Executive Summary:

The objective of ENRIECO was to advance our knowledge on specific environment and health causal relationships in European pregnancy and birth cohorts by providing support to exploitation of the wealth of data generated by past or ongoing studies funded by the EC and national programmes. Specific objectives were to make inventories of birth cohorts; assure quality and interoperability of exposure; health and exposure-response data; obtain data access; build databases; conduct analysis; make recommendations for data collection in the future to improve environment-health linkages and information, and disseminate the information. To achieve the aims and objectives the work was divided into six scientific work packages and 27 topical working groups. Report of these groups detailing methodology and recommendations can be found on the ENRIECO website: www.enrieco.org.

ENRIECO covers 36 birth cohorts in Europe, studying more than 350,000 mother-child pairs that have data that can be used to examine associations between chemical, physical and biological environmental exposures and child health. The full inventory of ENRIECO cohorts is publicly available as a searchable database on www.birthcohortsenrieco.net. The inventory will be updated on a regular basis, and will expand over time with additional contributions.

Considerable expertise and experience is associated with these birth cohorts. They provide important environmental exposure, health and environmental exposure-response data, yet the amount and detail of information provided on environment and health varies considerably.

Overall, greater and more efficient use needs to be made of the existing cohort data at the European level to provide timely response to key policy questions and concerns about "new" environmental exposures, and to improve methodology and power, understanding of geographical and cultural inequalities in disease, and exposure and health related behaviours. Replication of findings with important public health implications in different settings should be conducted, as well as improvement of statistical power through combined analysis. Cohorts should also improve use of routinely collected environmental and health data, as much data is currently available, but unused. Where data is difficult to access, stakeholders should make an increase effort to allow access.

Recent initiatives including ENRIECO have tried to combine data from various cohorts to increase e.g. power (overall and subgroups). Many cohorts were interested and very committed to this collaborative project of combined data analyses. The results showed that existing European birth and mother-child cohorts provide a real potential for combined analyses on pregnancy-related and child health outcomes in relation to environmental exposures, and add considerable value and insight in the exposure response relationships.

Combining data from various cohorts requires careful consideration of the aims, protocols, data, ethical issues, analyses and management. It is time and labour intensive but potential fruitful. However, there are currently limited resources for such initiatives at national and international level.

Follow-up of existing cohorts is essential to determine health effects in later life of pre natal and early childhood exposure, for which there is some but not conclusive evidence. New environmental exposures, or existing environmental exposures under new conditions would benefit in some cases from new pregnancy and birth cohorts to enable evaluation of any potential health effects.

Project Context and Objectives:

The structuring and consolidation of often fragmented data from various studies undertaken throughout Europe will improve the knowledge base for environment and health linkages. Data regarding environment-health causal relationships will be more readily available in a form useful for policy makers.

Epidemiological studies have shown associations between environmental pollutants and adverse child health outcomes, which may result in substantial economic and societal costs. There are many pregnancy and birth cohorts in Europe with information on environment and health. However, the wealth of available information has only been partially exploited, and there is a lack of statistical power in single studies which study rare health outcomes or exposures with a low prevalence. Therefore, an urgent need exists to evaluate, and where possible combine, the existing environmental exposure and health data, methods and tools from European birth cohort studies in order to evaluate any causal links between exposing agents and health and to provide recommendations for effective policy decisions to improve children's environmental health and reduce economic and societal costs.

Overall the focus of ENRIECO is on exposure response functions/relationships in environment and health in pregnancy and early childhood. This implies to a large extent extracting environmental exposure-response relationships from existing data with some new work on specific environmental exposure response relationships. From this leads preparatory work on how to obtain these data, such as standardizing exposure and health outcomes.

The overall objective of ENRIECO was to advance our knowledge on specific environment and health causal relationships in pregnancy and birth cohorts by providing support to exploitation of the wealth of data generated by past or ongoing studies funded by the EC and national programmes. Most importantly, the project was set to provide recommendations to the European Commission for data collection in the future to improve environment-health linkages and information, and to disseminate the resulting information. The project intended to bring together over 30 pregnancy and birth cohorts and information on around 250,000 newborns, infants and children from across Europe. The anticipated outcome was the structuring and consolidation of often fragmented data from various studies undertaken throughout Europe, which will improve the knowledge base for FP 7 Cooperation Work Programme 2008: Environment (including climate change) environment and health linkages. Furthermore, data regarding environment-health causal relationships were set to be more readily available in a form useful for policy makers.

To achieve the above, specific objectives determined by work packages were to

1. Make inventories of birth cohorts, including; health data; exposure data; biological samples; environmental exposure response functions; expertise and access.
2. Assure quality and interoperability and validate exposure, health and exposure-response data through extraction and rigorous evaluation of quality of the data, (including developing protocols describing the strategic approach); evaluation of opportunities and validation/testing studies (through case studies).
3. Obtain data access, build databases, and conduct analysis including setting up protocols for data access database building and analyses; setting up protocols for exposure response analyses; conducting specific analyses on exposure and health data to obtain exposure response functions (through case studies) and conducting specific meta/pooled analyses to obtain exposure response functions (through case studies).

4. Make recommendations for data collection in the future to improve environment-health linkages and information for data collection (exposure, health etc), possible analyses (laboratory and statistical) and exchange of knowledge between older and newer cohorts.
5. Disseminate information to the scientific community, policy makers and general public through a project website, virtual network, workshops, easy accessible info and a database with exposure response functions.

To this end, the project was divided into six workpackages: WP1 - Inventory of birth cohorts; WP2 - Evaluation of health outcomes; WP3 - Evaluation of health outcomes; WP4 - Evaluation of exposure-response relationships; WP5 - Database building; WP6 - Dissemination. These were further broken down into 27 topical working groups and three case studies. The overall management of the work is led by CREAL (WP7).

Project Results:

ENVIRONMENTAL HEALTH RISKS IN EUROPEAN BIRTH COHORTS (ENRIECO) 2009-2011

Aims and objectives

The overall aim of ENRIECO was to advance our knowledge on specific environment and health causal relationships in European pregnancy and birth cohorts by providing support to exploitation of the wealth of data generated by past or ongoing studies funded by the EC and national programmes. Specific objectives were to make inventories of birth cohorts, assure quality and interoperability of exposure, health and exposure-response data, obtain data access, build databases, conduct analysis, make recommendations for data collection in the future to improve environment-health linkages and information, and disseminate the information. To achieve the aims and objectives the work was divided into 6 work packages and 27 working groups.

FINDINGS

European Birth Cohorts

There are more than 35 birth cohorts in Europe, studying more than 350,000 mother-child pairs that have data that can be used to examine associations between chemical, physical and biological environmental exposures and child health. The cohorts are situated in 19 European countries, principally in Northern and Western Europe, with fewer cohorts in Southern and Eastern Europe. Twenty-four of the cohorts defined themselves as regionally-based studies, while the rest defined themselves as nationally-based or hospital-based. Two studies, the Danish National Birth Cohort (DNBC) and the Norwegian Mother and Babies study (MoBa) have recruited more than 100,000 mother-child pairs each. Ten studies have recruited between 5,000 and 20,000 pairs, and 18 between 1,000 and 5,000. The rest are cohorts of less than 1,000 subjects.

In many of cohorts (n=18) children are now aged between 5-10 years, in 12 cohorts children are over 10 years old, and in 5 cohorts the children are less than 5 years old. One cohort, ELFE in France, has not yet started data collection. Most of the cohorts started recruitment of mothers during pregnancy (n=22); the rest start at birth. Most cohorts have multiple follow-up points after birth, and the majority have follow-up points in each of the following relevant child age periods: 1-6 months, 6 to 18 months, 18 months to 5 years, 5 to10 years, over 10 years.

The full inventory of ENRIECO cohorts is publicly available as a searchable database on http://www.birthcohortsenrieco.net.

Health Outcomes

In general birth cohorts are most suitable to examine child health outcomes that are common or can be measured on a continuous scale. Rare pathologies such as childhood cancers, congenital anomalies and autism can only be studied in the very large cohorts, or with various cohorts combined. All cohorts collected information on pregnancy outcomes related to foetal growth and gestational length, and on childhood anthropometric measures. A number of cohorts specialise in the early causes of asthma and allergies; these are included in the ENRIECO inventory if they assessed one of the

environmental exposures. Neurodevelopment is a wide area that encompasses many cognitive and behavioural outcomes and even more tests to assess these, ranging from parental questionnaires on developmental milestones to detailed neuropsychological assessments.

As part of the ENRIECO study we evaluated in detail the following health outcomes: a) pregnancy-related outcomes, b) childhood allergies and asthma, c) neurobehavioral and cognitive function, d) cancer and e) child growth, metabolic and endocrine disorders. The aim was to evaluate the existing health information, methods and tools and to make recommendations for future work, including whether or not it would be possible to combine health outcomes from different cohorts.

The evaluation concluded that for existing cohorts, the health outcomes assessed in European birth and mother-child cohorts can be divided in 3 types:

1. Type 1 outcomes: Existing European birth and mother-child cohorts provide a real potential for combined analyses on pregnancy-related outcomes and child health outcomes in relation to environmental exposures. Key health outcomes could be used for further analyses, including time to pregnancy, birth weight, preterm births, wheeze or asthma and allergy (using e.g. ISAAC-based questionnaires), postnatal changes in body mass index, waist circumference, occurrence of obesity.
2. Type 2 outcomes: Additionally, specific congenital malformations, stillbirth, Intelligence Quotient, attention deficit/hyperactivity disorders and occurrence of puberty are worth considering, but the degree of harmonization between cohorts is more limited.
3. Type 3 outcomes: The existing European birth and mother-child cohorts provide a potential for combined analyses on cancer and cancer-related biomarkers. The main problem for childhood cancer is statistical power. Childhood cancer is a main cause of death in children but remains a rare event. For future studies, we encourage the participation and further development of the international consortium (I4C). The development of (early) biomarker-based studies is an important way forward.

Furthermore, children included in the European cohorts are getting older and a new challenge for existing cohorts is to investigate new health outcomes relevant at older childhood ages or early adulthood, such as biomarkers of cardiovascular disease, early puberty, infertility and evolution of neurodevelopment at older age.

Exposure

A detailed evaluation of environmental exposure and exposure assessment methods in the birth cohorts was conducted. The findings reported here focus on the frequency of assessment of exposures, exposure assessment methodology used and recommended and the main recommendations for further work.

Air pollution

Many (N=26) of the ENRIECO birth cohort studies have performed or are planning some assessment of exposure to outdoor air pollution. Exposure models are increasingly being used to estimate (mainly) residential exposures. Land-use regression models (N=16) are/will be used more often than dispersion models (N=9). Fifteen cohorts are currently participating in a collaborative EU-funded

project (ESCAPE) that adds land-use regression modelling of nitrogen oxides, particulate matter, soot and particle composition to existing cohort studies using a standardized protocol. Most cohort studies so far have estimates of pregnancy and/or early life exposure only.

Although it is in principle possible to use exposure modeling to estimate at all addresses within the study area for which the model has been developed, until now most of the studies defined exposure as exposure at the participant's residential address. Residential mobility, time-activity pattern and exposure at non-residential addresses such as daycare centers and schools, where children regularly spend considerable amounts of time were rarely taken into account. Studies comparing exposures estimated from land-use regression models with personal exposure measurements are scarce, but suggest stronger correlations for subjects who spend more time at home. Few studies until now compared residential exposures with time-weighted averages of residential and non-residential-exposures (i.e. at the participants' daycare, school and work addresses). Overall, differences found to be small, but we recommend more studies to confirm these findings.

While many cohorts do or will have estimates of long-term exposures to air pollutants such as NO2, NOx, particulate matter (PM10 and PM2.5) and soot, and to a much lesser extent for volatile organic compounds (VOCs) from land-use and/or dispersion models, there are currently no estimates of the long-term exposure to other pollutants such as ultrafine particulate matter (UFP), specific elements in particulate matter and polyaromatic hydrocarbons (PAHs) available in the cohorts, which may be of particular interest. ESCAPE will provide estimates for some cohorts for elemental analyses of PM and PAHs but further work is recommended in this area.

Water contamination

A total of twelve birth cohort studies included in the ENRIECO project have exposure assessment data on water contaminants. The most studied are disinfection by-products (DBPs), especially trihalomethane (THMs), partly because of the EC funded HIWATE study. Information on other contaminants (e.g. nitrates, metals, pesticides, and endocrine disruptors, pharmaceuticals) is much less available probably because they are not often found at high levels in the drinking water, except in some regions, and the lack of interest to study them for other reasons.

The most common methods used for the exposure assessment is to combine information of water related behaviours (ingestion, and for DBPs showering, bathing and swimming) obtained by questionnaire with newly or routinely collected water contaminant measurements. Routinely measured contaminants are often available but difficult to access and generally have fairly low levels.

Access to publicly collected data should be increased and European databases of drinking water contaminants should be made available to researchers.

In addition to the regulated substances, the collection of non-regulated substances such as pharmaceuticals, PFOS/PFOA or (other) endocrine disruptors should be considered since the cohorts provide a unique opportunity to collect this data.

Allergens and biological contaminants

A total of 26 ENRIECO cohorts have assessed at least one allergen or one biological organism exposures including, mould, mould components, and endotoxin during perinatal period and in early childhood. Overall, most of the indoor allergen and bio-containments exposures are assessed using information from questionnaires. This is the cheapest exposure assessment method, however the information is not accurate enough to discriminate exposure levels or to obtain exposures from all sources. As most of the European birth cohort studies have used this method, it is recommended for the future studies to also use the questions of interest in their questionnaires since the collected data can provide a good comparison between the studies and the geographical area.

The best exposure assessment for exposures to allergen and bio-containments is repeated sample collections through mobile personal air samplers, which can be carried by study subjects and directly sample the air that the study subjects are breathing in. However, the samplers are expansive and may cause inconvenience for the study subjects. Therefore, for studies which plan to further investigate the exposure-response relationships, measured allergen or bio-containment levels from indoor settled house dust or air samples using current state of the art techniques are recommended.

Future studies are also recommended to specifically address issues of timing and location of the exposures when planning indoor exposure assessments.

Metals

A total of 19 ENRIECO birth cohorts have evaluated metals or are planning to do it soon. Most cohorts (n=13) have determined the levels of mercury (Hg) and lead (Pb), whereas few of them have analyzed other metals such as cadmium (Cd) (n=10), selenium (Se) (n=6), manganese (Mn) (n=4), arsenic (As) (n=5), and nickel (Ni) (n=1). There are two cohorts that have determined (ALSPAC) or are planning to determine (INMA) metals by means of Total Metals Spectrum (TMS) which allows the analysis of a wide range of metals at the same time.

Human biological monitoring has been the most used method for ENRIECO birth cohorts to assess metals exposure. Most measurements have been performed in cord blood; other, non-invasive matrices such as hair and urine are gaining attention. Few cohorts have used questionnaires, mostly dietary and occupational questionnaires.

Exposure assessment by human biological monitoring is costly and therefore the number of subjects with assessment of exposure is generally small resulting in low statistical power. Pooling and/or meta-analysis of multiple cohorts can overcome this problem and improve causal inference

Even though some studies have shown good correlation between Hg concentrations in biological samples and fish/shellfish consumption through validated FFQ, more studies are needed to confirm these results.

Pesticides

Many of the ENRIECO birth cohort studies are interested in the health effects of pesticide exposure, but the exposure assessment is challenging because of the many pesticides involved, variability in use

and exposure and limited use of good exposure assessment methods. A total of 18 ENRIECO cohorts performed or are currently performing some assessment of exposure to pesticides. Most of these cohorts have evaluated or are planning to evaluate occupational exposure and/or the household use exposure to pesticides by questionnaire, while few assessed or will assess dietary and outdoor exposure (e.g. proximity to agricultural activities). Only a few (N=4) though use biological monitoring to assess pesticide exposure, or to validate questionnaire data.

There is little standardization of the timing of the exposure assessment varying from pregnancy to early childhood and infancy. Some cohorts considered several timings of exposure assessment (e.g. each trimester of pregnancy for biological monitoring, or at different ages during childhood for household use of pesticides) since very little is known on the critical window of susceptibility for these compounds.

No work has been conducted within these European cohorts to assess the quality of the exposure assessment and further work on this is recommended.

Existing European cohorts could take advantage of new GIS-modeling approaches to provide estimates of agricultural (bystander) pesticide exposure for entire cohorts, combining existing European data on soil occupancy (such as Corine Land Cover) or other more detailed maps of crops (satellite imagings) and pesticide use probability (expert based) data on crops.

Validation studies are crucial and should be part of the exposure assessment. Future work should include a subgroup of the cohort with monitoring data (biological and/or environmental) in order to validate other assessments for pesticide exposures and to identify the main determinants. Residential exposure is usually the main focus, but non-residential locations and time-activity patterns may improve the exposure assessments. In order to benefit from new technologies (such as GIS and satellite imaging), future studies should include systematic geocoding of locations of interest.

Emerging contaminants

Very few European cohorts (4-6 depending on the pollutant group) have carried out measurements of emerging contaminants such as brominated flame retardants (BFRs), perfluorinated compounds (PFCs), phthalates, bisphenol A (BPA) or other compounds. However, this is a rapidly developing field and further measurements are ongoing or planned in more cohorts (N=17). Generally, the measurements involve few subjects in each cohort (a few hundred maximum). The biological media measured and the timing of the measurements vary between cohorts. Few cohorts have measured in multiple media or at multiple time points.

For non-persistent exposures with very short half-lives, such as phthalates and BPA, exposure assessment is not straightforward. Almost all cohorts use urine as the biological medium as blood levels are extremely low. Spot urine sampling only provides an imprecise estimate of long-term exposure. Multiple measurements of these chemicals at different time points during pregnancy will therefore greatly improve exposure assessment. Issues of contamination from storage materials and lab equipment, and storage conditions are important to consider.

It is recommended to conduct a European evaluation of inter- and intra-laboratory variability. This is especially important for these emerging contaminants because expertise and methods are less-well established. Use of reference materials and participation in round robins are important prerequisites to

validate analytical methods. Regular comparisons and calibrations between labs are recommended, for example using by exchanging samples with a specialized lab regularly during the analytical phase.

Apart from the biological human monitoring, some cohorts report using questionnaires (cosmetic use, food containers, etc.), occupational JEMs, environmental measurements, and/or toxicokinetic models. Validation of such methods and models is needed before they can be widely applied.

This is an emerging field and there is a rapidly growing expertise in the cohorts which would benefit from continued communication and coordination. Through ENRIECO, cohorts are now aware of researchers in different countries working to develop methods for measurement of the emerging contaminants. Cohorts should work together on developing conversion models and inter laboratory comparisons that will allow future comparison and pooling studies.

Mechanisms need to be developed for the detection and prioritisation of new chemicals in cohort studies.

Coordination with other European projects such as COPHES (Consortium to Perform biomonitoring on a European Scale) will be crucial to harmonize research on emerging exposures in the birth cohorts in Europe.

Radiations

Ionising radiations

Main exposure sources of interest are medical x-ray and CT scan procedures. Additional exposures which might be of interest are (parental) occupational exposures to ionising radiation. However, only a very low number of exposed persons would be expected for these exposures. Prevalence of another exposure source to ionizing radiation, residential exposure to Radon, would depend highly on geographical region and might therefore be feasible to investigate in some, but not all cohorts.

Very few of the ENRIECO birth cohort studies have performed or are planning some assessment of exposure to ionising radiations. Three cohorts have included questions on maternal occupational exposures in their questionnaires, six have asked questions about prenatal medical ionising radiation exposures, and one is planning to assess residential radon exposure using geographical methods. Only two cohorts (NINFEA and ELFE) currently plan to ask questions about medical radiation exposures in children. There are no standardised questionnaires or protocols in this field.

Childhood medical diagnostic radiation sources, such as repeated X-rays used in small pre-term babies to monitor lung maturation and CT scans, are of much current concern because a) children may be more sensitive to health effects of radiation than adults, b) children tend to receive higher doses to specific organs from these procedures because of their smaller body size, and c) children have a longer life span to express any radiation-related health effect. Even though only a small proportion of children are exposed, birth cohorts could play a role in studying potential non-cancer effects (e.g. on cognition) of medical radiation exposures. Pooling across cohorts will be essential.

Large cohort studies of children exposed to CT scans are ongoing and planned in a number of European countries as part of the EPI-CT project (FP7 EURATOM). Possible links between such exposed cohorts and birth cohorts need further evaluation.

UV Radiations

Main source of UV radiation is the sun and the use of sun beds but effects on health are affected by a range of factors such as skin type, sun habits and UV risky or protective behaviour.

Only six cohorts are collecting UV-related data through questionnaire questions on sunburn in children, use of sunbeds during pregnancy, and time spent outdoors. None of the cohorts collect data on maternal and child skin type, sunscreen use, or clothing. Standard questionnaires are not available.

Considering the importance of beneficial and harmful effects of childhood UV exposure and the impact of vitamin D on foetal growth together with appropriate validity of questionnaires in estimating UV exposure in children, it is recommended to include UV and vitamin D related questions in birth cohort questionnaires enabling researchers to study UV-related effects (e.g. effects on the immune system) in children.

Non-ionising Radiations

Main exposure sources for radiofrequency fields are environmental sources such as base stations or broadcast transmitters, generally resulting in a low-level whole body exposure, and the use of telecommunication devices which can lead to peak exposures in some body parts (usually the head for the use of mobile or cordless phones). Main exposure sources for extremely low-frequency magnetic fields are power lines and potentially transformers that have been built into apartment houses.

Very few cohorts assess exposure to non-ionising radiations: 2 cohorts include parental occupational EMF exposure in their questionnaires, 2 cohorts assess ELF exposure to overhead high-voltage power lines through geographical information of the place of residence and power lines, 2 cohorts include questions about mobile phone use of the mother during pregnancy and 4 on children's mobile phone use. A few cohorts have started using base-station exposure models combined with information from home appliances and personal RF exposure meters, in order to estimate whole body RF/ELF-EMF exposure. There are no standardised or validated questionnaires, models or protocols in use at this moment.

The WHO has identified exposure to RF fields from mobile phones in young people as a main research priority and is now recommending that existing prospective cohort studies of children and adolescents are used for this purpose (http://www.who.int/peh-emf/research/agenda/en/index.html). At the moment, few of the birth cohorts in ENRIECO are old enough to be using mobile phones. The existing cohorts are ideally suited, however, to further investigate non-cancer effects of RF exposure in children in a prospective way and should integrate standardised questions on the use of mobile phones and other telecommunications equipment into their questionnaires as soon as the children are old enough (from age 7-8 onwards). This would facilitate combined analyses in the future.

Smoking and second hand tobacco smoke

Foetal tobacco smoke has been assessed in 36 European pregnancy or birth cohort. The majority (30) of these also obtained (or planned to obtain) postnatal second hand tobacco smoke exposure.

In all cohorts, information on second hand tobacco smoke was obtained by parental questionnaires. In addition, 11 studies had also collected biological samples (mostly urine) for analysis of cotinine in the children at different ages from infancy to school age.

Even though the knowledge of second hand tobacco smoke and effects on health in children is quite extensive, there are some gaps in knowledge such as the important of timing of the exposure. Future studies should assess exposure in different pregnancy trimester and in regular intervals during follow up. Both maternal and paternal smoking need sot be assessed.

Noise

A total of 14 ENRIECO cohorts previously assessed or are currently assessing noise exposure by questionnaires. In addition, five cohorts used objective measures such as noise propagation modelling, noise maps or noise meters. Twelve cohorts assessed noise annoyance and noise disturbance during pregnancy with a follow-up period of up to 5 years of age. The latest follow-ups were assessed at the ages of 8-12 years by ALSPAC (UK), Generation-R (Netherlands), LISA and MAS (both Germany). Generally, there is little standardization of subjective noise exposure assessment by questionnaire among the birth cohorts.

Considering potential effects of noise on pediatric health outcomes (immunosystem, cardiovascular system and psychological dimensions) it remains unclear whether objective or subjective measures are more relevant. Therefore, exposure assessments in pregnancy and birth cohort studies should consider both objective measures and subjective assessments such as noise annoyance and noise sensitivity. Furthermore, the assessment of time-activity patterns and the levels of exposure need to be considered.

Persistent organic pollutants

A total of 17 ENRIECO cohorts performed or are currently performing some assessment of POPs in biological samples. Most cohorts assessed exposure to DDT, DDE, HCB and PCB, while few assessed exposure to aldrin, chlordane, dieldrin, endrin, heptachlor, lindane, methoxychlor, endosulphane, mirex, toxaphene, HCH, dioxins, furans.

The state of the art method for measurements of POPs are HPLC derived methods, with minor variation between cohorts in the specific details. Especially for detecting POPs in low concentrations in small volumes it is needed to use equipment with high sensitivity.

Although a number of studies on exposure to persistent organochlorines have been performed, it is also evident that there is high degree of variability between studies in study design including timing of sample collection and collection medium. Therefore additional data collection may be needed, especially if the outcomes of interest are hypothesised to be related to exposure at specific time windows during foetal life or early childhood. Prospective birth cohort studies with repeated exposure and health outcome assessments offer a unique possibility to increase our knowledge with regard to the timing of exposure.

Occupation

Most ENRIECO cohorts (32 out of 36) have recorded at least maternal occupation at one point in time and 19 have collected some additional information concerning a number of maternal occupational exposures. Information on paternal occupation has been recorded in 25 cohorts. Five cohorts have collected detailed information on paternal exposures. Occupational exposures (chemical or physical

factors, factors related to work load and work organization) have mainly be assessed using questionnaires to the mother, a few cohorts mention use of Job Exposure Matrices (JEM). When cohorts have collected information on occupation/occupational exposure it usually concerns the whole population. Most cohorts that collected maternal occupational exposures data did this before birth, that is independently from pregnancy outcome.

Seventeen cohorts have recorded maternal occupations held at any time during pregnancy (including collected at birth) or paternal occupation at the beginning of pregnancy and have already translated this information into (occupational) codes. ISCO88 code or its national equivalents appears to be the most frequently reported in the participating cohorts. Questionnaires on occupational exposures include a large variety of exposures, and data collection strategy and their possible standardized use will have to be assessed.

For an adequate data collection on occupational exposures job title is not sufficient. In addition, one should collect description of task, type of industry, number of hours per week, and if possible name of company, existence of personal and/or biomonitoring data. Free text should be kept in the data base for additional details. A good training of coders should be organized for standardization. Standardized questionnaires for physical load should be published. Further development and validation of European and country specific JEMs is needed.

In conclusion

All cohorts do have some information on second hand tobacco smoke exposure and many cohorts assessed occupational exposures (n=32), exposure to allergens and biological organisms (n=26) and outdoor air pollution (n=26). Assessment of exposure to water contaminants (n=12), metals (n=19), pesticides (n=18), persistent organic pollutants (n=17), and noise (n-14), radiations (n=12) is limited to fewer cohorts.

Exposure information was generally available for the vast majority of the study participants if exposure is assessed by means of exposure modeling, questionnaires, routinely collected data or a combination of these. Biomonitoring was sometimes performed in addition (e.g. for assessment of exposure to water contaminants, smoking and second hand tobacco smoke exposure) usually for a small subset of the study population for validation purposes. For other exposures such as pesticides, persistent organic pollutants, Bisphenol A, phthalates and phenols, where exposure assessment largely relied on biomonitoring, the situation was different. Most of the smaller cohorts with roughly up to 1,300 participants tried to measure at least some of the biomarkers in the whole cohort, whereas the larger cohorts performed biomonitoring in a subset of a cohort's population

Standardization

There is general little standardization of exposure assessment methods between cohorts and even if the same method is used, protocols vary largely between cohorts. Some exceptions include studies in which a standardized exposure assessment was part of a collaborative effort, such as the TRAPCA and ESCAPE studies for outdoor air pollution, the HIWATE study for water contamination, the AIRALLERG and HITEA studies for indoor exposures including allergens and microbial agents; combustion products; and second hand tobacco smoke. Therefore, the standardization of the exposure

assessment methods and protocols in future studies has been recommended most groups. However, it should be noted that standardization may reduce the possibility of comparing different methods, and this may not in all cases be beneficial.

Likewise, there is little standardization of the timing of the exposure assessment varying from pregnancy to early childhood and infancy. However, cohorts have usually collected data allowing to separate prenatal and childhood exposures. Repeated exposure assessments that allow the study of changes in exposure as well as the role of the timing of exposure are available for some exposure topics (e.g. outdoor air pollution, allergens and biological organisms, smoking and second hand tobacco smoke exposure).

Validity of exposure assessment

Exposure assessment by means of individual environmental or biological measurements is costly and therefore usually not feasible in large cohort studies. Often, questionnaires are used instead to assess exposures. The validity of questionnaires for the assessment of pet allergen and mould exposure as well as second hand tobacco smoke exposure has been assessed in a number of studies. Despite some misclassification, questionnaire reports were found to be an inexpensive and valid estimate of residential environmental tobacco smoke exposure among preschool and school children. The specificity of questionnaire information on cat- and dog-ownership for cat and dog allergen levels in settled house dust was found to be high, but the sensitivity was found to be low. In other fields (e.g. household use of pesticides, non-ionizing radiation) where exposure assessment largely relies on questionnaires, such validation studies are still lacking and were recommended by the experts involved in this project. Furthermore, often little is known about the long(er)-term validity of a single exposure assessment for a longer period For non-persistent compounds such as bisphenol A and phtalates, that have short half lives and that are rapidly excreted from the body, the long(er)-term validity of a single measurement is limited and therefore it is recommended to collect multiple samples at different time points.

Timing of exposure assessment

For many exposures, we presently know very little about the relevance of the timing of the exposure in addition to the level of exposure, and it is unclear whether exposure during a specific period when organs develop and are considered being more susceptible, is more important than later exposure. Prospective birth cohort studies with repeated exposure and health outcome assessments offer a unique possibility to increase our knowledge with regard to the timing of exposure and therefore, more research on the relevance of the timing has been recommended by several groups (e.g. air pollution, allergens and biological contaminants, second hand tobacco smoke exposure, noise). Collecting data before birth or before any adverse health event is crucial whenever exposure assessment relies on maternal self-report (i.e. occupational exposures and pesticide domestic use).

Time-activity pattern, exposure at non-residential addresses and residential mobility (noise, water air pesticides)

For exposures such as air pollution, water contaminants, noise and bystander pesticide exposure individual exposure assessment by means of personal or biomonitoring alone will generally not be

feasible in birth cohorts, as the study populations generally comprise several hundreds to thousands of subjects, living or attending school/daycare at different places. Therefore, environmental exposure assessment in the European birth cohorts currently is very often limited to residential exposure although study participants regularly spend considerable amounts of their time outside their homes for instance at day care centers or schools where they may be exposed as well, possibly to higher levels of exposure (e.g. to higher levels of air pollution if a school is located in the vicinity of a highway). Consequently, little is known about the role of residential and non-residential exposure in the association between exposure and health. Some recent publications on the effects of ambient air pollution where exposure was estimated as a time-weighted average of several addresses where the participants spent considerable amounts of time indicated little differences between the estimated exposure at the home address and the time-weighted average exposure. This needs further evaluation and therefore, we recommend collecting information on residential history in birth cohort studies. Time-activity pattern, exposure at non-residential addresses and residential mobility are currently rarely included in the assessment of air pollution, water contaminants, noise and bystander pesticide exposure, but should be included in future studies to improve exposure assessment.

Exposure Response Relationship of Environmental Exposure and Health Outcomes

As part of the ENRIECO study the relationship between certain environmental exposures and health outcomes based on epidemiological studies were evaluated. Given the time limitations and limited resources the evaluations focussed on relationships that have been studied more frequently or are of particularly interest. The aim was to establish what the current epidemiological evidence for any relationship was, and what the birth cohorts could contribute in the future. The evidence is described by health outcome.

BIRTH OUTCOMES

Second hand smoke

There is very strong evidence for an association between exposure to second hand smoke during pregnancy and adverse birth outcomes, namely low birth weight (LBW), foetal growth restriction (FGR) and for delivering a small for gestational age baby (SGA). Part of this research has its origins in European birth cohorts studies. Further work should be conducted for the harmonization of assessing SHS exposure in cohort studies, and the development of a battery of questions that could be used as a standardized approach for assessing SHS exposure.

Occupation

There is good evidence that occupational hazards can adversely affect reproduction and pregnancy outcomes. Prospective birth cohorts have not contributed largely in establishing these occupational risk factors. This is due to rareness of such exposures and job titles, to the difficulties in assessing occupational exposure in a sufficiently accurate manner in general birth cohort questionnaires, and sometimes also due to the rareness of the outcomes of interest. European pooling in this area will be beneficial. 8 European birth cohorts have published on occupational risk factors, 6 of which are ENRIECO cohorts. The European birth cohorts can contribute to further analyse and understand these

relationships because they have important strengths, such as the collection of data prospectively for population-based samples, and the collection of data on many covariates.

Air pollution

The evidence on air pollution, specifically carbon monoxide, nitrogen dioxide, sulphur dioxide, and particulate matter, and measures of foetal growth assessed at birth, and gestational duration and preterm births, are suggestive of an association of air-pollution levels with adverse birth outcomes. Some European birth cohorts have reported associations between air pollution and birth outcomes, but the main evidence is coming from other sources. The evidence for congenital anomalies and air pollutants (e.g., ozone, polyaromatic hydrocarbons (PAHs)) is weak. In epidemiology the most important new developments in the next few years will be the completion of the ESCAPE project (www.escapeproject.eu), which includes many of the birth cohorts included in ENRIECO. The work includes the evaluation of air pollutants in relation to reproductive outcomes including birth weight, prematurity and small for gestational age/IUGR, in 70000 mother child pairs using harmonized protocols. PM10 and PM2.5 and specific composition (elemental, PAHs, oxidative state) in selected centres, and NOx in all centres, and are obtained using state of the art land use regressions models.

Drinking water contaminants

There is growing evidence for a weak association between drinking water exposure to disinfection by-products (DBPs), particularly trihalomethanes and some birth outcomes such as small for gestational age, but less for other birth outcomes. The evidence is much weaker for exposures such as nitrates, pesticides, and Perfluorooctane sulfonate (PFOS)/Perfluorooctanoic acid (PFOA). Little evidence is there for pharmaceuticals and (other) endocrine disrupting substances. Health effects of metals have been established through other pathways than water. Some of the evidence has come from European birth cohorts, while most of the evidence has come from registry based studies. Only a small number of the birth cohorts have analysed data on the association between drinking water contaminants and birth outcomes (e.g. the HIWATE cohorts), while in total 11 have information that exposure and health information that could be analysed. The European birth cohorts can contribute to the analyses and further understanding of exposure response relationships of disinfection by-products, for example because of the data on various pathways of exposure and availability of different DBPs (as is done in HIWATE) and contribute to examinations of health effects of pharmaceuticals in water, but water levels for contaminants such as pesticides, PFOS/PFOA, nitrates and metals may be too low, except in some circumstances (e.g. targeted regions). Further analyses should focus on exposure response analyses, modifying factors and susceptible groups (genetics, ethnicity), timing of exposure, and mobility for disinfection by-products and initially exposure assessment for pharmaceuticals and other emerging exposures.

Persistant organic pollutants

There is some evidence for an association between Polychlorinated biphenyl (PCB) exposure and birth weight, whereas associations between other persistant organic pollutant (POP) exposures and birth weight/gestational age have been less consistent. Other birth outcomes studied includes genital malformations and here at most weak associations between POP exposure and cryptorchidism and hypospadia have been found. Several of the studies come from European birth cohorts, while most

other information come from North American birth cohorts. A large part of the European birth cohorts (N=14) have analysed data on the association between PCB or dichlorodiphenyldichloroethylene (DDE) exposure and birth weight/gestational age and these data have been summarized in a meta-analysis case study as part of the ENRIECO project. Further analyses should focus on exposure response analyses, modifying factors and susceptible groups (genetics, ethnicity).

Metals

There is growing evidence for an association between mercury, lead, cadmium, arsenic, and manganese and low birth weight. Generally, the reduction of birth weight is shown in children exposed to high levels of these metals, except for lead, where the effects have been also shown at low levels of exposure. Furthermore, there is some evidence for an association between preterm birth and high levels of mercury and lead. There are some birth outcomes such as stillbirth, spontaneous abortion or birth defects that have been less studied within prospective birth cohorts, probably due to their low prevalence. The European birth cohorts have mainly studied the effects of mercury present in fish and in amalgam fillings, whereas studies in non-European regions have focused on mercury and other metals such as arsenic and cadmium. The latter have been studied in areas with high environmental concentrations such as cadmium in soil and arsenic in water. In Europe, there are approximately 12 pregnancy and birth cohort studies with information on metals biomonitoring for most of the metals. Pooling data from different European cohort studies will be beneficial, particularly to understand metals toxicity at low levels of exposure.

Pesticides

Little is known on the possible impact of agricultural and household pesticide exposure in the European area on foetal development. There are results from only one European birth cohort (the DNBC cohort). There are some consistent results showing a negative impact of the occupational exposure to pesticides during pregnancy on foetal development. Consistencies are also observed among results of the studies assessing exposure via drinking water contamination by atrazine (compounds for which its use is banned in most of European countries for several years, but not in the United States, Brazil, Argentina, Mexico or China). For other types of exposure to pesticides, evidence is still inadequate to conclude to an adverse effect on foetal growth and development. This may be explained partly by the great variety observed among the studies and the complexity of pesticide exposure assessment (e.g. many pesticides, many different pathways). Given the toxicological properties of some current compounds, it is clear from this review that further studies are needed, especially in Europe

There is no evidence for an association between chronic noise exposure during pregnancy and pregnancy outcomes but the number of studies are small.

NEUROBEHAVIORAL/COGNITIVE FUNCTION

Metals

There is good evidence for an association between high levels of lead and mercury and neurobehavioural/cognitive effects. Most studies have tried to disentangle the neurotoxic effects of metals at low levels of exposure. Several of these studies come from European birth cohorts, whilst most other information comes from North and South America, and Seychelles islands. There is some evidence for an association between cognitive effects and manganese and cadmium. Further analyses should focus on multicenter large-scale pregnancy and birth cohort studies with intensive environmental exposure assessment of metals and other neurotoxicants, as well as sociodemographic factors and diet. The focus should be on the effect of low doses. Follow up should go through the infancy, childhood and adolescence, and even into the adult life, to assess the potential role of metal exposures on long term neurodevelopment.

Persistent organic pollutants

There is good evidence for an association between exposure high levels of PCBs and dioxins and neurodevelopment impairment. However, the evidence is limited for low levels of exposure to PCBs and dioxins or for high and low levels of the other old POPs (Dichlorodiphenyltrichloroethane (DDT), DDE, Hexachlorobenzene (HCB)) and new POPs (polybrominated diphenyl ethers (PBDEs), Mirex, PFOS/A and others). Most of the evidence has come from United States of America, some from European birth cohorts and, in lesser extent, from Canada, Mexico and Japan. Since levels of most old POPs in Europe have generally decreased, European birth cohorts are a good resource to further analyse and understand the association between mid and low levels of exposure to these old POPs and neurodevelopment impairment. There are currently 12 birth cohorts in Europe that have existing data on exposure and health data to do this. Follow up until an older age (pre-adolescence and adolescence) is recommended in European birth cohorts, since most of the studies have only assessed the impacts of POPs on neurodevelopment until 4-6 years. Further work is needed to obtain comparable neurodevelopment data for the analyses in the various cohorts.

ALLERGY AND ASTHMA

Air pollution

There is good evidence for an association between traffic-related air pollution exposure and the prevalence of asthma and related symptoms and growing evidence for an association between traffic-related air pollution exposure and the incidence of asthma and allergic sensitization. Furthermore, there is some evidence for an association between traffic-related air pollution and eczema and suggestive evidence for associations with symptoms of rhinitis, which needs further study. Most of the evidence has come from the European PIAMA, GINI/LISA and BAMSE birth cohort studies as well as the US American CCAAPS and CHS studies. The role of the timing of exposure in addition to the level of exposure as well as the role of exposures at non-residential addresses is unclear and should be a focus of future investigations. More research is needed on factors modifying the association between traffic-related air pollution, asthma and allergies to identify susceptible subgroups. More research is currently ongoing within the EU-funded collaborative ESCAPE project,

where land-use regression models for traffic-related air pollution will be developed according to a standardized protocol in many countries and linked to existing birth cohort studies to assess the effects of traffic-related air pollution on a number of different health endpoints including asthma and allergy.

Allergens and biological organisms

There is good evidence for an association between exposure to domestic visible mould and allergic health outcomes such as wheeze, asthma and allergic rhinitis symptoms among European and non-European investigations of different study type. Most of the included studies from European and non-European countries have a cross-sectional based study design. A considerable part of these studies reported an increased risk of asthma and wheeze when exposed to visible mould. In contrast, exposure to higher levels of mould derived components such as (1,3)-ß-D-glucan and EPS might decrease the risk of allergic disorders, however, according to the literature available it is not conclusive. In order to assign the direction of causality, there is especially a need for prospective birth cohort studies. Some of the European birth cohort studies are part of ongoing European projects; HITEA (Health Effects of Indoor Pollutants: Integrating microbial, toxicological and epidemiological approaches) is a collaborative project of four European birth cohort studies with a similar age range investigating the long term health impacts of biological agents such as mould components. Pooling data from European birth cohorts is also an important part of the recently started MeDALL (Mechanisms of the Development of ALLergy) project.

CASE STUDIES

Background

As part of ENRIECO case studies were conducted to assess if it was feasible to combine the data from different cohorts and assess the obstacles, if any.

Two different approaches for cross-cohort analyses were used to explore feasibility, potentials and difficulties of harmonizing and merging partly heterogeneous datasets of European pregnancy and birth cohort studies. A decentralized approach was applied in a case study on the association of biological markers of exposure to persistent organic pollutants with low birth weight as the outcome using data from 14 cohorts. A centralized approach was applied in cases studies evaluating the effects of indoor environmental exposures on allergic and respiratory diseases using data from up to 19 cohorts.

Findings

Both approaches were feasible and obtained combined estimates of environmental health risks using data from European birth cohorts. Combined analyses help to avoid fragmentation of many individual and possibly inconclusive results by single cohort analyses, and reduce publication bias. For the success of both approaches, several personal meetings with all participating cohorts were necessary to discuss and agree on the final analysis plans.

Strengths and Weaknesses

In the decentralized approach the cohorts were maximally involved in decisions on analyses. At a later stage, the approach was less flexible. Reanalyses would be time-consuming as they imply the involvement of the working group leader and all participating cohorts. Analyses based upon a pooled dataset, needed for some purposes such as exposure response modelling, were not possible. The decentralized approach does not necessitate transfer of complete datasets across borders and may thus bypass legal or ethical constraints linked to the use of the datasets.

In the centralized approach the central storage allowed a flexible handling of data and with a single data collection and harmonization process, it was possible to conduct not only one but three combined analyses with different foci. Each cohort needed fewer resources of personnel, but as a consequence was less involved in the harmonization and analyses process. For a central storage of data at an external institution, a solid structure of trust and experience had to be established beforehand.

Recommendations

Many cohorts were interested and very committed to this collaborative project of combined data analyses. European birth cohorts provide in aggregate a unique research resource that can and should be exploited to obtain added value for research objectives that require large datasets.

The decentralized approach is recommended if cross-boarder data transfer is difficult and/or a solid basis of trust and experience still has to be established among partners. The centralized approach is recommended for combined analyses addressing variables with very heterogeneous assessments across cohorts where a flexible handling of data is essential and an established basis of trust and work experience between participating partners already exists.

It is strongly recommended that resources are carefully planned. At least a kick-off meeting and another 4 meetings should be held for the both approaches

In the decentralized approach each participating cohort will need 2-3 months to define the subset of data for the meta-analysis, to run programs, to format output and to participate in meetings. In addition to time for preparing and organising the study, a post doc for 6 months is needed to analyse data and draft papers.

In a centralized approach with data collection and harmonization of up to 19 cohort datasets, resources of a post doc would be needed for 9 months and an additional 2 months should be planned per each analyses and manuscript preparation.

To increase the willingness of birth cohorts to participate in collaborative projects on combined data analyses, financial reimbursement for time and effort to provide previously collected datasets should be considered.

GENERAL CONCLUSIONS

1. There are many pregnancy and birth cohorts in Europe with information on environmental exposures and health outcomes.

2. The sizes of the cohorts vary considerably. In the context of the project, it should be noted, however, that studies of environmental contaminant exposures, specially those measuring

exposure biomarkers, cannot cover generally large numbers of subjects, but can still make an important contribution.

3. There is fairly good cover of Europe, except Eastern Europe.

4. There is considerable expertise and experience associated with the cohorts.

5. The cohorts have provided important environmental exposure, health and environmental exposure-response data

6. The amount and detail of information provided by cohorts on environment and health differs considerably

7. Greater and more efficient use needs to be made of the existing cohort data at the European level to:
   - Provide speedy response to key policy questions
   - Provide speedy response to concerns about "new" environmental exposures
   - Improve understanding of geographical and cultural inequalities in disease, exposure, and health related behaviours
   - Replicate findings with important public health implications in different settings
   - Link with routinely collected environmental and health data
   - Improve methodological approaches, including validated exposure assessment tools, protocols of biological and environmental sample collection and analysis.
   - Improve statistical power through combined analyses

8. Cohorts tend to report individually, but recent initiatives have tried to combine data from various cohorts to increase e.g. power (overall and subgroups)

9. Existing European birth and mother-child cohorts provide a real potential for combined analyses on pregnancy-related outcomes and child health outcomes in relation to environmental exposures.

10. Combining information from different cohorts appears to be beneficial and increase the value of the cohorts and resulting information

11. Combining data from various cohorts requires careful consideration of the aims, protocols, data, ethical issues, analyses and management, and it is time and labour intensive but potential fruitful

12. There are currently limited resources to combine existing studies/data

13. Follow up of existing cohorts is essential to determine health effects in later life of pre natal and early childhood exposure, for which there is some but not conclusive evidence

14. New pregnancy and birth cohorts are needed to evaluate any potential health effects of new environmental exposures, or existing environmental exposures under new conditions

Potential Impact:

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

ENRIECO's main impact is the structuring and consolidation of fragmented data from cohort studies undertaken throughout Europe. ENRIECO has proven to provide a much needed resource for cohort experts in environmental health. ENRIECO could well form the basis for further coordinated research in the future, which will strengthen the European research base. The project has brought together information on 36 environmental birth cohorts, encompassing more than 350,000 newborns, infants and children. By doing so, it has stimulated the establishment of new links between cohorts and reinvigorated existing ones, thereby tightening the investigative network and providing new collaborative efforts.

This will in itself improve the knowledge base for FP 7 Cooperation Work Programme 2008: Environment (including climate change) environment and health linkages. Data regarding environment-health causal relationships from pregnancy and birth cohorts are more readily available to investigators and policy makers through the launch of the ENRIECO inventory. Following robust evaluation, specific findings and recommendations are also available in a more digestible format to policy makers; individual working groups within WP2, 3, 4 and 5 have published topical reports indicating current gaps in environment and health data. These reports were available as most up-to-date information resources at the time discussions were ongoing at the European Commission to determine the direction of the next research programme for Environment.

The project has also produced methodology and protocols for evaluation of environmental exposure assessments, health outcome assessments and environment exposure-response relationships.

Continued impact of the project will rely on the many experts involved in the project, who are involved in further, more topic-specific projects. They will have access to the rich ENRIECO data source. Also, as the project has provided recommendations for future approaches, significant impact will furthermore be expected if these are being taken into account in the development of new research strategy by policy professionals, both at European and national levels.

The environmental exposure assessment often is the weakest part in the studies as a result of lack of funding and expertise. Nevertheless, these cohorts often contain high quality data in many areas such as outcomes and possible confounders and have a team of highly experienced researchers working on them with great expertise and commitment. A number of the cohorts participate(d) in one or more EC funded studies such GA2LEN (biological exposures and asthma and allergy), ESCAPE (air pollution and allergy asthma, infections, cognitive function and pregnancy outcomes), HIWATE (water contaminants and still birth, congenital anomalies, birth weight, preterm delivery), INUENDO (POPs and reproductive health), HITEA (indoor exposures and asthma and allergies) and NEWGENERIS (food contaminants and genotoxic risks). These provide a great resource to explore environmental exposure response relationships, but lack at times coordination and funding to make the best and most efficient use of the available resources. While a number of the cohorts have been following up children for many years, others have just started with follow up of pregnant women/foetus and provide an excellent resource for future follow up into childhood to examine the existence of vulnerable periods during pregnancy and childhood for a range of environmental pollutants. The

exchange of information and experience between the older and newer cohorts is essential to formulate new hypothesis and use the best methods, tools and study designs to test these hypothesis. The objective of the ENRIECO coordination project was to bring together cohorts with environment and health information, share resources, expertise and experience in this area. Specifically, we have succeeded to extract environmental exposure-response relationships, and to evaluate the available information. Common databases have been built to explore environmental exposure response relationships. Potential new uses of the cohorts such as new exposures and health outcomes have been assessed and included in the recommendations to strategic research developers.

The main outcome of the project is the availability of environment and health information in birth cohorts in a centralised location, a database with available environmental exposure-response functions for various health outcomes that have been rigorously evaluated; www.birthcohortsenrieco.net. The ENRIECO inventory is the first to make this information publicly available. It is intended to facilitate collaborations between birth cohort researchers in this field and can be searched to identify cohorts relevant for comparison and replication studies, or for combined analyses with pooled or non-pooled data. Moreover, it may be used by policy makers and other stakeholders to identify birth cohorts that can provide specific information on environmental exposures or related outcomes. The inventory should form the basis for a long-term cohort coordination infrastructure.

As many of the highly experienced investigators associated with ENRIECO are involved with many other national and international health studies, findings are expected to be considered in appropriate projects. The impact of ENRIECO on scientific performance will hereby depend on the networking ("viral messaging") capacity of those involved. More explicit details about this are provided in the next section of the dissemination section of this report.

Support of current EC policies

In June 2004 the Commission launched an Environment and Health Action Plan covering the period of 2004-2010. This is the continuation of the Commission's European Environment and Health Strategy launched in June 2003, which served as the Commission's contribution to the Fourth Ministerial Conference on Environment and Health organised by the WHO in Budapest in June 2004. The Action plan was prepared based on extensive consultations with experts and stakeholders from the environment, health and research field across the enlarged Europe and builds on an assessment of the current baseline knowledge in various areas including:

(1) Integrated monitoring of dioxins & PCBs, heavy metals, endocrine disrupters; (2) Childhood cancer, neurodevelopmental disorders, respiratory health; (3) Human biomonitoring, environment and health indicators, research needs;

It was stated that this can be achieved by:

1. Improving the information chain by developing integrated environment and health information to understand the links between sources of pollutants and health effects:
   Action 4: Enhance coordination and joint activities on environment and health

2. Fill the knowledge gaps by strengthening research on environment and health and identifying emerging issues
   Action 5: Integrate and strengthen European environment and health research

Action 8: Ensure that potential hazards on environment and health are identified and addressed

3. Response: Review policies and improve communication by developing Awareness Raising, Risk Communication, Training & Education
   Action 10 : Promote training of professionals and improve organisational capacity in environment and health

During this initial period the Action Plan focuses particularly on gaining a better understanding of the links between environmental factors and respiratory diseases, neuro-developmental disorders, cancer and endocrine disrupting effects. For these multi-causal diseases and conditions, there are indications and some initial evidence that environmental factors can play a role in their development and aggravation. To characterise the environmental contribution more precisely and to focus on the most important diseases and conditions within the disease groups more information is needed. The Action Plan set up targeted research actions to improve and refine knowledge of the relevant causal links, and at the same time, health monitoring will be improved to obtain a better picture of disease occurrence across the Community.

The concerns of children are integrated throughout the Action Plan. A number of major child health issues have been covered in the monitoring, as well as exposure to the environmental stressors to which children are particularly sensitive. Research on susceptibility is particularly important, so that policy responses can be adjusted to the needs of children in those cases where they are particularly vulnerable. The proposals in the Action Plan on indoor air pollution are a case in point, as the scientific evidence shows that the health impacts of, for instance, Environmental Tobacco Smoke (ETS) are particularly evident for children.

The Commission communication in June 2003 highlighted the regional disparities that exist throughout Europe in relation to environmental health problems. For example, the prevalence of waterborne diseases and exposure to outdoor pollution is higher in a number of the new Member States while the prevalence of asthma is higher in other Member States. Much has been and is already being, undertaken to reduce these disparities and there has already been a notable reduction in the number of deaths and illnesses from respiratory diseases as a result of efforts to reduce air pollution. The Action Plan also seeks to improve information and knowledge on the disparities that exist between regions and countries in the enlarged Union, taking into account the results of ongoing EU funded projects on emissions in the new Member States. Because of the differences between different member states, an European wide approach is needed with coverage across Europe as far as possible.

ENRIECO has attempted to address the aspects from the action plan above, specifically items 4, 5, 8 and 10, with a major strength that it has conducted its assessment in many different European countries. We will continue to do so through other projects and activities through which awareness of the project is being raised as well.

The impact of the project is much dependent on effective dissemination of project information, to which WP6 was dedicated. Associated activities are described in the next chapter.

MAIN DISSEMINATION ACTIVITIES

WP6 was responsible for the dissemination of project results and related information to partners, cohorts and the public. The objective was to raise the profile of the project, ensure that collaborators

are up-to-date, and potential users are aware of the existence and application of the ENRIECO efforts, as well as, project results.

Dissemination Strategy: created to describe the principles of the dissemination strategy, tools and plan for effective dissemination of project results. The partnership is committed to disseminating the expected methodological and scientific developments and substantive results of this project to a wide user community of academics, public health departments, and policy makers throughout Europe (e.g. through stakeholder forum). The list of deliverables for "Work Package 6 - Dissemination" was specifically designed to promote and disseminate the results of the work.

The ENRIECO Logo was created for the ENRIECO project, to establish a project brand. Three different logos were created by a group of graphic designers and discussed by partners for their strength and affinity to ENRIECO's objectives. The one chosen was the pomegranate which is known as a symbol of fertility used in the arts, representing the infants and children of all the birth cohorts participating in this project.

ENRIECO Website: www.enrieco.org, launched at the start of the project to provide information, updates on progress and results, and a gateway to other relevant research and participating cohorts. It is intended to share information between project partners and stakeholders. It has both a general access area and a login-members' area where each WP has their own space to upload reports and documents in preparation. Both areas are actively managed with frequent updates of events and activities of the project, uploading of files either for the general public or the project's partners. WP6 is responsible for providing access to the login area (i.e. usernames and passwords) for partners and participating cohorts' members.

Following the completion of project, the ENRIECO website will continue to be actively managed and updated for the next 2 years (March 2011 - February 2013). It will continue to provide regularly news, reports, and publications related to the project and share these with the scientific community, policy makers, NGOs, the general public, and all related stakeholders.

ENRIECO Brochure: a web-based project brochure announcing the project, providing simple information about the project for interested parties. It was uploaded to the ENRIECO website, so that the general public, partners, participating cohorts and all other stakeholders have access to this information. The brochure was also emailed to all partners and participating cohorts, as well.

ENRIECO Newsletter No.1: The first issue of the project Newsletter was published and uploaded on the website for wide access to the general public and all relevant stakeholders, introducing the ENRIECO project and initial results. In the newsletter, all ENRIECO participating cohorts were presented, as well as, the themes of all WG Exposures Ascertained by the Birth Cohorts. It was also distributed electronically to project partners and participating cohorts.

Supplement to the ENRIECO Newsletter No.1: A supplement to the ENRIECO Newsletter No.1 was published and uploaded on the projects website in April 2010 with updated information on ENRIECO participating cohorts.

Two ENRIECO workshops: The ENRIECO kick-off meeting was held on May 28-29, 2009 at CREAL, Barcelona, Spain. WP6 maintains a master list of contacts (partners and non-partners participating cohorts), which was used to inform about and organize the workshop, and distribute related material. The first workshop brought together project partners and cohort members and evaluated the inventory and the protocols for the WPs. During and after the workshop, WGs were

formed to address the topics within WPs 2, 3 and 4 over the following year, objectives were formulated for each WG, and tasks divided among its members. Presentations and posters were collected for the project archive and website. The meeting was also advertised in the ENRIECO website and mentioned in the project Newsletter.

The second was held on 26-28 May 2010 in Utrecht, The Netherlands. The workshop was focused on the evaluations and recommendations of the WGs within each WP, the presentation and evaluation of the outcomes of the case studies. The workshop was advertised on the ENRIECO website and in the project Newsletter. A workshop report was published based on the presentations and discussion of findings during the meeting.

The cohorts who participated in the meeting were: ABCD Study, Amsterdam; ArcRisk; Born in Bradford (BiB); Children's Health and Environment in the Faroes, Cohorts 1, 2, 3 & 5; CO.N.ER; Danish National Birth Cohort (DNBC) ; DARC-cohort; Duisburg cohort; EDEN mother-child cohort; ELFE; FLEHS; GENERATION R; GENERATION XXI; GESP II, Rome; GINIplus; HUMIS; INMA Valencia; INMA Sabadell; INMA, Menorca; INUENDO; KANC, Kaunas; KOALA Birth Cohort Study; LISA; MAAS; MAS; PELAGIE; PIAMA, Nationwide; REPRO_PL (Polish Mother and Child Cohort) ; RHEA, Heraklion; SNiP; The Aarhus Birth Cohort Biobank.

ENRIECO Newsletter No.2: The second issue of the project Newsletter was published and uploaded on the website for wide access to the general public and all relevant stakeholders, with project finding and recommendations. It was also distributed electronically to project partners, participating cohorts, and other interested stakeholders.

Other activities included poster an oral presentation at scientific conference, coordination meetings, information on partner websites and a full page article in Dods Parliamentary Magazine.

Overview poster: summarizing key project outcomes was published for distribution simultaneously with the final leaflet to all targeted stakeholders and will be available on line, as well, at the ENRIECO website.

A 2-page leaflet targeting all relevant stakeholders and policy makers interest in environment and health was published with a summary of the projects finding and also the need to future actions.

Further exploitation of ENRIECO findings

Long-term uptake and use of the project outcomes requires that knowledge about the project is invested in a wide range of both end users and intermediate users (e.g. service providers).

To this end, we continue to exploit the findings from the ENRIECO project through various media

The ENRIECO website will be actively managed and updated for the next 2 years (March 2011 - February 2013) with new ENRIECO reports and partner publications. It will continue to provide regularly news, reports, and publications related to the project and share these with the scientific community, the policy makers, NGOs, the general public, and all related stakeholders.

The Web-based project brochure presenting the project, and providing simple information about ENRIECO to interested parties has been followed by a 2-page targeted technical leaflet to Policy-makers.

The ENRIECO newsletters and supplement will continue to be available on the ENRIECO website and have been emailed to partners and participating cohorts. The second newsletter, produced following the completion of the project, will be distributed amongst several organizations, NGOs and academic institutions in May 2011.

The newsletters will reach not only the partners but also an extended variety of organizations such as academic, research, consumer, regulatory, environmental, governmental or health-related organizations. In addition, it could reach several relevant social groups and stakeholders through the open access ENRIECO website.

An ENRIECO summary poster provides key project outcomes was published and will be distributed together with the final leaflet to all targeted stakeholders and will be available on line, as well, at the ENRIECO website.

Conference Presentations, Posters & Publications: ENRIECO findings will be published in leading, international, peer-reviewed journals. Because of the broad scope and interdisciplinary nature of the project, publication will deliberately be aimed at different journals, in order to access different audiences.

Papers derived from the study are aimed at major, peer-reviewed international journals in the key fields of interest, including exposure assessment, water, epidemiological, and public health journals.

Target journals for scientific publications include: Nature and Science for high level, overview papers; Epidemiology, British Medical Journal, Lancet, European Journal of Public Health and Environmental Health Perspectives for results relating to environmental epidemiology and public health; Environmental Science and Technology, Environmental Toxicology and Chemistry and Environmental Pollution for results relating to environmental monitoring, biomonitoring and environmental systems; Biostatistics, Statistics in Medicine and Journal of the Royal Statistical Society for statistical methodologies; and Risk Analysis and Environmental Modelling and Assessment for more general results on risk assessment methodologies.

In the long-run, eventually, dissemination of the knowledge gained in ENRIECO will be carried out via involvement of partners in other projects, funded both by the EU and by national and other international agencies.

Efforts will be made to raise awareness about the project and its outcomes, and to encourage their use, through the many policy networks with which partners are involved at national and international level. Inter alia, these include the various Directorates of the EU, the European Environment Agency and its topic centres, Members States' environmental and health ministries, and regional and local authorities.

The leaflet and final newsletter will be provided mainly by email and in few cases by regular mail to bureaus, Institutions, Agencies and Organizations, including:

1. Council of the European Union, Rue de la Loi 175, B-1048 Brussels
2. Main switchboard: (32-2) 281 61 11, Fax (32-2) 281 69 34 (the Policy Leaflet will be mailed)

3. Environment Directorate-General of the European Commission: Janez Potocnik (janez.potocnik@ec.europa.eu), European Commissioner for the Environment. (Source: http://ec.europa.eu/commission_2010-2014/potocnik/index_en.htm)

4. Directorate-General, Health & Consumers, European Commission, B - 1049 Brussels, Belgium (the Policy Leaflet will be mailed) (http://ec.europa.eu/dgs/health_consumer/mailbox/index_en.htm, last accessed 8 March 2011)

5. Executive Agency for Health and Consumers, EC: Luc BRIOL, Director (eahc@ec.europa.eu)

6. Committee on the Environment, Public Health and Food Safety (ENVI) (envi-secretariat@europarl.europa.eu or by fax in Brussels +32 2 284 90 14), Head of Unit: Andreas Huber (Andreas.huber@europarl.europa.eu) & Dorthe Schmidt (Dorthe.schmidt@europarl.europa.eu)

7. Climate Change and natural hazards, DG Research and Innovation, Directorate I: Environment, EC: Mr Andrea TILCHE, Head of Unit (B-1049 Brussels BELGIUM, fax +(32) 2 2994249) (the Policy Leaflet will be mailed)

8. European Environment and Health Committee (EEHC), WHO/Europe: Health impact assessment (healthimpact@ecr.euro.who.int)

9. European Chemicals Agency (ECHA) , an agency of the Eurpean Union: Geert Dancet, Executive Director (executive-director@echa.europa.eu) & Thomas Jakl, Chairman of the Management Board (mb-secretariat@echa.europa.eu

10. WHO European Centre for Environment and Health, Bonn (info@ecehbonn.euro.who.int) & WHO European Centre for Environment and Health, Rome, Italy (ecehr@ecr.euro.who.int)

11. WHO The Department of Public Health and Environment, Children's environmental health, World Health Organization, Avenue Appia, 1211 - Geneva 27, Switzerland (childrensenvhealth@who.int)

12. WHO/UNEP Health and Environment Linkages Initiative Secretariat (http://www.who.int/heli/en/) : heli@who.int

13. The International Agency for Research on Cancer (IARC), Christopher Wild, Director of IARC, 50 Cours Albert Thomas, 69372 Lyon CEDEX 08, France - Tel: +33 (0)4 72 73 84 85 - Fax: +33 (0)4 72 73 85 75 (the Policy Leaflet will be mailed)

14. The European Environment Agency (EEA), agency of the European Union with 32 member countries, has the task to provide "sound, independent information on the environment". EEA is considered an important source of information for those "involved in developing, adopting, implementing and evaluating environmental policy, and also the general public". (Source: http://www.eea.europa.eu/about-us/who, last accessed 8 March 2011) Jacqueline MCGLADE (Jacqueline.McGlade@eea.europa.eu) Executive Director EDO - Executive Directors Office

15. The Health Environment Alliance (HEAL), Genon Jensen, Executive Director, (genon@env-health.org) and info@env-health.org (international not-for profit, non-governmental organisation that aims to "raise awareness of how environmental protection improves health

by creating opportunities for better representation of citizens' and health experts' perspectives in the environment and health-related European policy-making. Set up in 2003, HEAL membership now includes a diverse network of more than 50 citizens', patients', women's, health professionals' and environmental organisations across Europe and has a strong track record in increasing public and expert engagement in both EU debates and the decision-making process. HEAL's underlying vision is that of a healthy planet for healthy people." (Source: Health and Environment Primer 2007, http://www.env-health.org/IMG/pdf/Health_and_Environment_Primer_2007_FINAL_MARCH_4_2008.pdf).

16. The Policy Leaflet and the 2nd ENRIECO Newsletter An detailed email with information on the Network of National Contact Points (NCPs) in Member States and Associated States in EC will be forwarded to the ENRIECO participating cohorts, so as to forward to their national contacts for health and environment the ENRIECO policy leaflet.

17. European Environmental Bureau (EEB) (Federation of environmental citizens organizations) : Pieter De Pous, Policy Director - EU-Policy Team (pieter.depous@eeb.org)

18. Transport and Environment (T&E) (http://www.transportenvironment.org/pages/staff-and-board/): Jos Dings, Director (jos.dings@transportenvironment.org) & Nina Renshaw, Deputy Director (nina.renshaw@transportenvironment.org)

19. European network for smoking and tobacco prevention (ENSP) (http://www.ensp.org/) ENSP Executive Board 2010: Panagiotis Behrakis (p-behr@otenet.gr) President & Lies van Gennip (lvangennip@stivoro.nl), Vice President

20. European Public Health Alliance (EUPHA) (http://www.epha.org/): Monika Kosinska (secretarygeneral@epha.org), Secretary General & Luisa Bara (l.bara@epha.org) Director of Policy and Strategy. Fax: +32 2 233 3880 / epha@epha.or

21. International network on children's health , environment & safety (INCHES) (http://inchesnetwork.ne) Maria Cherkasova, Director (cnep@glasnet.ru) & pvdhazel@inter.nl.net

22. International Society of Doctors for Environment (ISDE) (http://www.isde.org/) : info@isde.org

23. International POPs Elimination Network (http://www.ipen.org/), Co-chairs: Dr. Mariann Lloyd-Smith. Dr. Olga Speranskaya. IPEN Secretariat: ipen@ipen.org

(The current section has been greatly facilitated by information compiled in the "Health and Environment Primer", by Health & Environment Alliance, Latest version: December 2007, available online at http://www.env-health.org/IMG/pdf/Health_and_Environment_Primer_2007_FINAL_MARCH_4_2008.pdf, last accessed March 8th 2011)

Contact with other research projects: Active involvement will be pursued with other EU and non-EU funded research projects and ENRIECO project's findings forwarded, such as:

1. CHICOS (http://www.chicosproject.eu) - Project Coordinator: Dr. Martine Vrijheid, PhD, Email: mvrijheid@creal.cat & Communication/Disseination: Prof. Franco Merletti, MD , Email: franco.merletti@unito.it

2. HiWATE (http://www.hiwate.eu/about-us.htm)
3. Escape (http://www.escapeproject.eu) - Rob Beelen, E-mail: info@escapeproject.eu
4. EnviroGenoMarkers (http://www.envirogenomarkers.net/)
5. Dr. Maria Botsivali, Dissemination Officer, email : mbotsi@eie.gr
6. NewGeneris (www.newgeneris.org) Dr. Maria Botsivali, Dissemination Officer, email : mbotsi@eie.gr
7. MeDALL- Mechanisms of the Development of ALLergy (http://www.medall-fp7.eu/) - Delphine Smagghe, Project Manager Email: Delphine.smagghe@inserm-transfert.fr
8. Ga2len (http://www.ga2len.net) - [Noelie Auvergne, GA²LEN Dissemination, Email: noelie.auvergne@ga2len.net
9. The National Children's Study (http://www.nationalchildrensstudy.gov) - E-mail: ContactNCS@mail.nih.gov

A press release will be published to attract media attention during the period of May-June 2011. With this, we intend to reach a wide audience beyond the scientific and policy professionals, and to raise public awareness regarding ENRIECO and its findings in particular, and of environmental health research in general. This timing is chosen, to ensure that all the project findings and recommendations would be available, which means a more efficient use of our efforts. It may also provide a better window of opportunity in media impact, as the end of the project coincided with major international events.

List of Websites:

ENRIECO website: http://www.enrieco.org

ENRIECO cohort inventorty: http://www.birthcohortsenrieco.net/

Dissemination:

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