregnancy outcomes in italy. *J Water Health*, 2(4):233–47, 2004.

[60] T. E. Arbuckle, S. E. Hrudey, S. W. Krasner, J. R. Nuckols, S. D. Richardson, P. Singer, P. Mendola, L. Dodds, C. Weisel, D. L. Ashley, K. L. Froese, R. A. Pegram, I. R. Schultz, J. Reif, A. M. Bachand, F. M. Benoit, M. Lynberg, C. Poole, and K. Waller. 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, 2002.

[61] C. Y. Shiau, J. D. Wang, and P. C. Chen. Decreased fecundity among male lead workers. *Occup Environ Med*, 61(11):915–23, 2004.

[62] F. Bakir, S. F. Damluji, L. Amin-Zaki, M. Murtadha, A. Khalidi, N. Y. al Rawi, S. Tikriti, H. I. Dahahir, T. W. Clarkson, J. C. Smith, and R. A. Doherty. Methylmercury poisoning in Iraq. *Science*, 181(96):230–41, 1973.

[63] M. Harada. Minamata disease: methylmercury poisoning in Japan caused by environmental pollution. *Crit Rev Toxicol*, 25(1):1–24, 1995.

[64] J. L. Daniels, A. S. Rowland, M. P. Longnecker, P. Crawford, and J. Gold ing.Maternal dental history, child's birth outcome and early cognitive development. *Paediatr Perinat Epidemiol*, 21(5):448–57, 2007.

[65] F. Xue, C. Holzman, M. H. Rahbar, K. Trosko, and L. Fischer. Maternal fish consumption, mercury levels, and risk of preterm delivery. *Environ Health Perspect*, 115(1):42–7, 2007.

[66] P. Grandjean, P. Weihe, and J. B. Nielsen. Methylmercury: significance of intrauterine and postnatal exposures. *Clin Chem*, 40(7 Pt 2):1395–400, 1994.

[67] J. O. Odland, E. Nieboer, N. Romanova, Y. Thomassen, and E. Lund. Blood lead and cadmium and birth weight among sub-arctic and arctic populations of Norway and Russia. *Acta Obstet Gynecol Scand*, 78(10):852–60, 1999.

[68] G. Schoeters, E. Den Hond, M. Zuurbier, R. Naginiene, P. van den Hazel, N. Stilianakis, R. Ronchetti, and J. G. Koppe. Cadmium and children: exposure and health effects. *Acta Paediatr Suppl*, 95(453):50–4, 2006.

[69] G. Koppen, E. Den Hond, V. Nelen, E. Van De Mieroop, L. Bruckers, M. Bilau, H. Keune, N. Van Larebeke, A. Covaci, H. Van De Weghe, C. Schroijen, K. Desager, M. Stalpaert, W. Baeyens, and G. Schoeters. Organochlorine and heavy

metals in newborns: results from the Flemish environment and health survey (flehs 2002-2006). *Environ Int*, 35(7):1015–22, 2009.

[70] M. A. Philbert, M. L. Billingsley, and K. R. Reuhl. Mechanisms of injury in the central nervous system. *Toxicol Pathol*, 28(1):43–53, 2000.

[71] P. Grandjean and P. J. Landrigan. Developmental neurotoxicity of industrial chemicals. *Lancet*, 368(9553):2167–78, 2006.

[72] F. P. Perera, V. Rauh, R. M. Whyatt, D. Tang, W. Y. Tsai, J. T. Bernert, Y. H. Tu, H. Andrews, D. B. Barr, D. E. Camann, D. Diaz, J. Dietrich, A. Reyes, and P. L. Kinney. A summary of recent findings on birth outcomes and developmental effects of prenatal ETS, PAH, and pesticide exposures. *Neurotoxicology*, 26(4):573–87, 2005.

[73] R. G. Feldman and R. F. White. Lead neurotoxicity and disorders of learning. *J Child Neurol*, 7(4):354–9, 1992.

[74] P. Mendola, S. G. Selevan, S. Gutter, and D. Rice. Environmental factors associated with a spectrum of neurodevelopmental deficits. *Ment Retard Dev Disabil Res Rev*, 8(3):188–97, 2002.

[75] H. L. Needleman. Effects of low levels of lead exposure. *Science*, 256(5055):294–5, 1992.

[76] R. O. Wright, C. Amarasiriwardena, A. D. Woolf, R. Jim, and D. C. Bellinger. Neuropsychological correlates of hair arsenic, manganese, and cadmium levels in school-age children residing near a hazardous waste site. *Neurotoxicology*, 27(2):210–6, 2006.

[77] B. C. Gladen, M. P. Longnecker, and A. J. Schecter. Correlations among polychlorinated biphenyls, dioxins, and furans in humans. *Am J Ind Med*, 35(1):15–20, 1999.

[78] A. W. Glynn, A. Wolk, M. Aune, S. Atuma, S. Zettermark, M. Maehle-Schmid, P. O. Darnerud, W. Becker, B. Vessby, and H. O. Adami. Serum concentrations of organochlorines in men: a search for markers of exposure. *Sci Total Environ*, 263(1-3):197–208, 2000.

[79] G. Toft, L. Hagmar, A. Giwercman, and J. P. Bonde. Epidemiological evidence on reproductive effects of persistent organochlorines in humans. *Reprod Toxicol*, 19(1):5–26, 2004.

[80] N. Ribas-Fito, M. Sala, M. Kogevinas, and J. Sunyer. Polychlorinated biphenyls

(PCBs) and neurological development in children: a systematic review. *J Epidemiol Community Health*, 55(8):537–46, 2001.

[81] G. Reggiani and R. Bruppacher. Symptoms, signs and findings in humans exposed to PCBs and their derivatives. *Environ Health Perspect*, 60:225–32, 1985.

[82] D. T. Wigle, T. E. Arbuckle, M. Walker, M. G. Wade, S. Liu, and D. Krewski. Environmental hazards: evidence for effects on child health. *J Toxicol Environ Health B Crit Rev*, 10(1-2):3–39, 2007.

[83] M. Wilhelm, U. Ranft, U. Kramer, J. Wittsiepe, F. Lemm, P. Furst, G. Eberwein, and G. Winneke. Lack of neurodevelopmental adversity by prenatal exposure of infants to current lowered PCB levels: comparison of two German birth cohort studies. *J Toxicol Environ Health A*, 71(11-12):700–2, 2008.

[84] B. Berglund, T. Lindvall, and D. Schwela. Guidelines for community noise. Technical report, World Health Organisation, 1999.

[85] EEA. Are we moving in the right direction? indicators on transport and environmental integration in the EU. Technical report, EEA, 2009.

[86] N. Kuenzli, R. Kaiser, and R. Seethaler. Luftverschmutzung und gesundheit Quantitative risikoabschätzung. *Umweltmed Forsch Prax*, 6(4):202–212, 2009.

[87] G. W. Evans, P. Lercher, M. Meis, H. Ising, and W. W. Kofler. Community noise exposure and stress in children. *J Acoust Soc Am*, 109(3):1023–7, 2001.

[88] Y. M. Ulrich-Lai and J. P. Herman. Neural regulation of endocrine and autonomic stress responses. *Nat Rev Neurosci*, 10(6):397–409, 2009.

[89] H. Duhme, S. K. Weiland, U. Keil, B. Kraemer, M. Schmid, M. Stender, and L. Chambless. The association between self-reported symptoms of asthma and allergic rhinitis and self-reported traffic density on street of residence in adolescents. *Epidemiology*, 7(6):578–82, 1996.

[90] H. Ising, H. Lange-Asschenfeldt, G. F. Lieber, H. Weinhold, and M. Eilts. Respiratory and dermatological diseases in children with long-term exposure to road traffic emissions. *Noise Health*, 5(19):41–50, 2003.

[91] T. Behrens, D. Taeger, W. Maziak, H. Duhme, P. Rzehak, S. K. Weiland, and U. Keil. Self-reported traffic density and atopic disease in children. Results of the ISAAC phase iii survey in muenster, Germany. *Pediatr Al lergy Immunol*, 15(4):331–9, 2004.

[92] S. A. Stansfeld, B. Berglund, C. Clark, I. Lopez-Barrio, P. Fischer, E. Ohrstrom, M. M. Haines, J. Head, S. Hygge, I. van Kamp, and B. F. Berry. Aircraft and road traffic noise and children's cognition and health: a cross-national study. *Lancet*, 365(9475):1942–9, 2005.

[93] A. Bockelbrink, S. N. Willich, I. Dirzus, A. Reich, S. Lau, U. Wahn, and T. Keil. Environmental noise and asthma in children: sex-specific differences. *J Asthma*, 45(9):770–3, 2008.

[94] A. Fyhri and R. Klaeboe. Road traffic noise, sensitivity, annoyance and self-reported health–a structural equation model exercise. *Environ Int*, 35(1):91–7, 2009.

[95] D. Hruba, L. Kukla, and M. Tyrlik. Occupational risks for human reproduction: Elspac study. European longitudinal study of pregnancy and childhood. *Cent Eur J Public Health*, 7(4):210–5, 1999.

[96] E. F. Magann, S. F. Evans, S. P. Chauhan, T. E. Nolan, J. Henderson, J. H. Klausen, J. P. Newnham, and J. C. Morrison. The effects of standing, lifting and noise exposure on preterm birth, growth restriction, and peri-natal death in healthy low-risk working military women. *J Matern Fetal Neonatal Med*, 18(3):155–62, 2005.

[97] A. L. Hartikainen, M. Sorri, H. Anttonen, R. Tuimala, and E. Laara. Effect of occupational noise on the course and outcome of pregnancy. *Scand J Work Environ Health*, 20(6):444–50, 1994.

[98] T. N. Wu, L. J. Chen, J. S. Lai, G. N. Ko, C. Y. Shen, and P. Y. Chang. Prospective study of noise exposure during pregnancy on birth weight. *Am J Epidemiol*, 143(8):792–6, 1996.

[99] L. Shi and S. E. Chia. A review of studies on maternal occupational exposures and birth defects, and the limitations associated with these studies. *Occup Med (Lond)*, 51(4):230–44, 2001.

[100] I. Figa-Talamanca. Occupational risk factors and reproductive health of women. *Occup Med (Lond)*, 56(8):521–31, 2006.

[101] A. Burdorf, I. Figa-Talamanca, T. K. Jensen, and A. M. Thulstrup. Effects of occupational exposure on the reproductive system: core evidence and practical implications. *Occup Med (Lond)*, 56(8):516–20, 2006.

[102] R. Garlantezec, C. Monfort, F. Rouget, and S. Cordier. Maternal occupational exposure to solvents and congenital malformations: a prospective study in the general population. *Occup Environ Med*, 66(7):456–63, 2009.

[103] J. L. Zhu, L. E. Knudsen, A. M. Andersen, N. H. Hjollund, and J. Olsen. Laboratory work and pregnancy outcomes: a study within the national birth cohort in Denmark. *Occup Environ Med*, 63(1):53–8, 2006.

Annex

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 those 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 generalize and/or summarize 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 judgment.

References

Tables

Annexes