Report on Epidemiological Research for Children's Environmental Health

March 2008

Advisory Committee of the Epidemiological Research for Children's Environmental Health

The Advisory Committee of the Epidemiological Research for Children's Environmental Health

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History of Meetings:

First meeting	10 a.m.–12 p.m., Friday, October 5, 2007
Second meeting	1:30 p.m.–3:30 p.m., Tuesday, December 11, 2007
Third meeting	10 a.m.–12 p.m., Friday, March 21, 2008

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1. Introduction

In recent years, the increase in environmental risks for children has become an issue of concern, and the vulnerability of children to toxic substances in the environment has attracted considerable interest in Japan and abroad.

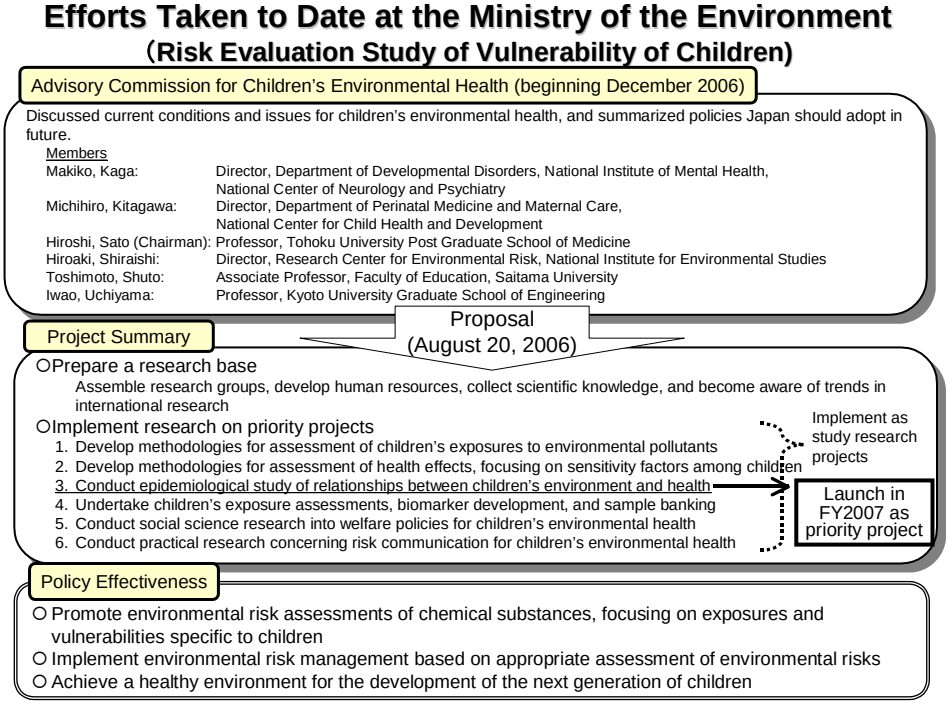
The Advisory Commission for Children's Environmental Health was established to discuss future efforts for children's environmental health. From its discussions on issues related to children's vulnerability to toxic substances and environmental health, it has formulated proposals regarding the direction that policies should take in the future. (See Advisory Commission's *Report on Children's Environmental Health* [August 2006]; http://www.env.go.jp/chemi/report/h18-04/index.html)

One of the Advisory Commission's proposals was to clarify the effects of environmental factors (such as chemical substance exposure and the living environment) on children's development through the use of tests that determine underlying mechanisms. It also proposed an "epidemiological study into the relationship between children's environment and health."

The Advisory Committee of the Epidemiological Research for Children's Environmental Health commenced research in October 2007. It met on three occasions to survey the extent of epidemiological studies in Japan and abroad, and to discuss harmonization with Japan's existing epidemiological studies and the commencement of a new epidemiological study.

This report provides a summation of the outlines of epidemiological studies discussed at the Advisory Committee. With respect to the new epidemiological study, the necessary details concerning its implementation will be examined by working groups, and a feasibility study to be implemented over a two-year period.

Figure 1 Efforts Taken to Date at the Ministry of the Environment



2. Objectives of the Children's Epidemiological Study

2.1 Role of the Study

Long-established methods for determining the effects of environmental risks on human health have been animal testing and basic research. With respect to animal testing, difficulties exist in applying results that do not account for the morphological and physiological differences between animals and humans.

Therefore, to accurately ascertain the effects of environmental risks on humans, an epidemiological approach that monitors actual human groups is essential. In carrying out such an epidemiological study, important elements include clearly framing objectives and implementing in-depth research designs and plans.

2.2 Objectives of the Study

The effects of environmental factors on children's development need to be clarified. In particular, interest is focused on what sort of effect chemical substance exposure and the living environment may have on children's development from the fetal stage through childhood.

An approach based on epidemiological studies is essential for clarifying these environmental factors.

Clarification of the environmental factors affecting children's development through epidemiological studies can be expected to lead to the relevant information being provided to risk management authorities, who can utilize the information in voluntary efforts and in regulation of chemical-substance screening standards, in conjunction with strengthening of environmental standards (for water and soil) and other suitable risk management systems.

Another important issue is the development of trained personnel in the field of environmental health, particularly among young people. The proposed study should become a catalyst for such personnel development, since active participation of young researchers can be anticipated.

2.3 Hypothesis to Be Tested in the Study

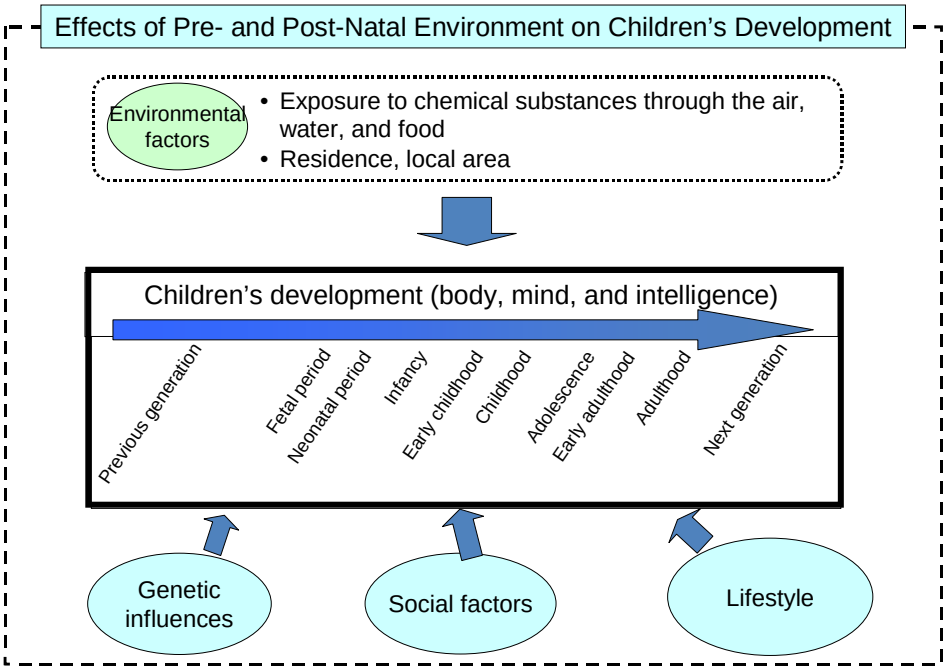
An essential element in the design of an epidemiological study is setting up a hypothesis. The hypothesis for this study has been formulated as follows.

"Exposure to chemical substances from the fetal stage to childhood affects such areas as physical development; congenital anomalies; mental and neurological development disorders; and immune system, metabolism, and endocrine system anomalies."

In addition to considering exposure to chemical substances, clarifying this hypothesis will require parallel investigation of other confounding factors. Some possible confounding factors to be investigated include genetic influences, social factors, and lifestyles.

Design of an epidemiological study entails proposing a number of detailed hypotheses, and then choosing the most suitable one from among them. As a result, all of the proposed hypotheses will need to be examined in working groups and the feasibility study.

Figure 2 Effects of Pre- and Post-Natal Environment on Children's Development



2.4 Environmental Factors Targeted in Study, and Health Effects Index (Outcome Endpoint)

2.4.1 Environmental factors (exposures) targeted in the epidemiological study

In the epidemiological study, the main environmental factors (exposures) requiring investigation are chemical substance exposure and other factors (confounding factors). In selecting the chemical substances to be measured, priority should be placed on substances that easily accumulate in the body or that are easily transmitted through the placenta, as well as substances with rising exposures to children. Confounding factors that should be considered include genetic influences, social factors and lifestyles.

Table 1 Environmental Factors (Exposures) Targeted in the Epidemiological Study (Example)

A.	Chemical substance exposure
	Persistent organic pollutants (POPs), dioxins, polychlorinated biphenyls (PCBs), mercury, lead, arsenic, cadmium, benzene, organofluoric compounds, endocrine disruptors, fire retardants, etc.
B.	Other factors (confounding factors)
	■ Genetic influences
	■ Social factors and lifestyles
	Region (address), residence (type, age, air conditioning, etc.)
	Parents' education, employment history, work conditions, income, smoking, and drinking
	Diet
	Family environment (such as number of siblings and pets)
	Playground environment, school environment, etc.

2.4.2 Index (outcome endpoint) of major health effects requiring monitoring

Any index of major health effects requiring monitoring will focus on substances that either may have increased in quantity in recent years, or that threaten to do so.

Table 2 Examples of Health Effects Index (Outcome Endpoint)

A.	Physical development:	Reduced birth weight, post-natal physical development, etc.
B.	Congenital anomalies:	Hypospadias, cryptorchidism, cleft lip or cleft palate, alimentary tract atresia, ventricular heart septal defect, Down syndrome, etc.
C.	Mental and neurological development disorders:	Autism, learning disabilities (LD), attention deficit hyperactivity disorder (ADHD), etc.
D.	Immune system anomalies:	Pediatric allergies, atopy, asthma, etc.
E.	Metabolism and endocrine system anomalies:	Thyroid function anomalies, glucose tolerance disorder, obesity, effects on genitals, brain sexual differentiation anomalies, etc.

Mass screenings of neonates are currently performed at public expense on the fifth to seventh day after birth, and collecting information from the screenings will also be significant.

Table 3 Congenital Metabolic Anomalies Studied in Mass Screening of Neonates

Phenylketonuria
Maple syrup urine disease
Homocystinuria
Galactosemia
Congenital hypothyroidism
Congenital adrenal hyperplasia

Listed here are the main environmental factors (exposures) and health effects indices (outcome endpoints), and the details will need to be examined in working groups and the feasibility study.

3. Implementation Outline Proposal for Children's Epidemiological Study

3.1 Design of Study

Epidemiological studies divide broadly into cohort studies (prospective research) and case–control studies (retrospective studies). A cohort study tracks and monitors a specific group to clarify the relationship between environmental factors and their effects. A case–control study compares a group with a certain disease (case) and a control group without that disease, to investigate the relationship extending into the past between factors and the disease (case).

While the case–control study can be performed in a relatively short period of time, at little cost in resources and personnel, it can tend to encounter such problems as difficulty in setting up a control group, occurrence of recall bias, and an inability to discriminate between unrelated factors that happen to appear coincidentally.

The objective of the epidemiological study for children's environmental health is to clarify the relationship between environmental factors and the health effect index (outcome endpoint). As this requires collection of reliable data, a cohort study (follow-up study) appears to be best suited because of its high reliability, despite the large amount of time and effort required.

Table 4: Comparison of Cohort Study with Case–Control Study

	Cohort Study	Case–Control Study
Characteristics	Performs follow-up monitoring of a specific group to clarify the relationship between environmental factors and their effects.	Compares a group with a certain disease (case) and a control group without the disease, to investigate relationships extending into the past between factors and the disease (case).
Strengths	Low bias. Highly reliable.	Obtained in short term with minimal effort.
Weaknesses	Requires much time and effort.	Selection bias (bias appears during establishing control group) and recall bias, etc., occur. Factor interpretation is difficult.

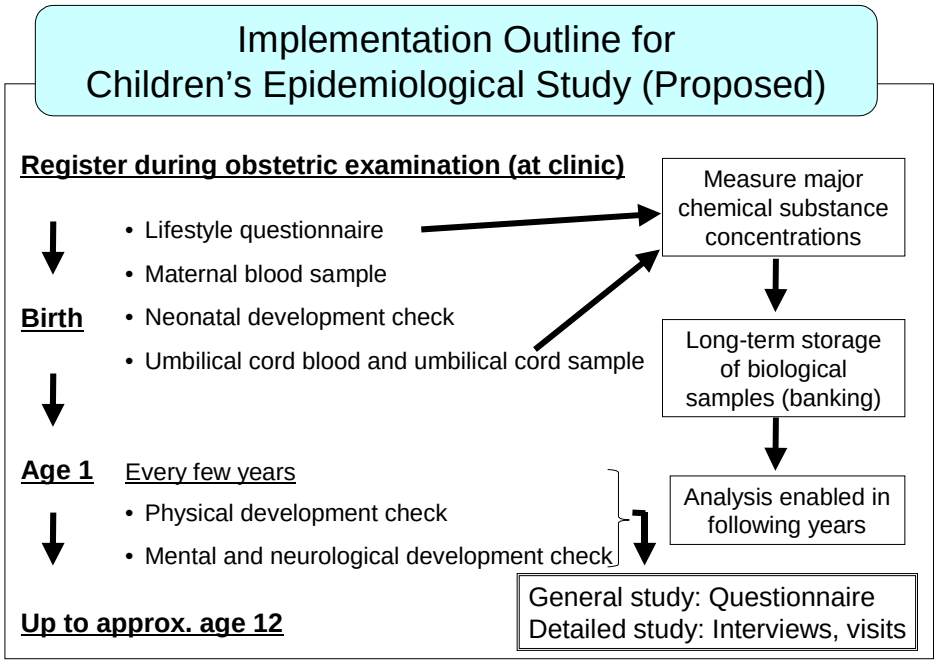
In this epidemiological study, long-term monitoring should be performed for each subject, from the fetal period when body organs are first formed in the womb through to childhood when mental and physical development is most active.

To study the exposure to chemical substances during the fetal period, this study should collect blood samples from mothers, as well as umbilical cord blood and umbilical cords at time of birth, and the chemical substances present in these biological samples should be measured.

Specifically, the study will approach pregnant and parturient women at obstetrics departments and clinics to recruit subjects for the study. After a full explanation of the purposes of the study is provided and consent is obtained, participants will be asked to give blood samples and to answer a questionnaire about their lifestyle. In addition, umbilical cord blood and umbilical cords will be collected at the time of birth, and the condition of the newborn infant will be checked. The child will be checked periodically to ascertain lifestyle conditions and the state of mental and physical development. This information will be collected and categorized as environmental factors and will be entered in a health effect index, and the relationship between environmental factors and the health effect index will be analyzed to clarify the effects of environmental factors on mental and physical development.

To enable more detailed factor analyses of cases where major variations in environmental factors arise, the ideal solution will be implementation of local studies in several parts of Japan under varying environmental conditions.

Figure 3 Implementation Outline for Epidemiological Study of Children's Environmental Health



3.2 Scale of Study

The health effect index (outcome endpoint) mentioned in the previous section includes diseases with low rates of incidence. Examining such indices will require large studies on the scale of tens of thousands of people.

For the study of mental and neurological development disorders, on the other hand, discernment of slight differences between individuals can be useful in the examination of environmental factors, which means that detailed monitoring of specific, strictly defined groups will probably be more effective.

As a result, the possibility of implementing the study in two stages will be discussed: a nationwide general study consisting of large-scale, simple study items; and a detailed study that is limited in scale and area. The subjects of the detailed study will be selected from among the subjects of the general study.

The general study will be in as simplified a format as possible, centered principally on a questionnaire. The detailed study, by contrast, will be centered around an interview format.

While the scale of the studies will depend on such issues as the rate of disease incidence, which will require careful investigation, one proposed broad measure is about 60,000 subjects for the general study and 2,000–3,000 subjects for the detailed study. The final numbers will be decided in the working group and the feasibility study, which will be established separately.

Table 5 General and Detailed Studies (Overview)

	General Study	Detailed Study
Scale	About 60,000 subjects	2,000–3,000 subjects
Approach	• Planning and adjustment implemented at Core Center. • Study items always implemented in all regions nationwide (at all units).	• Study items may be independently set at Unit Centers. • Implement independent study items locally (separately at each unit).
Study Items	Limited study items	May include detailed study items
Instruments	Questionnaires	May include interviews and visits

3.3 Period of Study

Because this study targets children, a suitable period of study should last from the fetal period until the subjects reach the age of 12 years.

Some members of the Advisory Committee favored examination of the effects on mental and physical development during adolescence, and of the effects on the next generation, for extremely long-term follow-ups. For this study, however, the objective will initially be limited to age 12, with further studies to be made at that time to determine whether a longer follow-up extending beyond age 12 should be implemented.

Furthermore, because of the possibility that the period required by married couples for conceiving a child through normal sexual activity may be prolonged due to exposure to chemical substances, some in the Advisory Committee proposed framing a study that targets women before they become pregnant. While the study limits its focus to exposure to chemical

substances during pregnancy and to children's development, implementation of this other topics of study will continue to be discussed as a possibility in the future.

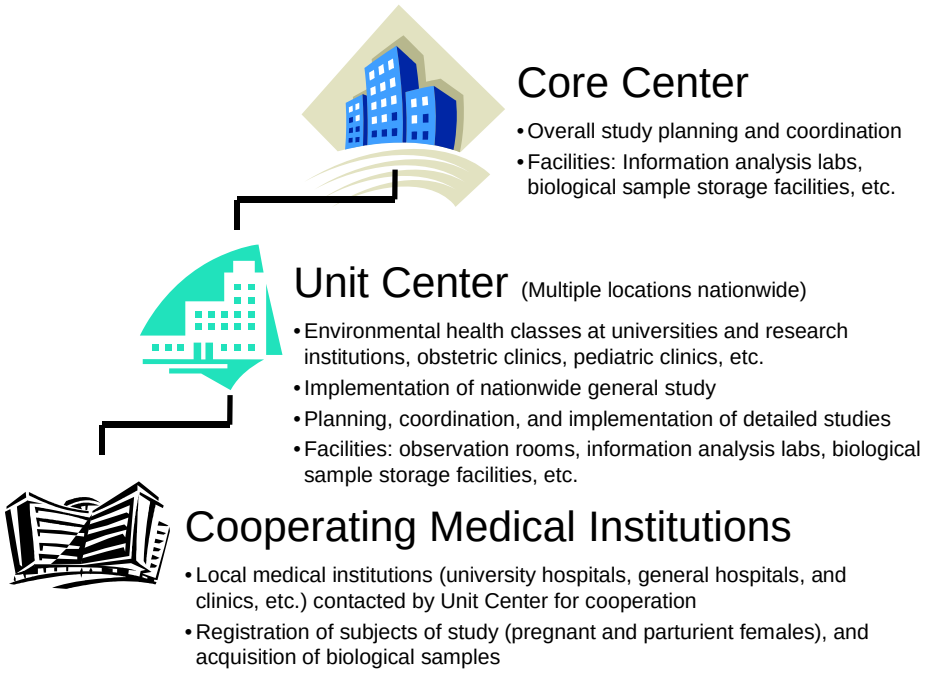
3.4 Registration Period for Subjects of Study (Pregnant and Parturient Women)

Three years is deemed to be a suitable registration period for the subjects of the study (pregnant and parturient women).

3.5 Network for Implementation of Study

A Core Center will be established for general supervision of the study, together with a network of local Unit Centers located all over Japan. These Unit Centers will coordinate the study in local areas, contacting local medical institutions for cooperation in recruiting the subjects of the study, providing explanations and obtaining consent, handling registration, and collecting biological samples.

Figure 4 Network for Implementation of Study



3.5.1 Core Center

The Core Center will gather information about children's environmental health. As a result, a public institution with experience in epidemiological studies is preferred.

3.5.2 Unit Centers

Unit Centers will be established in multiple locations nationwide. As much as possible, their establishment should be deliberately directed to ensure wide dispersal all across Japan. Study

planning and implementation should center on environmental health classes and research laboratories at universities and research institutions. In addition, cooperation with obstetrics departments is needed for registering subjects for the study (pregnant and parturient women) and collecting biological samples, while the follow-up studies of children will require coordination with pediatrics departments. As a result, the environmental health classes and research laboratories at universities and research institutions could become the core for the Unit Centers, with obstetrics and pediatrics departments at university hospitals and medical centers appended to form a cooperative operations structure.

The Unit Centers will include such facilities as observation rooms, information analysis laboratories, and storage facilities for biological samples for the study.

To select these Unit Centers, the Ministry of the Environment will need to establish a new organization that can set up a public selection process and then make selections based on study planning and implementation capabilities and on past implementation performance.

Because the study is intended to continue for a long period of time, provisions should be made to ensure continuity of the test even in the event of changes in directors of the Core Center and Unit Centers.

3.5.3 Cooperating Medical Institutions (Recruitment Points)

Unit Centers will request the cooperation of local medical institutions in the registration of subjects of the study (pregnant and parturient women) and collection of biological samples. Cooperating medical institutions are assumed to include university hospitals, regular hospitals, and obstetrics outpatient clinics.

The cooperating medical institutions will provide the subjects of the study with explanations about the study, obtain their consent, administer questionnaires, and collect biological samples. Whether to reimburse these cooperating medical institutions for expenses related to the study should be discussed.

In recognition of the fact that the examination environment at obstetrics departments in medical institutions, and at obstetrics clinics, has become extremely severe in recent years, due caution will be taken when making requests for cooperation. In addition, winning the support of related academic institutions, of related groups that provide back-up for local medicine, and of administrative institutions is an important strategy for securing the cooperation of local medical institutions.

3.6 Research Personnel and Incentives

Securing personnel with the requisite skills in environmental health, and in maternal and child health, is an essential prerequisite for implementing the children’s epidemiological study. Personnel shortages in the environmental epidemiology sector and the maternal and children’s health sector have become a concern in recent years. As a result, there should be discussion of provisions for appropriate incentives to ensure adequate research personnel for the study, and measures taken to prepare the environment and to create a structure capable of implementing the study. In addition, training is needed to develop human resources for filling positions for the next generation in environmental health and maternal and children’s health.

The Core Center will work to ensure the research organization and personnel for implementing the children’s epidemiological study. Because the workload related to the study

is expected to be enormous at the Core Center, the administrative operations may well need to be outsourced to private institutions. In such a case, personal information will be stringently handled, based on the “Ethical Guidelines for Epidemiological Research” (issued by the Ministry of Education, Culture, Sports, Science and Technology [MEXT], and the Ministry of Health, Labour and Welfare).

The Unit Centers will recruit researchers and graduate students to participate in the study. This researcher recruitment effort will likely include incentives such as remuneration for expenses incurred in performing the study.

For cooperating medical institutions, remuneration for study expenses will likely be based on the number of newly registered subjects (pregnant and parturient women), because the number of women receiving examinations or giving birth, etc., varies from one medical institution to another.

3.7 Recruitment of Subjects of Study (Pregnant and Parturient Women)

3.7.1 Approaches to Pregnant and Parturient Women

A public relations campaign targeting pregnant and parturient women should be used to encourage their participation in the study. Such a campaign would include public relations efforts aimed at the media, administrative institutions, medical institutions, academic institutions, NGO groups, and others, and the preparation and distribution of posters and pamphlets.

The approach to pregnant and parturient women should include posters at medical institutions, as well as reliance on community health centers to include information when distributing maternal and children’s health handbooks or holding maternity classes.

3.7.2 Recruitment Method

Registration of the subjects of the study (pregnant and parturient women) will be performed at the medical institutions cooperating at the request of the Unit Centers. The registration period for subjects will be about three years. The registration process will begin with a full explanation of the study, followed by the subjects’ consent.

3.7.3 Compensation for Subjects of the Study

Compensation for subjects cooperating with the study will be considered. This compensation will take into account the extent of the cooperation and the amount of time spent, without exceeding the bounds of common sense or introducing a bias.

3.7.4 Response to Inquiries from Subjects of Study

The test results for biological samples should be returned to the subjects of the study if at all possible. However, separate discussion will be required for test result items that are returned. In addition, if a disease or other anomaly is discovered during the study, the subject will be immediately notified and, if possible, a system will be established to facilitate introductions to medical institutions. Because personal inquiries in the course of the study can be expected, a system for responding to these inquiries should be established.

3.8 Study Method

3.8.1 Philosophy

The general study will be implemented on a nationwide scale with a large number of subjects. As a result, the study items should be carefully focused to ensure solid implementation in all areas. Where possible, methods that are well established in the global arena will be used in the general study.

Because detailed studies are to be performed in each area, focusing on individuals selected from among the subjects of the general study, each Unit Center will be allowed to set study items on its own initiative. Such a method will enable the Unit Centers to take pioneering approaches to the studies that can lead to new knowledge. Any new study items, however, must be appropriate to the study and must not affect the general study.

In addition to the budget set for the study, possible sources of research funding for independent studies at the Unit Centers include the Grants-in-Aid for Scientific Research provided by MEXT and the Ministry of Health, Labour and Welfare, and the Environmental Technology Development Fund. However, before applications are made for competitive funding, they will need to be reviewed by the Ministry of the Environment and by the Core Center.

3.8.2 Study Items

Study items considered for implementation in the general study and detailed study are shown in the table below. The study items here are shown for illustrative purposes only, with the final determination to be made in the working group and feasibility study. The questionnaire, meanwhile, will be implemented at community health centers during the children’s health examinations that are performed at ages three to four months, 18 months, and three years, in a format designed to reflect the examination results.

Study items for the detailed study are shown here as examples. These will be decided independently by the Unit Centers.

Table 6 List of Study Items (tentative only)

	General study (60,000 people)	Detailed study (2,000–3,000 people)
Philosophy	Target all areas nationwide (all Unit Centers). Always implement all study items.	Set in each local area (Unit Center). Independent study item setting is acceptable.
Recruitment time (Fetal period)	Questionnaire Maternal blood sample	Ex.: Questionnaire added (dietary survey) Urine, hair, nail samples
Home visit		Ex.: Visit: Survey of living environment Dietary survey
Pregnancy mid-term		Ex.: Questionnaire added (dietary survey) Urine, hair, nail samples
Pregnancy late term		Ex.: Questionnaire added (dietary survey) Urine, hair, nail samples
Childbirth time	Maternal blood, umbilical cord blood, umbilical cord samples Examination and observation	Ex.: Neonatal blood, vernix, saliva samples Breast milk (colostrum) sample
1 month after birth	Questionnaire	Ex.: Questionnaire added (dietary survey) Breast milk sample
3 months after birth	Questionnaire	Ex.: Questionnaire added (dietary survey) Interview (physical, mental, and neurological development check)
Home visit		Ex.: Visit: Survey of living environment Dietary survey
6 months after birth	Questionnaire	Ex.: Questionnaire added (dietary survey) Interview (physical, mental, and neurological development check)
Age 1	Questionnaire	Ex.: Questionnaire added (dietary survey) Interview (physical, mental, and neurological development check) Child’s blood, hair, nails sample
Home visit		Ex.: Visit: Survey of living environment Dietary survey
Age 3	Questionnaire	Ex.: Questionnaire added (food survey) Interview (physical, mental, and neurological development check) Child’s blood, hair, nails sample
Home visit		Ex.: Visit: Survey of living environment Dietary survey
Age 6	Questionnaire	Ex.: Questionnaire added (dietary survey) Interview (physical, mental, and neurological development check) Child’s blood, hair, nails sample
Home visit		Ex.: Visit: Survey of living environment Dietary survey
Age 12	Questionnaire	Ex.: Questionnaire added (dietary survey) Interview (physical, mental, and neurological development check) Child’s blood, hair, nails sample

3.8.3 Questionnaire

Information technology can ensure more efficient implementation of the study. For the questionnaire, this means developing a system that can allow questionnaire recipients to post their responses via the Internet as well as through the postal system. Moreover, installation of electronic terminals in the waiting rooms and examination rooms of cooperating medical institutions is a possibility. If implemented, it would allow the subjects of the study to post questionnaire responses during their regular examination visits.

Collection, aggregation, and analysis of the questionnaires will be implemented at the Core Center, while data processing and aggregation is to be outsourced to take advantage of private-sector skills. In particular, because interrogation of subjects regarding inadequate responses to the questionnaire is an important element in this process, all such activity will be concentrated at the Core Center.

3.9 Follow-Up

In cohort studies designed to last over many years, one major problem is the increasing number of subjects who drop out of a study. To assure data significance in the study, a high follow-up rate is needed.

In principle, the Unit Centers will be responsible for follow-up. Continuous vigilance will be needed to ensure that a high follow-up rate is maintained.

3.9.1 Response to Natural Attrition

To minimize dropouts, interest among the subjects needs to be maintained at a high level. This can be done by producing a regularly scheduled newsletter that is distributed to all subjects.

Moreover, steps should be discussed to ensure that the subjects who want to consult regarding their children’s development can be referred to specialist facilities. It also will be necessary to obtain sufficient personnel for production of the newsletter.

In setting up the interviews for the detailed study, care will be taken regarding dates and times to ensure that proper consideration is given to households where both spouses are working, by offering interviews on weekday nights and on weekends.

3.9.2 Response to Change of Residence

One cause of dropouts in epidemiological studies is change of residence. This study can forestall such an outcome by setting up a system for the subjects of the study to send notification by telephone, email, postal service, or some other method when changing residences.

In addition, there may be cases where subjects have changed residence without notifying the Unit Center. To ensure that resident cards can be used to locate the new residence, prior consent should be obtained from the persons with parental rights over children targeted by the study, and then the relevant administrative institutions should be contacted for permission to view the resident cards when necessary.

Most epidemiological studies are limited in area, with the result that studies often have no choice but to drop subjects who have moved to distant locations. Because the children’s

epidemiological study is to be implemented on a nationwide scale, however, follow-up can still be performed for any subjects who have relocated so long as a Unit Center is sufficiently close by. As a result, the system will be developed to ensure that subjects can be transferred to nearby Unit Centers at the new locations.

3.10 Collection of Biological Samples

The biological samples to be collected for this study are assumed to include blood samples from the mother, and umbilical cord blood and umbilical cord samples from the newborn child.

Strict control systems founded on due conformity with various ethical guidelines are essential requirements for collection of biological samples. Moreover, full explanations should be given to the subjects of the study before collection of biological samples begins, and the burden imposed on the subjects (pregnant and parturient women, and children) during the collection should be held to an absolute minimum.

3.11 Analysis of Biological Samples

3.11.1 Philosophy

Because the objective of this study is to clarify the effects of exposure to chemical substances on children's development during the fetal period, analysis of biological samples is an important element of the study.

To ensure that suitable analysis is performed, studies will first need to be done on what analyses are feasible, analysis manuals prepared, and a system set up for accuracy controls. A working group consisting of experts in analysis technology will need to be established to study the issue of analysis of biological samples.

3.11.2 Analysis Items

Because the items to be measured in analysis are closely linked to the basic design for the study, this issue will be examined in the working group and feasibility study.

Some types of chemical substances, such as dioxins and PCBs, demonstrate a strong correlation with measurement values. As a result, discussions are necessary on whether to perform measurement of all items, or to narrow the focus to particular items.

In recent years, genes have become a focus of interest, enough so that a separate study of genetic analysis may be needed. Such a study should receive careful attention, because gaining the public's understanding of genetic analysis may prove to be difficult.

3.11.3 Accuracy Controls

Because of the large scale of the study, it can be expected to involve a large number of institutions for the test analyses. Variation in analysis results between individual institutions must be kept to a minimum. As a result, implementation of a round-robin test system, where the same tests are analyzed by each of the analysis institutions, is being considered. Consultations with the core institutions regarding creation of tests usable for round-robin testing will be needed.

Cross-checks in cooperation with public institutions will also be performed.

3.12 Storage of Biological Samples

3.12.1 Philosophy

Long-term storage (banking) is being considered for biological samples where measurement has been completed. Of course, such long-term storage will require the consent of the mothers and of the persons with parental rights over the children.

The biological samples will be divided between the Core Center and the Unit Centers for storage. Such division will increase the chances that at least some biological samples are preserved even in the face of earthquakes or other disasters.

The long-term storage (banking) facility at the Core Center should incorporate measures to survive major disasters, including installation of reserve liquid oxygen supplies and emergency power generators.

A study is also needed regarding the cost of materials and installation.

3.12.2 Rules for Use of Biological Samples

It is likely that stored biological samples will be accessed in later years for analysis. To prepare for such an eventuality, rules will need to be prepared beforehand regarding preservation and utilization of the biological samples. Also needed will be studies of how to obtain consent from mothers and persons with parental rights over children targeted in the study.

3.13 Ethical and Safety Concerns

3.13.1 Ethics Guidelines, and Ethics Committee

Rules regarding the study implementation method, collection of personal data, and handling of biological samples will be prepared based on the “Ethical Guidelines for Epidemiological Research” (issued by MEXT, and the Ministry of Health, Labour and Welfare), and will need to be stringently applied.

Moreover, adherence to the “Ethical Guidelines for Human Genome and Gene Analysis Research” (issued by MEXT, the Ministry of Health, Labour and Welfare, and the Ministry of Economy, Trade and Industry [METI]) will be strictly enforced.

To ensure security of information, the Ministry of the Environment Information Security Policy will be strictly followed. For electronic media, this will mean replacing the names of individuals with ID numbers to protect anonymity. Electronic terminals should have security controls that isolate them from the Internet or networking environment.

Ethical cases related to the general study will be referred to the Screening Panel for Epidemiological Research at the Ministry of the Environment. Issues related to study items independently set at Unit Centers will be referred to the ethics committees of the institutions (universities, etc.) working directly with the Unit Centers.

3.13.2 Informed Consent (Explanation and Consent)

Informed consent (explanation and consent) for the subjects of the study will be performed by medical staff at cooperating medical institutions, using explanatory texts prepared for the purpose. The staff members will provide a general summary of the study and offer carefully prepared explanations of the analysis and long-term storage (banking) of biological samples, to lay the foundation for obtaining the subjects' consent.

To prepare for the need in later years to access biological samples for analysis, studies will be needed to determine beforehand what the response should be for items where consent was never obtained.

3.13.3 Safety Management System

Invasive collection of biological samples will be performed only at medical institutions with the requisite medical staff.

3.14 Use and Analysis of Data Obtained from the Study

The objective of the study is to clarify environmental factors that have an effect on children's development. As a result, analysis of the data and presentation of results is just as important as data collection.

Rules for the use and analysis of the collected data must be established. Data users should be limited to researchers and administrative personnel. Anyone wishing to use the data will be asked to file an application, prior to use of data, and undergo rigorous screening regarding the purpose of use, method of analysis, and method of publication, etc. The screening must ensure that the objective of the data use is limited to academic research or administrative purposes, and that it is not connected to commercial gain or other inappropriate use.

When use has been approved, data will be transferred to the user for a specific time period for analysis. When that period has elapsed, the user will need to be notified to return the data or to destroy the data and report its destruction to the designated center. The users will also be asked to send any research papers or other results obtained from the data.

The system for use and analysis of data should give priority of use and analysis to the researchers who were involved in the design and implementation of the study. When those needs are satisfied, attention can then be given to building a system enabling use and analysis by other researchers not initially involved in the study.

3.15 Method for Disclosure of Knowledge Obtained from Study

3.15.1 To the Public At Large

As this study is being pursued as a national project, emphasis on providing information announcements to the public at large will be an important element. The materials, with content that is easy for the average citizen to understand, will need to be prepared and disseminated. Information disclosure activities under consideration include creation of a web site, and preparation and distribution of newsletters, posters, and pamphlets.

3.15.2 Academic Papers

The study should result in much new knowledge. Therefore, a procedure should be established to promote active dissemination of information to academic societies and journals in Japan and abroad.

A committee of experts will be set up to coordinate academic publication, and all papers will in principle be published after review by the committee. Researchers who were most involved in the study will be given first priority in presenting academic papers.

3.15.3 Information Announcements Abroad

Because this study can be expected to attract attention abroad as well, the information should also be disseminated in English. Information will be translated into English as much as possible and be published or posted on a web site.

3.16 Links with Birth Cohort Studies Abroad

Epidemiological studies for children are currently being planned in the United States, South Korea, Taiwan, and elsewhere. Close exchange of information with these epidemiological studies should be considered, with a view toward cooperation in the future in the Asia-Pacific region.

3.17 Convening of Outside Evaluation Committees

Outside evaluation committees will be convened to conduct interim evaluations at regular intervals.

4. The Way Forward

4.1 Implementation of the Feasibility Study

4.1.1 Establishment of Working Groups

To ensure flexible and practical studies in the details of the epidemiological study, working groups will be established under the Advisory Committee of the Epidemiological Research for Children's Environmental Health.

Examples of possible working groups are listed below.

- Working Group for Basic Design
  Studies the basic design and system for implementation of the epidemiological study. Prioritizes proposed hypotheses that should be examined, and selects the hypotheses for the study.
  Also examines the sample size, the recruitment method, and follow-up method.
- Working Group for Examination Standards
  Studies the examination standards. For certain diseases, examination standards have not yet been established. As a result, there will likely be a need for review or establishment of

standards in the course of the study. Therefore, examination standards would best be reviewed by experts actually involved in the study.

- Working Group for Sample Analysis
  Studies rules for analysis of biological samples, accuracy control, banking, and use of stored materials.
- Working Group for Coordination of Data Use, Analysis, and Results
  Prepares rules for the use and analysis of collected data, methods for publishing the results, information management, information dissemination, etc.
- Working Group for Ethics and Security
  Studies methods from the perspective of ethical and security management for implementing the study and for handling personal data and biological samples, and establishes the rules and methods of actual operation.
- Working Group for Coordination of Unit Centers
  Performs coordination of general study, adjustment of detailed study items, coordination between Unit Centers, etc.

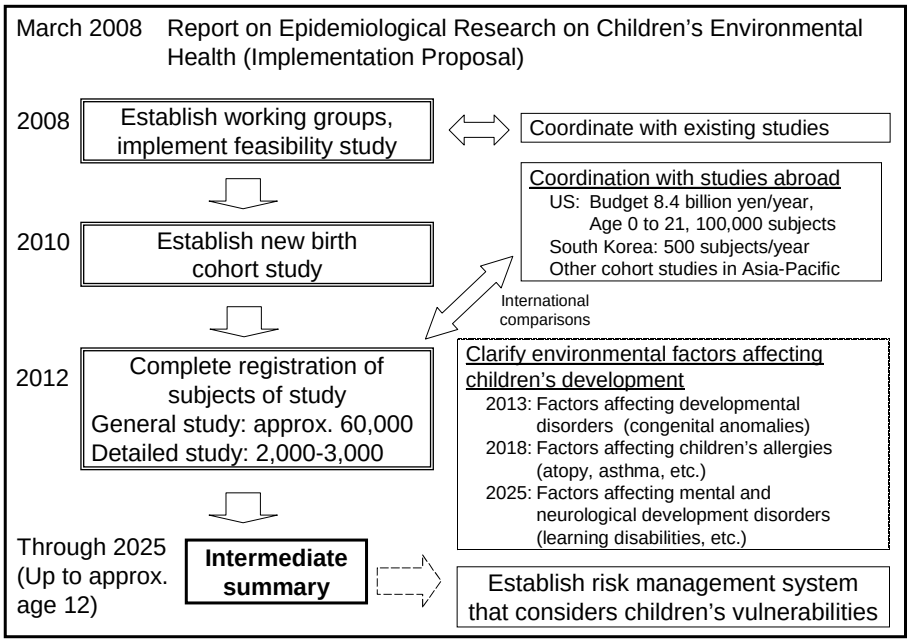
4.1.2 Implementation of Small-Scale Study

A small-scale study will be implemented to determine the feasibility of the general study at several locations nationwide. This study will be conducted in close coordination with the working groups, to establish whether a unified nationwide protocol can be implemented for the general study.

This study will cover as much of Japan as possible, to enable discernment of regional differences.

Figure 5: Schedule Proposal

Schedule for Epidemiological Study of Children's Environmental Health



4.2 Coordination with Existing Studies

Such studies as the Hokkaido Study of the Environment and Children's Health and the Tohoku Study of Child Development are currently in progress in Japan. The planning and proposals for this new study are to proceed based on comprehensive investigations in close coordination with these existing studies.

4.3 Coordination with Related Institutions

Coordination with related groups, related academic institutions, and research institutions is essential for smooth implementation of the study. Sharing information and opinions with these related organizations is to be promoted to ensure smooth coordination.

5. Name of the Study

An official name for this study has not yet been determined. Whatever the name, it should be one that is familiar and easily understood.

6. Conclusion

The working groups will be established in FY2008 and will implement the feasibility study over a period of two years. This report summarizes the efforts at the present stage. Future studies and discussions will provide more specific details.

7. Reference Bibliography

Reference A	Children's Cohort Studies
Reference B	Children's Cohort Studies Examining the Effects of Exposures to Environmental Pollutants
Reference C	Sample of Children's Cohort Studies
Reference D	Incidence Rates of Major Health Effects and Diseases
Reference E	Trends in Studies and Research for Child Cohort Studies
Reference F	FY2008 Ministry of Environment Proposed Budget: Overview of Major New Budgetary Items
Reference G	Annual Budget for Study to Examine Risk Assessments of Vulnerabilities in Children
Reference H	Report on European Children's and Birth Cohort Studies, Part A Study Precedents
Reference I	Report on European Children's and Birth Cohort Studies, Part B WHO's Programs for Children's Environmental Health

Children's Cohort Studies

Table 1. Studies Examining the Effects of Exposures to Environmental Pollutants: Methyl Mercury, PCBs, and Dioxins

No.	Study Name, Recruitment Period, Tracking Period	Country	Sample Size	Exposures	Outcomes	Principal Investigator	Summary	Conclusions
1	The Hokkaido Study of Environment and Children's Health (The Hokkaido Cohort Study) 2002–2005 Age 5–6 years	Japan	Approx. 20,000(focus study: n=514)	Endocrine disruptors (maternal blood, umbilical cord blood, breast milk, hair)	Congenital anomalies, birth weight, gestational age Allergies, neurodevelopmental and behavioral disorders	Hokkaido University	Prospective cohort for the purpose of monitoring congenital anomalies: particularly examination of risk factors for hypospadias and cryptorchidism, and sensitivity to endocrine disruptors	–
2	The Tohoku Study of Child Development 2001–2003 Age 6–7 years	Japan	Approx. 1,300	PCBs, methyl mercury, POPs, dioxins (mother's hair, maternal blood, umbilical cord blood, placenta, breast milk)	Effect on development (NBAS[1], KSPD[2], BSID[3], FTII[4], K-ABC[5], other)	Tohoku University	Examine the effects of perinatal exposures of persistent organic pollutants (POPs) on the development of children	–
3	The New Zealand Study 1980s Until age 6–7 years	New Zealand	238	Methyl mercury (mother's hair)	Effect on development (WISC-R[6], MCC[7], TOLD, other)	Kjellstrom et al. (1986,1989), no peer review Crump et al. (1998)	Study the effects of methyl mercury exposures on the development of children	At 4 years: A number of tests revealed a correlation between the concentration of methyl mercury in the mother's hair and negative effects on the development of the child. At 6–7 years: A negative correlation was observed if an extreme outlier (one case) of total mercury in the mother's hair was excluded. No negative correlation was observed if the outlier was included.

1 Neonatal Behavioral Assessment Scale
2 Kyoto Scale of Psychological Development
3 Bayley Scales of Infant Development
4 Fagan Test of Infant Intelligence
5 Kaufman Assessment Battery for Children
6 Wechsler Intelligence Scale for Children–Revised
7 Mother-Child Counseling

Table 1. Studies Examining the Effects of Exposures to Environmental Pollutants: Methyl Mercury, PCBs, and Dioxins (Continue)

No.	Study Name, Recruitment Period, Tracking Period	Country	Sample Size	Exposures	Outcomes	Principal Investigator	Summary	Conclusions
4	The Seychelles Child Development Study 1984–1994 Until age 20 years (scheduled)	Republic of Seychelles	779	Methyl mercury (mother's hair)	Effect on development (WISC-III[8], CVLT[9], VIMI[10], BNT[11], WRAML[12])	Rochester University, WHO, Seychelles Ministry of Health (1986–)	Study the effects of methyl mercury exposures on the development of children	No negative effects were observed at 29, 66, and 107 months.
5	The Faroese Birth Cohort Study (Children's Health and the Environment in the Faroes—Cohort 1) 1986–1987	Faroe Islands (Denmark)	1,022	Methyl mercury, PCBs, lead, etc. (umbilical cord blood, hair)	Effect on development (WISC-R, CVLT, Bender-Gestalt Test, BNT)	Institute of Public Health (Denmark), The Faroese Hospital System	Study the effects of contaminants in seafood on the development of children	
	Study results available at current age of 14 years		878	Methyl mercury (umbilical cord blood, hair, blood)	Neurodevelopment			A significant correlation was observed between mercury concentrations in umbilical cord blood and both neuropsychological and neurophysiological testing results.
	(Cohort 2) 1994–1995		182	Methyl mercury, PCBs, DDEs, selenium (umbilical cord blood, hair, breast milk, maternal blood)	Neurodevelopment (NOS) Effect on thyroid gland hormones	Institute of Public Health (Denmark), The Faroese Hospital System	Same as above	A significant correlation was observed between concentrations of mercury in umbilical cord blood and decreases in NOS at postnatal week 2. At 7 years, concentrations of mercury in umbilical cord blood and mother's hair were observed to have a statistically significant effect on motor functions and language ability.
	(Cohort 3) 1998–2000		547	Methyl mercury, PCBs, etc. (umbilical cord blood, hair, maternal blood, breast milk)	Effect on neurodevelopment, immune system and endocrine system	Institute of Public Health (DK), The Faroese Hospital System	Same as above	Study terminated

8 Wechsler Intelligence Scale for Children—Third Edition
9 California Verbal Learning Test
10 Visual impairments and multiple impairments
11 Boston Naming Test
12 Wide-Range Assessment of Memory and Learning

Table 1. Studies Examining the Effects of Exposures to Environmental Pollutants: Methyl Mercury, PCBs, and Dioxins (Continue)

No.	Study Name, Recruitment Period, Tracking Period	Country	Sample Size	Exposures	Outcomes	Principal Investigator	Summary	Conclusions
6	The Dutch PCB/Dioxin Study 1990–1992 Ongoing	Netherlands	418	PCBs (maternal blood, breast milk, umbilical cord blood, child's blood)	Physiological effect, effect on development	University of Groningen; Erasmus University Rotterdam; Agricultural University, Wageningen; TNO Nutrition and Food Research; TNO Medical Biological Laboratory; DLO State Institute for Quality Control of Agricultural Products	Study of thyroid gland hormone levels, intelligence, play behavior at school age, etc.	At 10–21days: A correlation was observed between medium and high levels of PCBs, PCDDs, and PCDFs in breast milk, and less optimal scores for neonatal development. At 3 months: A slight negative correlation was observed between concentrations of PCBs in pregnant women's blood plasma, and mental/motor development measured by Bayley Scales of Infant Development (BSID) scores. At 7 months: Medium and high levels of PCBs and dioxins in breast milk were observed to have a negative effect on BSID scores. At 42 months: A significant correlation was observed between fetal exposure to PCBs and low cognition scores.
7	The German Cohort Study 1992–1997 Age 3.5 years	Germany	171	PCBs (umbilical cord blood, breast milk)	Effect on development (BSID, Fagan visual recognition memory test)	Winneke et al.	Study the effects of maternal intake of PCBs on development of children	At 7 months: A significant correlation was observed between concentrations of PCBs in breast milk and mental development index.
8	The Oswego Newborn and Infant Development Project 1991–1994	USA	559	PCBs (records of maternal dietary intake of fish)	Effect on development	Lonky et al.	Study the effects of maternal intake of PCBs (from fish) on development of children	At 12–48 hours after birth: The group exposed to high concentrations of PCBs were linked to lower evoked responses and underdevelopment of autonomic nervous system, measured by Neonatal Behavioral Assessment Scale (NBAS). At 4.5 years (n=189): An association was observed between PCB concentrations in umbilical cord blood and increases in errors of commission measured by Continuous Performance Test (CPT), and decreases in the size of the splenium of the corpus callosum from MRI imaging.
	Study results available through ages 4.5 years, 8 years, and 9.5 years		189 202			Stewart et al.		At 8 and 9.5 years (n=202): An association was observed between concentrations of PCBs in umbilical cord blood and errors of commission measured by CPT. After 1.5 years, increases in errors of commission were observed to impair response inhibition.

Table 1. Studies Examining the Effects of Exposures to Environmental Pollutants: Methyl Mercury, PCBs, and Dioxins (Continue)

No.	Study Name, Recruitment Period, Tracking Period	Country	Sample Size	Exposures	Outcomes	Principal Investigator	Summary	Conclusions
9	The Michigan Cohort Study (Michigan/Maternal Infant Cohort Study) 1980–1981 Until age 11 years	USA	313	PCBs (umbilical cord blood, maternal blood)	Effect on development	Fein et al.	Study the effects of maternal intake of PCBs (from fish) on development of children	At 7 months (n=123): An association was observed between exposures to PCBs and lower responsiveness to visual recognition memory, measured by Pagan Test of Infant Intelligence (FTII). At 4 years (n=236): An association was observed between PCB concentrations in umbilical cord blood and lower test scores for language and short-term memory of quantities measured by McCarthy Scales of Children's Abilities (MSCA). At 11 years (n=212): An association was observed between fetal exposures to PCBs, and full-scale IQ and language IQ scores measured by Wechsler Intelligence Scale for Children (WISC-R).
10	The North Carolina Cohort Study (The North Carolina Breast Milk and Formula Project) 1978–1982 Until age 5 years	USA	912	PCB, DDEs, other	Effect on development, other	Rogan et al.	Prospective cohort study on general population	Neonatal period (n=867): An association was observed between the group exposed to high concentrations of PCBs in breast milk, and diminished muscle tone and reflexes measured by Neonatal Behavioral Assessment Scale (NBAS). An association was also observed between exposures to high concentrations of DDEs in breast milk and diminished reflexes. At 6 and 12 months (n=802): An association was observed between concentrations of neonatal exposures to DDEs and gross motor development (BPDI scores). A meaningful association was observed between concentrations of neonatal exposures to PCBs and BPDI scores. At 18 and 24 months (n=676, n=670): The group with the highest exposure was observed to have BPDI scale scores that were 4–9 points below mean scores. At 3, 4 and 5 years (n=506): No association was observed between exposures and MSCA scores.

Table 1. Studies Examining the Effects of Exposures to Environmental Pollutants: Methyl Mercury, PCBs, and Dioxins (Continue)

No.	Study Name, Recruitment Period, Tracking Period	Country	Sample Size	Exposures	Outcomes	Principal Investigator	Summary	Conclusions
11	German Environmental Survey (GerES) IV 2003–ongoing Until age 14 years	Germany	550	Lead, cadmium, mercury, organic chlorine compounds, IgE antibodies (blood) Stress markers (urine) House dust, drinking water, indoor air Noise	Hearing	German Federal Environmental Agency	Collect exposure data in various parts of Germany	–

Table 2. Studies Examining the Effects of Exposures to Environmental Pollutants: Lead

No.	Study Name, Recruitment Period, Tracking Period	Country	Sample Size	Exposures	Outcomes	Principal Investigator	Summary	Conclusions
12	Port Pirie Cohort Study 1978–1982 Into adulthood	Australia	831 (at recruitment) 537 (at age 4 years) 372 (at age 11–13 years)	Lead (blood)	Effect on development	McMichael, A.J. et al. (1988) Tong, S. (1996)	Recruitment of pregnant women in community situated near lead smelter	Lower IQ scores were observed among the high-exposure group. At 4 years, subjects with an average postnatal blood lead concentration of 1.50 µmol/lwere observed to have general cognitive scores that were 7.2 points below the mean (95% confidence interval, 0.3 to 13.2; mean score of 107.1). At 11–13 years, subjects whose average lifetime blood lead concentration increased from 10 to 20 µg/dl had IQ scores that were 3 points below the mean (95% confidence interval, 0.07 to 5.93).
13	Cincinnati Lead Study Cohort 1987–ongoing	USA	305 (at recruitment) 253 (at age 6.5 years)	Lead (blood)	Effect on development	Dietrich, K. et al. (1987) Dietrich, K. et al. (1993)	Recruitment of low-income mothers from neighborhoods with high risk of lead exposure	At both 3 and 6 months: A negative correlation was observed between children's blood lead concentrations and Bayley Scales of Mental Developmental Index (MDI) scores. At 6.5 years: Subjects with average lifetime blood lead concentrations over 20 µg/dl had WISC-R Performance IQ scores that were seven points lower than subjects under 10 µg/dl.
14	Boston Birth Cohort Study 1979–1981	USA	249 (at recruitment) 148 (at age 10 years)	Lead (blood)	Effect on development	Bellinger, D. C. et al. (1992)	Children born at Brigham & Women's Hospital (Boston, MA)	A correlation was observed between exposure levels at 2 years of age and lower WISC-R and K-TEA scores at 10 years. At 24 months, subjects with higher blood lead concentrations of 0.48 µmol/l (10 µg/dl) had WISC-R Full-Scale IQ scores that were 5.8 points below the mean (95% confidence interval, 1.7 to 9.9; P=0.007). The same subjects had K-TEA Battery Composite scores that were 8.9 points lower (95% confidence interval, 4.2 to 13.6; P=0.0003).
15	Christchurch Health and Development Study (CHDS) 1977 Tracked until age 21 years	New Zealand	1,265	Lead (teeth) One of a number of study items	Effect on mental and neurological development	Fergusson, D.M. et al. (1997) Fergusson, D.M. Horwood, L. J. (2001)	Residents of Christchurch, New Zealand	A negative correlation was observed between lead exposure levels detected in deciduous teeth shed at 6–8 years, and lower scores for word recognition. Lower-than-average scores were also observed at 18 years.
16	Cleveland Cohort Study	USA	160	Lead (maternal blood, umbilical cord blood, blood)	Effect on development	Ernhart, C.B. et al. (1989)	Low-income residents of Cleveland, Ohio	At five years, a clear association had not been established between blood lead concentrations and intelligence measured by Wechsler Preschool and Primary Scale of Intelligence (WPPSI) scores.

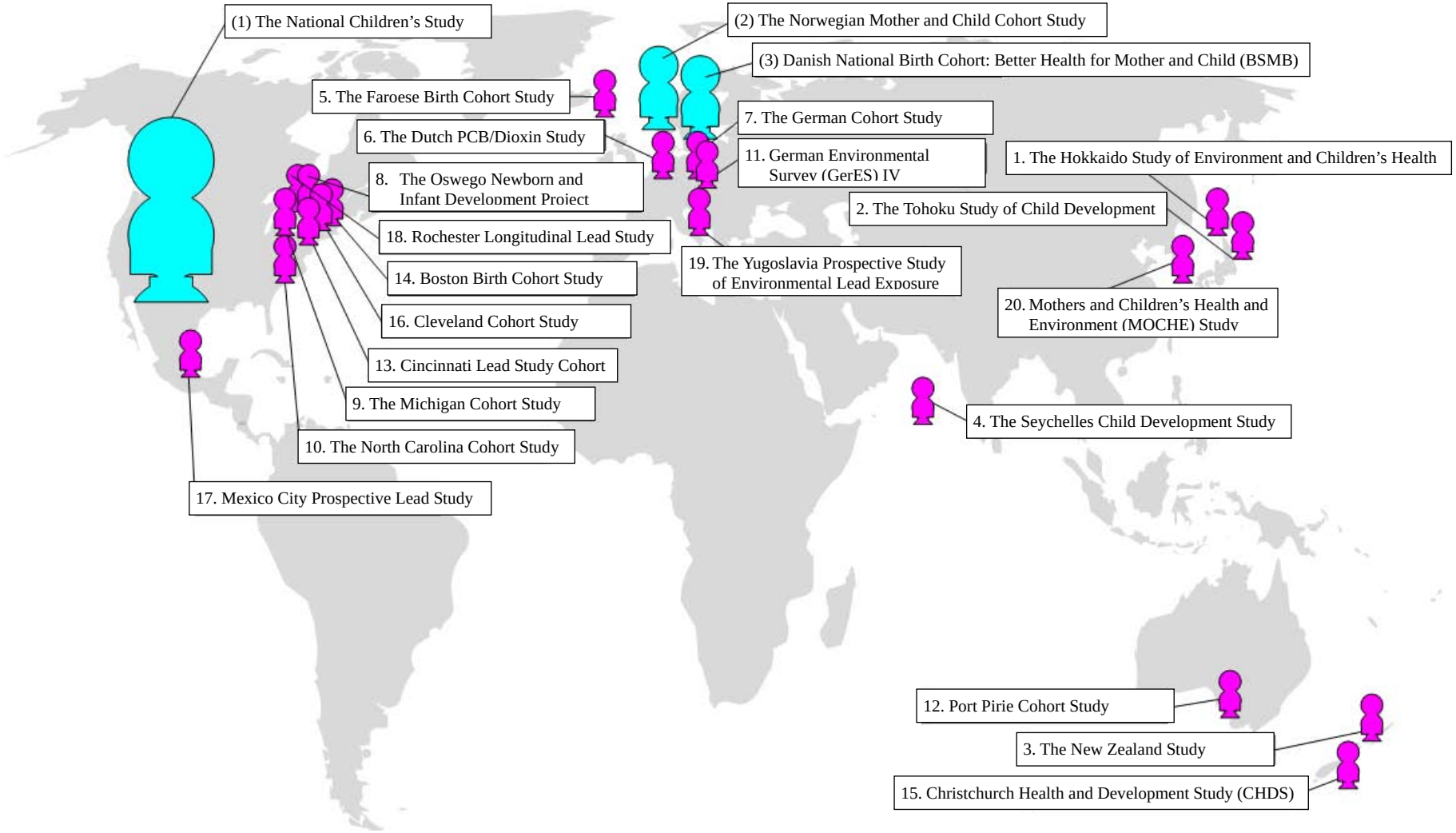
Table 2. Studies Examining the Effects of Exposures to Environmental Pollutants: Lead (Continue)

No.	Study Name, Recruitment Period, Tracking Period	Country	Sample Size	Exposures	Outcomes	Principal Investigator	Summary	Conclusions
17	Mexico City Prospective Lead Study 1987–1992 Tracked until age 10 years	Mexico	157 (complete data at age 10 years: n=150)	Lead (blood)	Effect on development	Schnaas, L. et al. (2006)	Children born in Mexico City (part of cohort by National Institute of Perinatology)	An association was observed only between maternal blood lead concentration at 28 weeks gestation and lower recognition scores of children at 6–10 years, measured using Spanish-language version of Wechsler Intelligence Scale for Children.
18	Rochester Longitudinal Lead Study 1994–1995	USA	240	Lead (blood)	Effect on development	Canfield, R.L. et al. (2003)	Residents of Rochester, New York (part of large cohort to study and test effects of indoor dust management)	A significant negative correlation was observed between average lifetime blood lead concentration and IQ scores (P=0.004). For each increase of 1 µg/dl, IQ scores were 0.46 points lower. Blood lead concentrations were measured at 6, 12, 18, 24, 36, 48, and 60 months. IQ was tested at 3 and 5 years using Stanford-Binet Intelligence Scale.
19	The Yugoslavia Prospective Study of Environmental Lead Exposure 1985–1986	Yugoslavia	Recruitment of 1,502 mothers from two towns (900 from Pristina, 602 from K. Mitrovica) 577 children tracked until age 7.5 years	Lead (blood)	Effect on development, etc.	Factor-Litvak, P. (1999)	Residents of two towns in Kosovo, Yugoslavia	A correlation was observed between increases in blood lead concentration and lower scores on a variety of tests including for intelligence. Subjects with higher blood lead concentrations of 10–30 µg/dl had scores that were 2.5 points lower at 2 years (95% confidence interval, 0.2 to 4.8), 4.5 points lower at 4 years (95% confidence interval, 2.2 to 6.8), and 4.3 points lower at 7 years (95% confidence interval, 3.5 to 5.1). Subjects were tested using Bayley Scales of Mental Development Index (MDI) at 6, 12, 18, and 24 months, McCarthy Scales of Children's Abilities (MSCA) at 4 years, and Wechsler Intelligence Scale for Children-III (WISC-III) at 7 years.
20	Mothers and Children's Health and Environment (MOCHE) Study 2006–2010	South Korea	Recruitment of 500 mothers in first year only	Blood, biomarkers in urine (including lead, mercury, and cadmium) Environmental factors	Effect on development, allergies, eczema, asthma, etc.	Ha, E. (2007)	Three cities in South Korea	Based on preliminary results, an analysis of 300 subjects revealed a significant correlation between the blood lead concentration of mothers and femur length of their children. The correlation was not established for mercury levels.

Table 3. Large-Scale Studies on Exposures to Environmental Pollutants

No.	Study Name, Recruitment Period, Tracking Period	Country	Sample Size	Exposures	Outcomes	Principal Investigator	Summary
(1)	The National Children's Study 2008–2013 Until age 21 years	USA	100,000	• Natural and man-made environmental factors • Biological and chemical factors • Physical surroundings • Social factors • Behavioral influences • Genetic influences • Cultural and family influences • Geographic influences	Children's health • Asthma • Congenital anomalies • Development and behavior • Growth • Fertility and pregnancy	• U.S. Department of Health and Human Services (DHHS) • National Institutes of Health (NIH) • The Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD) • The National Institute of Environmental Health Sciences (NIEHS) • Centers for Disease Control and Prevention (CDC) • U.S. Environmental Protection Agency (EPA)	• Tracking from prenatal to adulthood • Prospective cohort study implemented throughout the United States
(2)	The Norwegian Mother and Child Cohort Study (MoBa) 1999–2007 Until age 6 years	Norway	90,000 (from 1999 to September 2007)	• Health • Infection • Nutrition • Medication • Occupation • Lifestyle (alcohol, drugs, smoking, social status) • Banking of maternal blood and umbilical cord blood • Dietary survey, questionnaires	• Pregnancy (childbirth, eclampsia, premature birth, low birth weight, congenital anomalies) • Children (asthma, allergies, diabetes, cancer, polyarthritis, autism, ADHD)	• Norwegian Institute of Public Health	• Scheduled to track subjects from prenatal to age 6 years • Seeks to clarify the relationship between the health of Norwegian mothers and children, and environmental and genetic influences
(3)	Danish National Birth Cohort: Better Health for Mother and Child (BSMB) 1997–2002	Denmark	101,042 (1997–2002)	• No specific exposures set in advance • Banking of maternal blood and umbilical cord blood • Dietary survey, phone interviews with mothers	• Complications from pregnancy • Childhood disease from early exposure • Fetal development and determinants • Effect of medication and infectious disease, etc.	• Denmark Statens Serum Institut (Danish State Serum Institute)	• Improvement of prenatal care • Nested case-control investigation • Use of registries: natal treatment registries (illnesses during pregnancy, childbirth status, child body measurements), registry of special diseases (childhood cancer, childhood paralysis, diabetes, autism) • Clarify effects of disease infection, diet, genetic background and social environment on congenital anomalies, asthma, cancer and behavioral disorders in children, as well as testicular cancer and other pathologies in adulthood

Reference B



Children's Cohort Studies Examining the Effects of Exposures to Environmental Pollutants

Reference C

Sample of Children's Cohort Studies

1. Japanese Studies

The Hokkaido Study of Environment and Children's Health (The Hokkaido Cohort Study)

Principal Investigator	Hokkaido University
Recruitment Period	2002–2005
Tracking Period	Age 5–6 years
Country	Japan
Sample Size	Approx. 20,000 (focus study: n=514)
Main Study Items−Exposures	Endocrine disruptors (maternal blood, umbilical cord blood, breast milk, hair)
Main Study Items−Outcomes	Congenital anomalies, birth weight, gestational age Allergies, neurodevelopmental and behavioral disorders
Purpose	Prospective cohort study for the purpose of monitoring congenital anomalies: particularly examination of risk factors for hypospadias and cryptorchidism and sensitivity to endocrine disruptors

The Tohoku Study of Child Development

Principal Investigator	Tohoku University
Recruitment Period	2001–2003
Tracking Period	Age 6–7 years
Country	Japan
Sample Size	Approx. 1,300
Main Study Items−Exposures	PCBs, methyl mercury, POPs, dioxins (mother's hair, maternal blood, umbilical cord blood, placenta, breast milk)
Main Study Items−Outcomes	Effect on development (NBAS, KSPD, BSID, FTII, K-ABC, other)
Purpose	Examine the effects of perinatal exposures of persistent organic pollutants (POPs) on the development of children

Japan Children's Study

Principal Investigator	Japan Science and Technology Agency
Recruitment Period	20052006 (started recruitment for longitudinal cohort study from 2007)
Tracking Period	―
Country	Japan
Sample Size	―
Main Study Items—Exposures	Growth environment study, behavioral observation, and brain image analysis
Main Study Items—Outcomes	Development
Purpose	To scientifically investigate methods and environments that better promote a balance of mental and physical development. The study is a central part of a research project by the Japan Science and Technology Agency (an independent administrative agency) that is focused on the growth of the brain and healthy development of mind, body, and language.

2. International Studies

The National Children's Study

Principal Investigator	U.S. Department of Health and Human Services (DHHS), National Institutes of Health (NIH), The Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD), The National Institute of Environmental Health Sciences (NIEHS), Centers for Disease Control and Prevention (CDC), and U.S. Environmental Protection Agency (EPA)
Recruitment Period	2008–2013
Tracking Period	Until age 21 years
Country	USA
Sample Size	100,000
Main Study Items−Exposures	• Physical environment (quality of home, community enviroment) • Chemical environment (insecticides, phthalates, heavy metals, air/water quality) • Biological environment (infection factors, endotoxins, diet) • Genetic influences (interaction of environmental factors and genetics) • Social factors (family, socioeconomic status, facilities, social network)
Main Study Items−Outcomes	• Outcome of pregnancy (premature delivery, congenital anomalies) • Neurodevelopment and behavior (autism, schizophrenia, learning disabilities) • Injuries (head injuries, hospitalization due to external injuries) • Asthma (development and worsening of asthma) • Obesity and physical development (obesity, diabetes, onset of puberty)
Purpose	To grasp the effects of environmental factors on the development of children and identify preventable factors. The study is implemented by seeking to verify preselected hypotheses, and examines the interactions of genetics and environmental factors including exposures in both pregnant women and mothers. The study will provide a solid foundation of data for diverse future studies and research, and will be an asset to the United States. The adoption of research that uses a cohort requires that the research be based on working hypotheses. For this purpose, the following 26 hypotheses (28 hypotheses at Nov. 2008) have been established for the study. ・ Congenital anomalies from impaired glucose metabolism of mothers ・ Increased risk of premature delivery from intrauterine exposure to mediators of inflammation ・ Increased risk of fetal growth restriction, premature delivery, congenital anomalies, and development disorders in children born through assisted reproductive technologies ・ Maternal subclinical hypothyroidism and neurodevelopmental disorders/adverse pregnancy outcomes ・ Non-persistent pesticides and poor neurobehavioral and cognitive skills ・ Prenatal infection and neurodevelopmental disorders

	• Genetic–environmental interactions and behavior • Prenatal and perinatal infection and schizophrenia • Family influences on child health and development • Impact of neighborhoods and communities on child health • Impact of media (television, Internet, games, etc.) exposure on child health and development • Social institutions (school and religious institutions) and child health and development • The role of prenatal maternal stress and genetics in childhood asthma • Exposure to indoor and outdoor air pollution, aeroallergens, and asthma risk • Dietary antioxidants and asthma risk • Social environmental influences on asthma disparities • Decrease in the risk of asthma due to early exposure to structural components and products of microorganisms • Obesity and insulin resistance from impaired maternal glucose metabolism • Obesity and insulin resistance from intrauterine growth restriction • Breastfeeding associated with lower rates of obesity and lower risk of insulin resistance • Fiber, whole grains, high glycemic index foods, and obesity and insulin resistance • Genetics, environmental exposures, and Type I diabetes • Repeated mild traumatic brain injury and neurocognitive development • Behavioral exposures, genetics, and childhood- or adolescent-onset aggression • Antecedents and resiliency to traumatic life events in childhood • Hormonally active environmental agents and reproductive development

Mothers and Children's Health and Environment (MOCHE) Study

Principal Investigator	MOCHE Coordinating Center, Ministry of Environment
Recruitment Period	2006–2010
Tracking Period	Until age 5 years (scheduled)
Country	South Korea
Sample Size	Recruitment of 500 mothers in first year only
Main Study Items—Exposures	Blood, biomarkers in urine (including lead, mercury, and cadmium) Environmental factors
Main Study Items—Outcomes	Effect on development, allergies, eczema, asthma, etc.
Purpose	To study the impact of environmental exposures on the health of mothers and children, and use the results to propose policies for environmental health.

The Norwegian Mother and Child Cohort Study (MoBa)

Principal Investigator	Norwegian Institution of Public Health
Recruitment Period	1999–2007
Tracking Period	Until age 6 years
Country	Norway
Sample Size	90,000 (from 1999 to September 2007)
Main Study Items—Exposures	Health, infection, nutrition, medication, occupation, lifestyle (alcohol, drugs, smoking, social status) • Banking of maternal blood and umbilical cord blood • Questionnaire-based study including dietary survey
Main Study Items—Outcomes	Pregnancy (childbirth, eclampsia, premature birth, low birth weight, congenital anomalies) Children (asthma, allergies, diabetes, cancer, polyarthritis, autism, ADHD)
Purpose	To collect as much data as possible concerning exposures and health outcomes, in order to respond to hypotheses that may arise in the future. The study is not aimed at proving specific etiological hypotheses.

Danish National Birth Cohort: Better Health for Mother and Child (BSMB)

Principal Investigator	Denmark Statens Serum Institut (Danish State Serum Institute)
Recruitment Period	1997–2002
Tracking Period	Tracking past adulthood (through use of registry systems)
Country	Denmark
Sample Size	101,042
Main Study Items—Exposures	No specific exposures set in advance Banking of maternal blood and umbilical cord blood Dietary survey, phone interviews with mothers
Main Study Items—Outcomes	Complications from pregnancy Childhood disease from early exposure Fetal development and determinants Effect of medication and infectious disease, etc.
Purpose	To learn about childhood disease and fetal development and their determinants from the perspective of complications at pregnancy and early exposures. The study places a particular emphasis on learning about the impacts of medication and infectious disease. The scope of the study covers all diseases that could be due to fetal exposures affecting childhood and beyond. The study establishes both a medication database and a biobank.

Generation R Study

Principal Investigator	Erasmus University Medical Center
Recruitment Period	2002–2006
Tracking Period	Until adulthood
Country	Netherlands
Sample Size	9,778 (n=1,232 for focus cohort study)
Main Study Items—Exposures	Biological factors (parents' traits, early growth, endocrine and immunocharacteristics, genetic background) Environmental factors (diet, parents' smoking, home) Social factors (parents' education, occupation, income, and marital status)
Main Study Items—Outcomes	Growth Behavior and development of cognitive skills Childhood disease Health care
Purpose	To identify environmental and genetic factors that impact development and health from the fetal period through adolescence. The study has four main areas of focus: (1) Growth and physical development, (2) behavior and development of cognitive skills, (3) childhood illness, and (4) health status and health management of pregnant women and children. The major purposes of the study are as follows: • Record growth from fetal period through adolescence • Identify biological, environmental and social factors that have an impact on growth from the fetal period through adolescence • Verify the effectiveness of current methodologies for early identification and prevention of high-risk groups

Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study

Principal Investigator	Utrecht University
Recruitment Period	1996–1997
Tracking Period	More than 8 years
Country	Netherlands
Sample Size	4,146 (n=855 for intervention study)
Main Study Items—Exposures	Indoor dust, distance from nearby roads, medication Diet
Main Study Items—Outcomes	Asthma, allergies
Purpose	To study the effect of reductions in allergens on childhood development of asthma, by recruiting mothers with allergic anamnesis and conducting a double-blind test of their children involving the use of mite-impermeable bedding. Also, to evaluate the role of environmental and dietary risk factors in relation to childhood development of allergic diseases, by recruiting mothers with and without allergic anamnesis and observing the development of asthma in their children.

3. Studies by International Organizations

Initiatives by the World Health Organization

The World Health Organization (WHO) since 2003 has operated an advisory committee for longitudinal cohort studies with funding from the U.S. National Institutes of Health (NIH), the Environmental Protection Agency (EPA), and the Centers for Disease Control (CDC). The advisory committee promotes mutual exchanges between researchers who are involved in longitudinal cohort studies in various countries, with a particular emphasis on assisting longitudinal cohort studies in developing countries. The aims of the advisory committee are to develop core protocols that can be commonly applied for longitudinal cohort studies to study the effects of the environment on the health and development of children, and to collect data in order to increase the value of information assets in each country.

Following are examples of hypotheses from current longitudinal cohort studies:

- There is a link between environmental exposures during early pregnancy and undesirable pregnancy outcomes such as congenital anomalies.
- Physicochemical and environmental causes have an impact on the sexual maturation of children.
- There is a link between childhood exposures to polluted air and increases in the risk of acute lower respiratory tract infection.
- There is a link between exposures to indoor air pollution and middle ear infections.
- There is a link between fetal exposures and increases in the risk of childhood cancer.
- Fetal and childhood exposures to heavy metals and other environmental pollutants with neurotoxic effects have a negative impact on neurodevelopment.

Following are examples of schemes from current longitudinal cohort studies:

- Sample-taking: Blood (maternal blood, paternal blood, children's blood, umbilical cord blood), amniotic fluid, placenta, meconium, urine (maternal urine, children's urine), sperm, hair, nail, mucous swab samples (oral, vaginal, and cervical), saliva, teeth, feces, and other environmental mediums
- Timing of sample-taking: At the time of enrollment, at second and third trimester, at birth, at 3/6/12 months, at each year of age, and other

Reference D

Incidence Rates of Major Health Effects and Diseases

Effect on Health	FY2006 Study on School Health Statistics[1]	2000 Infant Physical Development Study[2]	FY2005 Maternal and Child Health Statistics of Japan[3]	FY2005 Annual Report of Environment Health Surveillance for Air Pollution[4]	Other Documents
Physical Development					
Lower birth weight	–	–	9.6% (under 2,500 g) 0.7% (under 1,500 g)	–	–
Language impairment	0.37% (kindergarten) 0.30% (elementary school) 0.09% (junior high school) 0.02% (senior high school)	Passing rate for language function (ability to speak words) 95.0% (age 5–6 years) 97.6% (age 6–7 years)	–	–	–
Motor function	–	Passing rate for motor function (ability to walk unassisted) 93.8% (age 3–4 years) 99.6% (age 4–5 years)	–	–	–
Mental and Neurological Developmental Impairment (Autism, ADHD)	–	–	–	–	Using Diagnostic and Statistical Manual-III-Revised (DSM-III-R) diagnostic criteria for ADHD[5] 5.6% (age 3 years) 3.0% (age 5 years)
Immunological Abnormality					
Asthma	2.36% (kindergarten) 3.74% (elementary school) 2.95% (junior high school) 1.71% (senior high school)	–	–	3.32% (age 3 years) 5.88% (age 6 years)	–

Effect on Health	FY2006 Study on School Health Statistics[1]	2000 Infant Physical Development Study[2]	FY2005 Maternal and Child Health Statistics of Japan[3]	FY2005 Annual Report of Environment Health Surveillance for Air Pollution[4]	Other Documents
Atopic dermatitis	3.77% (kindergarten) 3.62% (elementary school) 2.76% (junior high school) 2.25% (senior high school)	–	–	11.1% (age 3 years) 14.8% (age 6 years)	–
Metabolic and Endocrine Anomalies					
Liver disease	0.03% (kindergarten) 0.18% (elementary school) 0.24% (junior high school) 0.23% (senior high school)	–	–	–	–
Congenital anomalies	–	–	Rate of persons identified with anomalies by examination 0.0016% (phenylketonuria) 0.0005% (maple syrup urine disease) 0.0004% (homocystinuria) 0.0029% (galactosemia) 0.0057% (congenital adrenal hyperplasia)	–	–

Sources:

1. Ministry of Education, Culture, Sports, Science and Technology
2. Ministry of Health, Labour and Welfare
3. K.K. Boshi Hoken Jigyodan, 2005
4. Environmental Health Department, Ministry of Environment, 2005
5. Soma, Yukio. 20

06, “A Study on Attention-Deficit Hyperactivity Disorder (ADHD) at Nursery School and Kindergarten in Niigata City,” *Niigata Igaku Gakkai Zasshi* 120:324-328

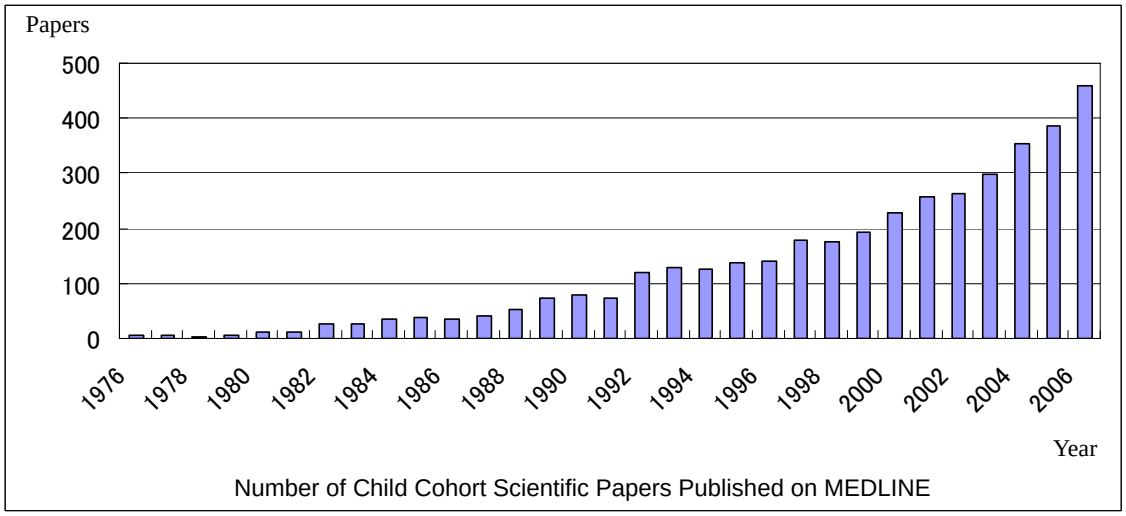
Reference E

Trends in Studies and Research for Child Cohort Studies

1. Number of Scientific Papers on MEDLINE by Year

A search of was conducted on MEDLINE (PubMed) using the keywords “birth,” “cohort,” and “child.” The graph below summarizes the number of scientific papers found on MEDLINE by year of publication.

Fig. 1. Number of Child Cohort Scientific Papers on MEDLINE

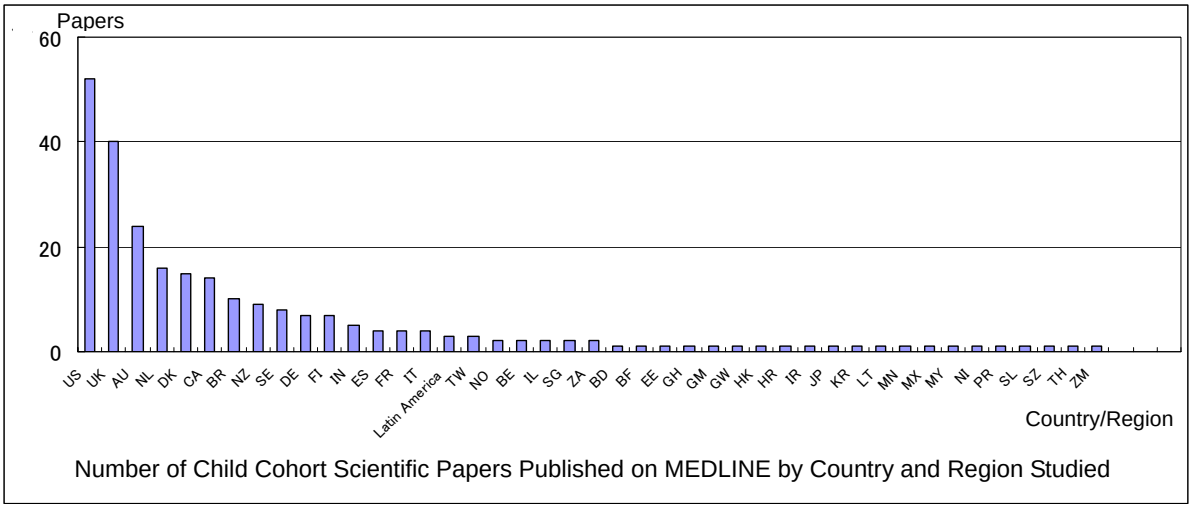


Note: At the time that this document was prepared (March 2008), a full listing of scientific papers published in 2007 was not yet complete for the MEDLINE database. Therefore, the above chart is restricted to scientific papers published through 2006.

2. Number of Scientific Papers on MEDLINE by Country and Region Studied

The chart below summarizes the number of new scientific papers published on MEDLINE by country and region studied, for papers released in January 2007 or later and published on MEDLINE through September 2007.

Fig. 2. Number of Child Cohort Scientific Papers on MEDLINE by Country and Region Studied
(From January–September 2007)



Note: The data are based on the country or region studied by the cohort, as indicated in abstracts. Excluded are cohort studies that involved new recruitment of adults and papers involving review or meta-analysis.

3. Types of Outcomes Studied in Scientific Papers

The charts below summarize the type of outcomes studied in the 290 scientific papers that were published on MEDLINE from January–September 2007 (Fig. 2).

Table 1. Outcomes by Order of Frequency

Outcomes	No.
Weight	23
Mental and neurological illness	18
Health	17
Asthma	13
Intelligence	12
Allergies	11
Respiratory symptoms	9
Behavior	8
Biochemistry	6
Neurodevelopment	6
Mother-to-child HIV infection	6
Growth	5
Antisocial behavior	5
Blood pressure	5
Development	4
Diameter of retinal blood vessels	3
Diabetes	3
Autism	3
Accidents	3
Infectious disease	3
Survival	3
Leukemia	2
Sex characteristics	2
Socioeconomic status	2
Eczema	2
Teeth	2
Eyesight	2
Epilepsy	2
Care	2
Attention Deficit Hyperactivity Disorder (ADHD)	2
Brachial plexus palsy	1
Nasal congestion	1
Pneumonia	1
Pain	1
Middle ear infection	1
Physiology	1
Sleep disorder	1
Nephritis	1
Heart attack	1
Food intake	1
Diet	1
Digestive disease	1
Infectious digestive disease	1
Menarche age	1
Plagiocephaly	1
Adipose tissue	1
Melanoma	1
Cleft palate	1
Thrombocytopenia	1
Smoking	1
Ophthalmic nerve	1
Coronary heart disease	1
Pollutant intake	1
Use of medical facilities	1
Genetics	1
Teenage pregnancy	1
Cytomegalovirus infection	1
Hepatitis B	1
Hepatitis A	1

Table 2. Outcomes by Grouping

Outcomes	No.	Subtotal
Mental and neurological illness	18	60
Intelligence	12	
Development	4	
Neurodevelopment	6	
Behavior	8	
Antisocial behavior	5	
Autism	3	
Attention Deficit Hyperactivity Disorder (ADHD)	2	
Epilepsy	2	
Asthma	13	33
Allergies	11	
Respiratory symptoms	9	
Weight	23	23
Health	16	21
Growth	5	
Blood pressure	5	
Biochemistry	6	
Mother-to-child HIV infection	6	
Socioeconomic status	2	
Diameter of retinal blood vessels	3	
Diabetes	3	
Accidents	3	
Infectious disease	3	
Survival	3	
Leukemia	2	
Sex characteristics	2	
Eczema	2	
Teeth	2	
Eyesight	2	
Healthcare	2	
Brachial plexus palsy	1	
Nasal congestion	1	
Pneumonia	1	
Pain	1	
Middle ear infection	1	
Physiology	1	
Sleep disorder	1	
Nephritis	1	
Heart attack	1	
Food intake	1	
Diet	1	
Digestive disease	1	
Infectious digestive disease	1	
Menarche age	1	
Plagiocephaly	1	
Adipose tissue	1	
Melanoma	1	
Cleft palate	1	
Thrombocytopenia	1	
Smoking	1	
Ophthalmic nerve	1	
Coronary heart disease	1	
Pollutant intake	1	
Use of medical facilities	1	
Genetics	1	
Teenage pregnancy	1	
Cytomegalovirus infection	1	
Hepatitis B	1	
Hepatitis A	1	

Note: Table 3-1 lists outcomes by order of frequency. Table 3-2 groups similar outcomes, and lists the outcomes by grouping order. Both tables use identical data.

4. Types of Exposures Studied in Scientific Papers

The charts below summarize the types of exposures studied in the 290 scientific papers that were published on MEDLINE from January–September 2007 (Fig. 2).

Table 3. Type of Exposures

Exposures	No.
Birth weight	19
General exposures	16
Parents' smoking	9
Economic status	8
Maturity at birth	8
Breast milk	6
Genetics*	5
Medical treatment	5
Vaccination	4
Mental and neurological illness	4
Allergens*	4
HIV	3
Antibiotics	3
Weight	3
Comprehension	3
Ethnicity	3
Virus infection*	2
Home environment	2
No. of children	2
Medical treatment	2
Father's education	2
Father's weight	2
Feeding behavior	2
Weight, height	
Intelligence	2
Mother's age	
Intelligence	2
Mother's age	2
Hepatitis A vaccine	1
Intracytoplasmic sperm injection (ICSI)	1
Immunoglobulin E (IgE)*	1
In vitro fertilization (IVF)	1
Bullying	1
Care	1
Tobacco, alcohol	1
Tobacco, alcohol, coffee	1
Dexamethasone	1
Television viewing	1
Cats	1
Homocysteine*	1
Leptins, etc.*	1
Period of vaccination	1
Perineal sensation	1
Ocular tension	1
Bronchopulmonary dysplasia	1
Weight of siblings	1
Blood pressure	1
Language ability	1
Respiratory disease	1
Thyroid hormones	1
Behavior	1
Fatty acid intake	1

Exposures	No.
Amblyopia	1
Perinatal events	1
Growth spurts after birth	1
Delayed fetal development	1
Impairments	1
Superior vena cava (SVC) flow	1
Humerus growth	1
Diet concerns	1
Parents' age	1
Parent–child relationship	1
Hydronephrosis	1
Sexual abuse	1
Growth stimulation	1
Biochemistry	1
Place of birth	1
Congenital anomalies	1
Twins	1
Fetal brain sparing	1
Placenta anomalies	1
Air pollution*	1
Cerebral cortex growth	1
Cannabis	1
Dehydration symptoms	1
Long gestation period	1
Cesarean birth	1
Violence against dependent's mother	1
Tachypnea	1
Infertility treatment	1
Father's criminal history	1
Welfare status	1
Mother's alcohol intake	1
Care provided by mother	1
Mother's cocaine use	1
Mother's testosterone level	1
Mother's intake of vitamin supplements	1
Mother's involvement	1
Mother's health	1
Mother's employment status	1
Mother's difficulties	1
Mother's menarche age	1
Mother's diet	1
Mother's mental condition	1
Mother's obesity	1
Breastfeeding	1
Organophosphorous pesticides	1
Childhood allergic rhinitis	1
Childhood respiratory disease	1
Childhood middle ear infection	1
Adoption	1
Asthma	1

Many of the exposure values are obtained from responses to questionnaires. The table below lists exposures that require chemical analysis of biological or environmental samples in order to obtain exposure values.

Table 4. Exposures Requiring Measurement by Chemical Analysis

Exposures	Medium	Items Measured
Genetic	Blood, urine	TCF7L2 rs7903146 T allele IL13 polymorphism Interleukin-1 receptor antagonist (IL1RN) polymorphism Integrin beta 3 genotype (SNPs in ITGB3) Haplotype of SFTPA
Allergens	Dust	Dust mite, grass allergen Bacterial endotoxin, beta (1,3)-glucans and fungal extracellular polysaccharides (EPS) (dust) Endotoxin and allergen exposures (dust) Dust mite allergen and endotoxin
Virus	Blood Feces	Human parechovirus 1 (HPeV1) Rotavirus infections by G12 strains
IgE	Blood	IgE
Homocysteine	Maternal blood	Homocysteine
Leptin, etc.	Blood	Glucose, insulin, and leptin concentrations
Fatty acids	Blood	Omega-3 / omega-6 fatty acids
Air pollutants	Air	Nitrogen dioxide PM(2.5), particles with a 50% cut-off aerodynamic diameter of 2.5 μm and soot
Organophosphorous pesticides	Urine (mother, child) Urine (mother)	Six nonspecific dialkylphosphate (DAP) metabolites Metabolites specific to malathion (MDA) and chlorpyrifos (TCPy)

Reference F

FY2008 Ministry of Environment Proposed Budget: Overview of Major New Budgetary Items

Study to Examine Risk Assessments of Vulnerabilities in Children

¥146 million (FY2007: ¥83 million)

Office of Environment Impact Assessment Review,
Environmental Health and Safety Division,
Environmental Health Department

1. Overview of Study

There is growing concern today that environmental risks for children are increasing, as international attention focuses on children's environmental health. In August 2006, the Advisory Commission for Children's Environmental Health recommended that Japan should implement initiatives for risk assessment of children's environmental health, through measures such as preparing a research base and promoting research concerning children's environmental health.

The pressing tasks in the future are to implement a birth cohort (tracking) study for epidemiological study to identify environmental factors that affect children's development, and establish a framework for risk management. Toward this end, examination of the study methodology should begin in FY2008 and the study should be initiated in FY2010. Accordingly, Japan will implement proposals and promote initiatives for appropriate assessment and management of environmental risks in order to achieve a healthy environment for the development of the next generation of children.

2. Project Plan (Starting from FY2003)

- Prepare a research base (by assembling research groups, developing human resources, collecting scientific knowledge, and becoming aware of trends in international research)
- Promote critical research projects

  (1) Develop methodologies for assessment of children's exposures to environmental pollutants

  (2) Develop methodologies for assessment of health effects, focusing on sensitivity factors among children

  (3) Conduct epidemiological study of relationships between children's environment and health

  Conduct a feasibility study to examine methodologies for epidemiological study, beginning in FY2008

  Launch a birth cohort (tracking) study for epidemiological study, beginning in FY2010

  (4) Undertake children's exposure assessments, biomarker development, and sample banking

(5) Conduct social science research into welfare policies for children's environmental health

(6) Conduct practical research concerning risk communication for children's environmental health

3. Benefits of Policy Measures

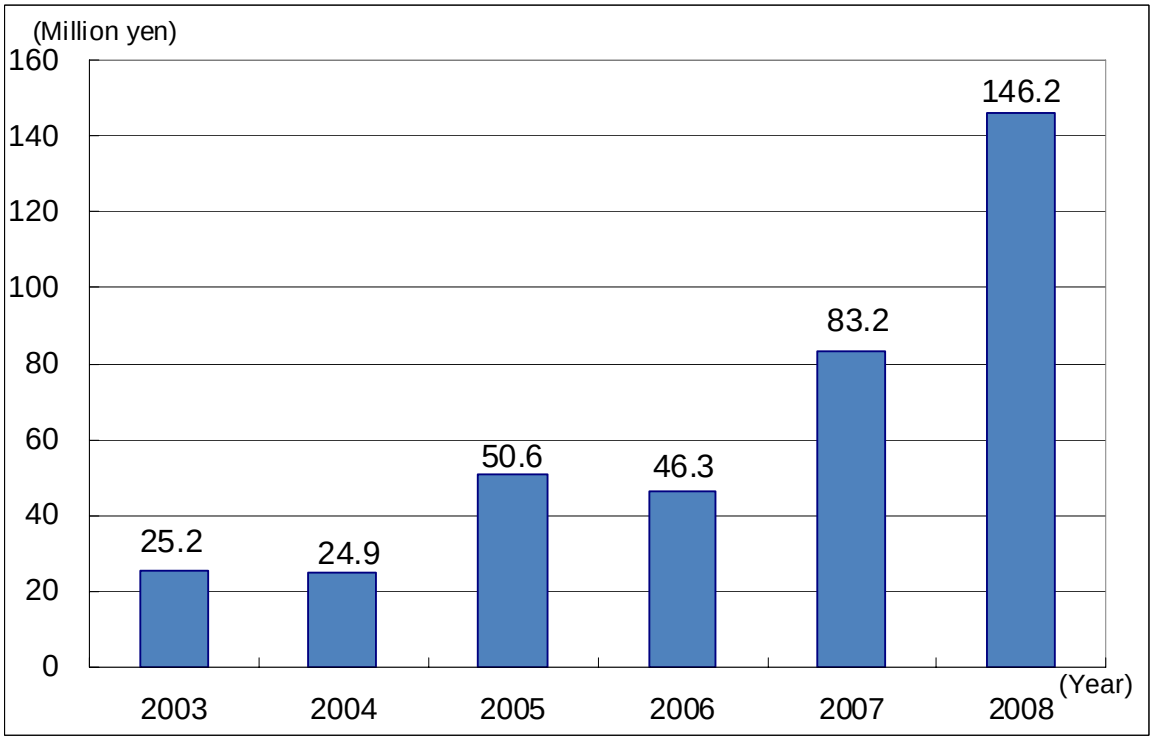
- Promote environmental risk assessments of chemical substances, focusing on exposures and vulnerabilities specific to children
- Implement environmental risk management based on appropriate assessment of environmental risks
- Achieve a healthy environment for the development of the next generation of children

4. Notes

Honorariums, committee travel expenses:	¥1.365 million
(Description: Expenses for convening panel to study risk assessments)	
Study expenses	¥144.856 million
Convening of symposium	¥5.009 million
Epidemiological study of relationship between children's environment and health	¥135.747 million
Research into welfare policies and risk communication	¥4.100 million

Reference G

Annual Budget for Study to Examine Risk Assessments of Vulnerabilities in Children



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Report on European Children's and Birth Cohort Studies, Part A Study Precedents

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1. European Child Cohort Studies Survey Summary

Survey Panel

Manabu, Hasegawa	Ministry of the Environment
Fujio, Kayama	Jichi Medical University
Rie, Masho	Center for Environmental Information Science
Motoyuki, Yuasa	Hokkaido University

Period of Survey

November 4–14, 2007

Purpose of Survey

To obtain an understanding of cohort precedents from other countries, as part of the planning and review process for Japan to implement a children's and birth cohort, with a particular focus on gaining an awareness of the status of large-scale birth cohorts implemented as national projects. The survey panel will also seek to identify important technical considerations through interviews with persons involved in maintaining and managing cohorts, and who are engaged in other cohort tasks such as collection and storage of data and biological samples.

In addition, the survey panel will interview a medical officer in charge of children's environmental health from the World Health Organization (WHO), in order to understand WHO's initiatives in this area.

Studies Surveyed in Person

The scope of the survey focuses on large-scale birth cohorts with a sample size of 100,000 or more subjects that were conducted by Norway and Denmark. These studies were chosen in order to understand the circumstances that led to the establishment of a large-scale birth cohort implemented at the national level, and to grasp their current status. Also included in the scope of candidate studies were birth cohorts by hospitals and researchers that are comparatively large in scale and involved the taking and storage of biological samples. Of the candidate studies, the actual investigation abroad was restricted to studies that agreed to receive a visit from the survey panel and whose schedule permitted a visit during the investigative trip to Europe. The survey panel was aware of other cohort studies in the United States and Australia and in other parts of Europe that could have been included in the scope of the study, but time and expense considerations prevented the survey panel from scheduling visits to these studies.

The actual studies that were surveyed in person were, in chronological order of visit, as follows:

A. Generation R Study
Erasmus University Rotterdam (Hospital-Based)

Cohort Name:	Generation R
Principal investigator:	Albert Hofman Department of Epidemiology & Biostatistics, Erasmus Medical Center Erasmus University
Website:	http://www.generationr.nl

B. Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study
Utrecht University (Researcher-Based Cohort)

Cohort name:	PIAMA
Principal investigator:	Bert Brunekreef The Institute for Risk Assessment Sciences (IRAS) Centre for Prevention and Health Services Research Utrecht University
Website:	None

C. The Norwegian Mother and Child Cohort Study (MoBa)
Norwegian Institute of Public Health (National Cohort)

Cohort name:	The Norwegian Mother and Child Cohort Study
Principal investigator:	Per Magnus Norwegian Institute of Public Health Division of Epidemiology
Website:	http://www.fhi.no/tema/morogbarn

D. Danish National Birth Cohort: Better Health for Mother and Child (BSMB) Study
Danish State Serum Institute (National Cohort)

Cohort name:	Bedre sundhed for mor og barn
Principal investigator:	Mads Melbye Statens Seruminstitut
Website:	http://www.bsmb.dk

E. Children's Environmental Health
World Health Organization (WHO)

Medical Officer:	Dr. Jenny Pronczuk Public Health and Environment, World Health Organization
Website:	http://www.who.int/ceh/en/

2. Study Results

2-1. Types of Cohorts and Study Characteristics

A. National Cohort—The Norwegian Mother and Child Cohort Study (MoBa)

B. National Cohort—Danish National Birth Cohort: Better Health for Mother and Child (BSMB) Study

The characteristics of the large-scale national birth cohort studies conducted by Norway and Denmark are summarized below.

Social Background

- Norway has a population of 4,698,000. The total fertility rate is 1.80 with 56,000 births per year (UN survey, 2000–2005).
- Denmark has a population of 5,442,000. The total fertility rate is 1.76 with 65,000 births per year (UN survey, 2000–2005).

The majority of people in both countries are registered with general practitioners (GPs) who are supported through a publicly funded health care system. GPs receive public funds based on the number of registered patients they have and the actual treatment they provide. There is no cost to the patient for medical care related to childbirth. When a woman is pregnant, she is diagnosed by her GP, who refers her to a midwife. Almost all births take place in a hospital. Various registry systems such as for birth, medical care, and hospital discharges have been established through legislation. The registry system for hospital discharges is currently being prepared.

Advantages for Study Subjects

Subjects who join the study are entered for a chance to win prizes in drawings. Subjects also gain satisfaction from knowing that they are contributing to health policies that will improve the health of future children. (Data are not returned to subjects.)

Framework of Cohort Study

- Cohort size: 90,000 subjects for MoBa Study (1999 to September 2007), and 101,042 subjects for BSMB Study (1997–2002).
- Recruitment of subjects: For the MoBa Study, pregnant women who scheduled an ultrasound examination were mailed an application package (with questionnaire and consent form) inviting them to participate in the cohort. For the BSMB Study, pregnant women who were diagnosed as being pregnant by their GP received an application package from the GP inviting them to participate in the cohort.
- Biological samples: Maternal blood samples were taken by a GP during routine checkups, which were then sent to the study center by GPs. Umbilical cord blood samples were taken at birth at hospitals and were sent to the study center by hospitals.
- Survey forms (consent forms): Mothers sent their consent forms to the study centers. For the MoBa Study, the children themselves were notified upon reaching 15 years of age, and were required to fill out their own consent form at 18 years of age. The BSMB Study is

designed to keep data and conduct follow-up study using registries until the child reaches 20 years of age.

- Study centers: All survey forms and biological samples were comprehensively managed by a central institution (Norwegian Institute of Public Health and Danish State Serum Institute respectively). Phone inquiries from study subjects were also handled by the central institution.
- Scientific study projects: Researchers and other parties can apply for access to the data and samples, subject to review of the application.

C. Hospital-Based Cohort—Generation R Study

The characteristics of the hospital-based birth cohort conducted by the Erasmus University Medical Center of the Netherlands are summarized below.

Social Background

The Netherlands has a population of 16,419,000 (UN survey, 2007). The total fertility rate is 1.73 with 199,000 births per year (UN survey, 2000–2005). National health care basically covers all costs related to birth. When it is discovered that a woman is pregnant, the family doctor refers the woman to a local midwife center, where pregnant women receive advice and routine checkups. Childbirth typically takes place at the home, with the assistance of a midwife.

The cohort target area was Rotterdam, which has a population of approximately 600,000 including a sizable population of immigrants. (Only 56% of the population in the target area are of Dutch origin). There are 4,300 births per year in Rotterdam.

Advantages for Subjects

Subjects are informed of the overall status of the cohort through newsletters, symposiums, and other avenues. Children receive a birthday gift when turning 5 years of age. In addition, subjects receive various giveaways that are provided by sponsors of the study, such as discount coupons for amusement facilities. Subjects also gain the satisfaction of knowing that they are contributing to health policies that will improve the health of future children.

Subjects who choose to take part in the focus cohort are referred to a specialist if their tests reveal any irregularities.

Framework of Cohort Study

- Cohort size: 9,778 including 1,232 subjects for the focus cohort (2002–2006).
- Recruitment of subjects: Recruitment was concentrated on women from the target study area who became pregnant during the study period and visited a midwife or obstetrician. These women received a Generation R Study information package from the midwife or physician. The study staff then contacted the pregnant women by phone in order to have them fill out a consent form at the first ultrasound examination. Subjects were asked to fill out written consent forms leading up to each of four study phases (at birth, 1–4 years of

age, 4–12 years of age, and 12–20 years of age). Fathers were recruited for the study (for questionnaires and blood samples) through the mothers.

- Focus cohort: Of the subjects in the regular study, subjects born to two generations of Dutch-born citizens (parents and grandparents, on both the maternal and paternal side) were recruited for a focus cohort prior to postnatal week 25.
- Biological samples: Blood and urine samples were taken during routine checkups.
- Survey forms: Forms were sent to mothers by postal mail.
- Study centers: The contact center for subjects was the Generation R Study office within the Erasmus University Medical Center. A Generation R Study examination room was established within the Sophia Children's Hospital and equipped with facilities for performing ultrasound examination, taking blood samples, and testing for sinus infections. A behavioral observation room for children was also established and equipped with one-way mirrors and video cameras.

  Measurements were taken at two centers.

  Storage and analysis of samples is performed at the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR), Rotterdam Medical Diagnostic Center.
- Scientific study projects: Projects are conducted by researchers and graduate students from the university. Joint research is also conducted with researchers from outside the university.

D. Research-Based Cohort—Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study

The characteristics of the birth cohort conducted by researchers from Utrecht University of the Netherlands are summarized below.

Social Background

Same as for BSMB Study.

Advantages for Subjects

Parents with concerns about allergies and asthma gain the reassurance of having these aspects investigated from participating in the study. Subjects also receive a newsletter and a gift on their child's birth. In addition, subjects gain the satisfaction of knowing that they are contributing to promoting better health for future children.

Framework of Cohort Study

- Cohort size: 4,146 including 855 subjects for intervention study (1996–1997). Subjects are tracked for at least 8 years.
- Recruitment of subjects: Subjects were recruited from throughout the Netherlands by midwives. Participation started from the third month of pregnancy.
- Intervention study: Involved a double-blind test using mite-impermeable bedding (mattress and pillow covers) and placebos (standard cotton bedding).

- Biological samples: Heel-prick blood (for phenylketonuria screening), venous blood, and DNA of parents and children.
- Environmental exposures: Analysis of indoor dust and assessment of exposures from nearby roads.
- Survey forms: Forms were filled out by subjects.
- Study centers: The study was mainly implemented by the Institute for Risk Assessment Sciences of Utrecht University and the Netherlands' National Institute of Public Health and the Environment (RIVM), with the cooperation of university hospitals (Utrecht University, University of Groningen and Erasmus University, Rotterdam) and Sanquin Research of Amsterdam.
- Scientific study projects: Projects are conducted by researchers and graduate students of the cooperating institutions.

2-2. Cohort Study Design and Status

A. The Norwegian Mother and Child Cohort Study (MoBa)

Purpose

To collect as much data as possible concerning exposures and health outcomes, in order to respond to hypotheses that may arise in the future. The study is not aimed at proving specific etiological hypotheses.

Statistical Premise

No basis was given for specific hypotheses.

Table 1
Examples of exposures and health outcomes to be investigated in the Norwegian Mother and Child Cohort Study.

Examples of exposures	Examples of diseases
Medication	Pelvic pain
Hereditary factors	Congenital malformations
Infections	Stillbirth
Dietary factors	Premature birth
Environmental toxins	Cancer
Physical activity	Diabetes
Work situation	Asthma/allergy
Occupational hazards	Rheumatism
Interpersonal relationships	Depression
Personal habits	Breast cancer

Source: Protocol—the Norwegian Mother and Child Cohort Study

Recruitment of Subjects

Recruitment was concentrated on pregnant women who scheduled an ultrasound examination at hospitals or clinics that met the criteria of handling at least 100 childbirths annually. The women were mailed an invitation to participate in the study that also included a brochure, consent form, first questionnaire, and paternal questionnaire.

Profile of Subjects

All births in the Netherlands were eligible for the study. Invitations were sent at each pregnancy, with a 42.7% rate of return. The participation rate was 45% among those recruited. At postnatal 18 months, the interview response rate was 77%.

Data Collection

Mailed Questionnaires:

- The study was conducted by mailing questionnaires at the following stages:
  - 13–17th week of pregnancy (questions about previous outcomes of pregnancy, history of medication and medical treatment, occupation, exposures in workplace and home, lifestyle and habits, and mental condition)
  - 22nd week of pregnancy (frequency of food intake)
  - 30th week of pregnancy (health condition during pregnancy, changes in lifestyle and occupation)
  - Postnatal 6 months (health and nutritional status of child, status of mother's physical and mental health),
  - Postnatal 18 months (status of child's development),
  - 3 years (status of child's development),
  - 7 years (to be implemented)
- The paternal questionnaire contained questions about the father's workplace exposures, lifestyle, and clinical history.
- The survey forms were automatically tabulated by scanning.
- The survey forms to be used at 7 years of age are currently being prepared, with an option for respondents to choose from a mailed written survey or an online survey.

Dietary Survey

The frequency of food intake was studied through the questionnaire at the 22nd week of pregnancy.

Biological Samples

Blood samples were taken at the time of ultrasound examination (17th week) for women who had already mailed in their consent forms. Paternal blood samples were also taken if the father attended the examination and consented to giving a sample. The mother's consent form was filled out at this time if it was not already mailed in. Maternal and umbilical cord blood samples were taken at birth. Blood and DNA samples are stored at the Norwegian

Institute of Public Health and preserved at temperatures of −85°C and −25°C, respectively. Blood samples were dispensed in multi-well trays.

Information from Registries

Registry information for childbirth, medication, cancer, cause of death, and immunizations can be accessed. Norway is also preparing a patient discharge registry, whose information can eventually be linked.

Information Management

All working information was managed for each pregnancy using an Oracle database. The database is also linked to the registries.

B. Danish National Birth Cohort: Better Health for Mother and Child (BSMB) Study

Purpose

To learn about childhood disease and fetal development and their determinants from the perspective of complications at pregnancy and early exposures. The study places a particular emphasis on learning about the impacts of medication and infectious disease. The scope of the study covers all diseases that could be due to fetal exposures affecting childhood and beyond. The study establishes both a medication database and a biobank.

Statistical Premise

Table I. *Smallest detectable relative risk (RR) in a case-control analysis nested within the cohort, using four controls per case*[a]

		Exposure prevalence among controls		
Expected cases	Outcome	10% RR	5% RR	1% RR
3,400	All congenital malformations	1.14	1.25	1.60
560	Genital malformations	1.5	1.7	2.7
150	Facial clefts	2.1	2.5	5.0
220	All child cancers	1.8	2.2	4.1
55	Leukaemia	3.1	3.9	9.4

The estimates are based on 80% power to detect the indicated relative risk (or higher) at a testing level of 0.05 in a cohort of 100,000 newborns.
[a]*Sources*: Sundhedsstyrelsen Sundhedsstatistik 1999: 3 and Basso et al. Am J Epidemiol 1999; 150: 598–604.

Source: Scand. J. Public Health 29 300-307. 2001.

Recruitment of Subjects

Ninety-five percent of female subjects received an application package from a GP inviting them to participate in the cohort study, at the time of receiving a medical examination from a GP for pregnancy diagnosis (6–12th week of pregnancy). The remainder of the female subjects received an application package from a midwife.

Profile of Subjects

Recruitment was concentrated on all pregnant women who visited a GP and intended to carry through with their pregnancy, and who possessed an adequate knowledge of the Danish language. The participation rate was approximately 30% among those recruited. At postnatal 18 months, the interview response rate was 75%.

Data Collection

Phone Interviews

Computer-assisted phone interviews were conducted at four stages in order to collect information not recorded in medical histories. The four stages and average duration of phone interviews were as follows: 12th week of pregnancy (18 minutes), 30th week of pregnancy (10 minutes), postnatal 6 months (16 minutes), and postnatal 18 months (10 minutes).

Dietary Survey

Survey forms were sent to all subjects at the 25th–26th week of pregnancy, containing questions about intake of supplements and diet during the previous month. The survey forms were automatically tabulated by scanning.

Social and Occupational Status

Data concerning social and occupational status were obtained from registries.

Air Quality, Drinking Water Quality

Associations with air quality and drinking water quality can be analyzed based on address data.

Biological Samples

Maternal blood samples were taken by a GP during routine checkups conducted at the 6th, 12th, and 24th weeks of pregnancy. Whole blood samples were mixed with EDTA and sent to the study center by standard postal mail. Umbilical cord blood samples were taken immediately after birth at the hospital by a midwife or nurse and were kept in refrigerated storage until they were sent by standard postal mail.

When blood samples were received by the Danish State Serum Institute, four whole blood spots are put on filter paper. The blood sample is then separated. Plasma and buffy coats are put into liquid nitrogen and in freezers at −20°C.

Information Management

All working information is managed by computer and consists of interview schedules, deadlines for mailing letters, addresses, phone numbers, and changes to this information. The computing platform is keyed by the participant ID number, and is also linked to biobank and questionnaire data. It can also be linked to registry data based on national ID numbers.

Framework for Implementation

Management Body

Comprises approximately four researchers responsible for implementation of the study.

Steering Committee

Comprises representatives of the Danish National Research Foundation, National Board of Health, Danish State Serum Institute, county governments, and midwives organizations. The project leader is Jorn Olsen.

Advisory Board

Comprises representatives of professional organizations for midwives, GPs, obstetricians, pediatricians, child nurses, and a member from a parenthood organization.

C. Generation R Study

Purpose

To identify environmental and genetic factors that impact development and health from the fetal period through adolescence. The study has four main areas of focus: (1) Growth and physical development, (2) behavior and development of cognitive skills, (3) childhood illness, and (4) health status and health management of pregnant women and children.

The major purposes of the study are as follows:

- Record growth from fetal period through adolescence
- Identify biological, environmental, and social factors that have an impact on growth from the fetal period through adolescence
- Verify the effectiveness of current methodologies for early identification and prevention of high-risk groups

Statistical Premise

No premise is provided for concrete hypotheses. The general discourse is as follows:

Table 9. Effects sizes in standard deviation that minimally can be detected according to the prevalence of the exposure

Proportion exposed (%)	Whole cohort (n = 7000)	Focus cohort (n = 700)
50	0.067	0.212
25	0.077	0.276
10	0.112	0.353
5	0.154	0.486
1	0.337	1.064

The presented effect sizes are detectable proportions of the standard deviation with a type I error of 5% and a type II error of 20% (power 80%).

Table 10. Relative risks that minimally can be detected according to the prevalence of the exposure

	Incidence (1 year) of outcome of interest					
	Whole cohort (n = 7000)			Focus cohort (n = 700)		
Proportion exposed (%)	10%	5%	1%	10%	5%	1%
50	1.23	1.33	1.83	1.83	2.28	4.94
25	1.26	1.38	1.94	1.96	2.46	5.41
10	1.39	1.56	2.42	2.48	3.26	7.92
5	1.55	1.80	3.09	3.20	4.39	11.74
1	2.36	3.04	6.83	7.75	11.61	37.55

The presented effect sizes are detectable relative risks with a type I error of 5% and a type II error of 20% (power 80%).

Source: European Journal of Epidemiology 21, 475-484. 2006.

Recruitment of Subjects

Pregnant women received a Generation R Study information package from a midwife or physician. Study staff then contacted the pregnant women by phone and interviewed the women at the first ultrasound examination in order to have them fill out a consent form. Fathers were indirectly recruited for the study (questionnaires and blood samples) through the mothers. The participation rate among pregnant women (prior to birth) was 91%.

Profile of Subjects

Recruitment was concentrated on individuals who were residents of the target study area (Rotterdam) at the time of giving birth, and who gave birth during the period of the study between April 2002 and January 2006. The study sought to recruit subjects during early pregnancy, but pregnant women were also recruited up until the time of birth. The participation rate was 61% among those recruited.

Data Collection

Medical Examinations

- The study sought to learn the health status of mothers through three sets of medical examinations conducted in early (for subjects who joined in early pregnancy), mid-, and late pregnancy.

- Children's growth was recorded through ultrasound examination at each routine checkup and by collecting information from examinations conducted at birth. Additional information is currently being collected from physical examinations, questionnaires, and routine checkups conducted through 4 years of age. For the focus cohort, additional ultrasound examinations (to measure brain, heart and kidney development) were conducted as well as taking biological samples (blood and saliva).
- At 5 years of age, a session lasting from 2.5 to 3 hours is implemented for ultrasound examination and behavioral observation, and for taking biological samples (saliva, mucous, etc.).

Questionnaires

Information was collected through questionnaires sent by postal mail. Subjects who joined in early pregnancy were sent separate questionnaires at the 12th, 15th, 20th, and 30th weeks of pregnancy.

Complications During Pregnancy, Pregnancy Outcomes

A coding system was used to classify complications and outcomes from hospital and midwife records.

Information on Paternal Exposures

Information was collected through medical examinations and questionnaires for the fathers. Biological samples (blood) were also taken.

Dietary Survey

The survey forms included questions about the mother and child's diet.

Biological Samples

- Maternal blood samples were taken in early pregnancy (35 ml) and mid-pregnancy (20 ml). Paternal blood samples were taken prior to birth (10 ml). The plasma and serum volume were distributed into 250 μl aliquots and stored at −80°C. DNA was extracted from buffy coat and stored leukocytes.
- Children's DNA was extracted from umbilical cord blood. DNA was supplemented by obtaining mucous samples from the cheek after birth.
- Samples of maternal urine were taken only during the period from February 2004 to November 2005. The samples have been stored.

Table 1. Main outcomes per research area

Growth and physical development
Fetal growth patterns and organ development
Pregnancy complications
Postnatal growth patterns
Obesity
Risk factors for development of cardiovascular disease
Risk factors for type 2 diabetes
Behavior and cognitive development
Maternal and paternal psychopathology
Fetal and postnatal brain development
Behavior, psychopathology and cognition
Neuromotor development
Chronic pain
Attachment
Stress reactivity
Diseases in childhood
Infectious diseases in childhood
Development of the immune system
Asthma and asthma related symptoms
Paroxysmal neurological disorders
Health and healthcare
Quality of life
Health care utilization
Effectiveness of screening programs

Table 2. Main determinants

Biological determinants
Parental anthropometrics and blood pressure
Fetal and postnatal growth characteristics
Endocrine and immunological factors
Genetic variants
Environmental determinants
Maternal and childhood diet
Parental life style habits (including smoking, alcohol consumption)
Housing conditions
Social determinants
Parental education, employment status and household income
Parental marital status
Ethnicity

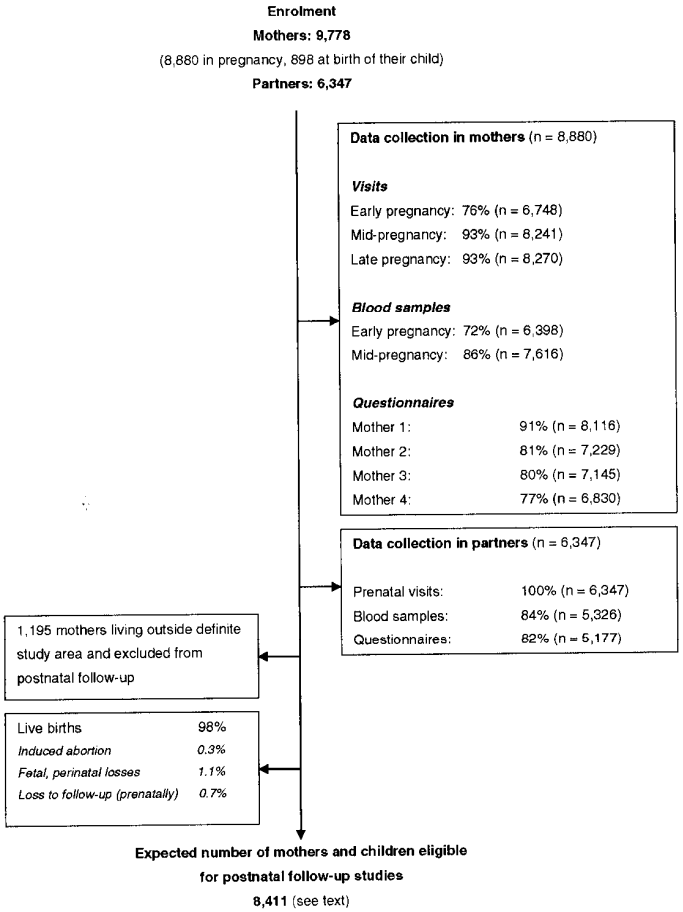


Figure 2. Participant enrolment and measurements in the first phase.

Table 3. Assessments in the prenatal phase

Assessments in mothers
Physical examinations: height, weight, blood pressure
Questionnaires: socio-economic status, ethnicity, housing, living conditions, diet, medical history, family history, drug use, life style habits, use of medical services
Interviews: expectations of parents to be (only in focus cohort)
Biological samples: blood and urine samples (storage, DNA)
Fetal ultrasounds: gestational age, fetal growth and in the focus cohort fetal brain, heart and kidney development, fetal blood flow distribution and placental function
Assessments in partners
Physical examinations: height, weight, blood pressure
Questionnaires: socio-economic status, ethnicity, housing, living conditions, medical history, family history, drug use, life style habits,
Use of medical services
Interviews: expectations of parents to be (only in focus cohort)
Biological samples: blood samples (storage, DNA)
Assessments in newborns at birth
Physical examinations: weight
Cord blood sample (storage, DNA)

Table 4. Assessments in mothers, their partners and their children in the prenatal phase

	Early pregnancy	Mid-pregnancy	Late pregnancy	Birth
Mother				
Physical examination	+	+	+	
Questionnaire	+	+	+	
Interview			F	
Fetal ultrasound examination	+	+	+	
Additional detailed fetal ultrasound			F	
Blood sample	+	+		
Urine sample	+	+	+	
Partner				
Physical examination	+			
Questionnaire		+		
Interview			F	
Blood sample	+			
Child				
Physical examination				+
Cord blood sample				+

+ = Assessment in whole cohort.
F = assessment only in focus cohort.
Early pregnancy: gestational age < 18 weeks; mid-pregnancy: gestational age 18–25 weeks; late pregnancy: gestational age ≥25 weeks.

Source: European Journal of Epidemiology 21, 475-484. 2006.

Environmental Exposures

A geographic information system (GIS) was used to obtain the distance from roads using address data. This was combined with models for dispersion of noise and pollutants, in order to analyze the association between exposures from vehicle traffic and the impact on health.

Information Management

Subjects were assigned a unique code for management of study data and other information. Data were stored in a separate database from the personal information database.

Framework for Implementation

Measurements were taken at two centers.

Storage and analysis of biological samples is performed at the STAR, Rotterdam medical diagnosis center.

Research based on the cohort is conducted by a number of teams from the Erasmus University Medical Center, with the cooperation of Erasmus University and the Public Health Service of the Rotterdam Region. Outside requests for research are reviewed by the Generation R Study Research and Management Group, and the ethical committee of the Erasmus University Medical Center.

D. Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Study

Purpose

To study the effect of reductions in allergens on childhood development of asthma, by recruiting mothers with allergic anamnesis and conducting a double-blind test of their children involving the use of mite-impermeable bedding. Also, to evaluate the role of environmental and dietary risk factors in relation to childhood development of allergic diseases, by recruiting mothers with and without allergic anamnesis and observing the development of asthma in their children.

Statistical Premise

Of the placebo group, 50% of subjects developed allergies until 8 years of age. It was postulated that treatment through the use of mite-impermeable bedding would have a 1.5-fold effect on reducing the development of allergies, lowering the rate of developing allergies to 33%. In order to detect these effects, it was determined that at least 200 subjects were needed in each group. Consequently, the design of the study enabled a statistical tolerance of up to 50% variation without bias.

Recruitment of Subjects

Questionnaires were distributed for screening purposes at approximately 50 prenatal health clinics (altogether handling roughly 12,000 births per year). The questionnaires were distributed by midwives at the first prenatal examination. The total number of usable returns was 10,232 (out of 10,819 responses), of which 2,949 persons were found to match the criteria of atopic mothers, for a rate of 28.8% of all usable returns. Of this group, 1,986 persons were invited to participate in the intervention study and 965 persons were invited to participate in the follow-up study. The rate of consent for participating in the study was 42% (855 persons) and 49% (472 persons), respectively, in the intervention study and follow-up study. Of the 5,084 persons who matched the criteria of non-atopic mothers, 55% (2,819 persons) consented to participate. Participation in the cohort took place in the third month of pregnancy.

Profile of Subjects

Recruitment was concentrated on individuals who were residents of the target study area at the time of giving birth, and who gave birth during the period of study between the summer of 1996 and fall of 1997. The rate of ongoing participation was high, at greater than 90% at 3 years of age. The dropout rate was slightly higher in the intervention study group, which is thought to be related to the higher demands for subjects in the intervention study. One of the reasons for the high rate of ongoing participation overall is due to the study's emphasis on requiring long-term cooperation from subjects. This point was stressed at the time of recruitment, and individuals were advised not to participate if they could not fulfill the long-term obligation.

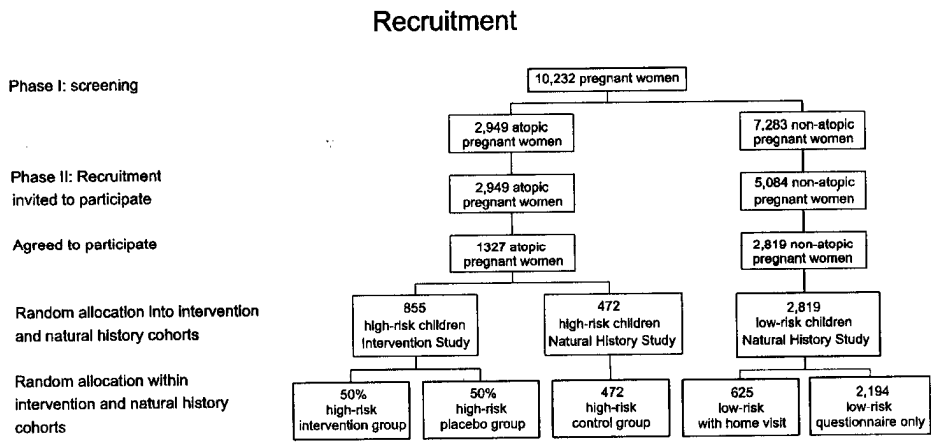


Fig. 2. The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) recruitment scheme.

Source: Brunekreef B. et al, (2002) The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study: Design and first results. Pediatr. Allergy Immunol 2002: 13 (Suppl. 15): 55-60.

- Recruited: 3291
- entry questionnaire: 3289
- 3 months q sent: 3283
- 3 months q rec'd: 3174
- 1 yr q sent: 3243
- 1 yr q received: 3029
- 2 yr q sent: 3167
- 2 yr q received: 3053

- definitely lost: 8
- definitely lost: 40 (+8=48)
- definitely lost: 76 (+48=124)

Fig. 4. Loss to follow-up in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) 'natural history' cohort.

Source: Brunekreef B. et al, (2002) The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study: Design and first results. Pediatr. Allergy Immunol 2002: 13 (Suppl. 15): 55-60.

Data Collection

Medical Examinations

Medical examinations were implemented by taking venous blood samples for IgE measurement, taking measurements of height and body weight, and checking for atopic inflammation of the skin. Pulmonary functions in the form of peak flow, respiratory NO, and airway resistance (Rint) were also measured.

Records

Records of allergy symptoms and symptoms of respiratory tract infection were obtained from parents until the first year after birth. Records were also kept of medical examinations, diagnosis, treatments, and medications.

Questionnaires

Questionnaires were implemented at each home visit and included questions about the family history of allergies, nutrition, passive smoking, breastfeeding, home situation, and daycare use.

Dietary Survey

Questions about diet were included in the questionnaires.

Biological Samples

Heel-prick blood samples (for phenylketonuria screening) were taken from the intervention study group during a home visit conducted at postnatal 12 months. The samples were subjected to IgE analysis. DNA samples were also taken from parents and children.

Survey Forms

Survey forms were filled out by the subjects.

Table: PIAMA Observation Scheme

Study Population Study Time Frame	Intervention Study Intervention Group	Intervention Study Placebo Group	Natural History Study Atopic control	Natural History Study non-atopic: with home visit	Atopic control non-atopic: Questionnaire only
2 Month before Birth	Questionnaire, Covers, Dust, Visit	Questionnaire, Covers, Dust, Visit	Questionnaire	Questionnaire	Questionnaire
3 Month after Birth	Questionnaire, Dust, Visit	Questionnaire, Dust, Visit	Questionnaire, Dust, Visit	Questionnaire, Dust, Visit	Questionnaire
1 Year after Birth	Questionnaire, Examination, Visit, Dust	Questionnaire, Examination, Visit, Dust	Questionnaire	Questionnaire	Questionnaire
2 Years	Questionnaire	Questionnaire	Questionnaire	Questionnaire	Questionnaire
3 Years	Questionnaire	Questionnaire	Questionnaire	Questionnaire	Questionnaire
4 Years	Questionnaire, Examination, Visit, Dust	Questionnaire, Examination, Visit, Dust	Questionnaire, Examination, Visit, Dust	Questionnaire, Examination, Visit, Dust	Questionnaire
5 Years	Questionnaire	Questionnaire	Questionnaire	Questionnaire	Questionnaire
6 Years	Questionnaire	Questionnaire	Questionnaire	Questionnaire	Questionnaire
7 Years	Questionnaire	Questionnaire	Questionnaire	Questionnaire	Questionnaire
8 Years End of Study	Questionnaire, Examination	Questionnaire, Examination	Questionnaire, Examination	Questionnaire, Examination	Questionnaire, Examination

Source: Fig. 3 The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) observation scheme. Brunekreef B. et al, (2002) The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study: Design and first results. Pediatr. Allergy Immunol 2002: 13 (Suppl. 15): 55-60.

Environmental Exposures

Dust Samples

For the intervention study group, dust samples were obtained from floors and mattresses during home visits conducted prior to birth and at 3 and 6 months after birth. For the follow-up study group, dust samples were obtained from floors and mattresses during home visits, but at one-third of the frequency (taken at 3 months after birth only).

Use of Geographic Information System

A geographic information system (GIS) was used for assessment of environmental exposures (distance from nearby roads).

Use of Registries

Information about medications dispensed by pharmacies was accessed from registries.

Table: Strengths and Limitations of PIAMA Study Topics

Topic	Strength	Limitation
• Diet and physical activity	• Included in questionnaire	• Not validated
• Environmental exposures: home characteristics, pets, combustion products, siblings, daycare, passive smoking	• Includes passive smoking Validated Rest: used frequently	
• Circumstances of birth	• Registered during check-up	
• Respiratory and eczema ISAAC	• Validated for 7-12 years of age Standardized Worldwide application	• Not validated at early age Longitudinality not validated "Too European?"
• Respiratory, allergy, and eczema in parents and siblings ISAAC and European Community Respiratory Health Survey	• Validated and standardized	
• Other: quality of life, health services use, and so on		

Source: National Children's Study Workshop Methods for the Assessment of Asthma-Related Health Outcomes. May 27–28, 2004. Rosen Centre Hotel Orlando, FL
http://www.nationalchildrensstudy.gov/events/ncs_assembly/2004_May/Asthma-outcomes052004.cfm

Framework for Implementation

The study was mainly implemented by the Institute for Risk Assessment Sciences of Utrecht University and the Netherlands' National Institute of Public Health and the Environment (RIVM), with the cooperation of university hospitals (Utrecht University, University of Groningen and Erasmus University, Rotterdam) and Sanquin Research of Amsterdam.

3. Issues for Discussion

3-1. Cohort Design

A. Important Considerations for Cohort Design

At each visit by the survey panel, it was indicated that the cohort design had increased in importance at the present juncture. The panel was therefore advised to publish a research paper on the cohort design in conjunction with launching the cohort.

The survey panel was also advised that it is necessary to spend sufficient time at the design stage to discuss the rationale and logic of the research. In particular, the PIAMA Study staff advised that it is necessary to clearly identify the purposes of the cohort study and information that had to be obtained for these purposes in designing the cohort. The PIAMA Study staff further emphasized that the purposes of the study should not be changed after they are initially established.

Each of the cohort staff advised that there is a tendency from their perspective to seek as much information as possible by increasing the frequency of asking questions and sample-taking and the volume of questions and samples. At the same time, there is a tendency for study subjects to drop out of the study if the demands of the study take up too much time. Since participation tends to decline when cohort staff demand too much from subjects, the cohort design should also consider the reactions of subjects as well as the scientific validity.

Regarding the feasibility of implementing the cohort as it was designed, it was repeatedly stressed that cohort staff should conduct thorough verification and make any adjustments that are needed during the pilot study. Of course, any circumstances that require changes to the cohort design (after the actual study launch) can endanger the feasibility for continuing the cohort. It is therefore necessary to identify all possible issues and carefully consider the countermeasures during the pilot study, while accounting for the differences in scale between the pilot study and actual study.

B. National-Scale Cohorts

Comprehensive, nationwide studies are best conducted as national projects. The national cohort projects implemented by Norway and Denmark both were successful in collecting homogeneous, nationwide data by implementing the same schedule and identical survey forms across their respective countries. The large-scale, nationwide cohorts implemented by Norway and Denmark were also successful because they were comprehensively managed by an independent central institution.

Relating to the discussion below, it is also possible to execute a nationwide cohort by dividing the cohort into geographic regions and establishing study centers in each region, with each study center responsible for starting and managing the cohort. However, this can result in multiple parallel cohorts, so that the overall project ceases to exist as a large-scale cohort. Furthermore, a comprehensive cohort cannot be achieved if the study centers adopt different study designs for their own research purposes.

C. Multicenter Cohorts

In the case of the PIAMA Study, the target study area was spread across three geographically separate regions. A university in each region was responsible for implementing the study in that region under comprehensive design guidelines. The PIAMA cohort staff indicated that there were serious issues with the standardization of various procedures and methodologies, and the cohesiveness of the criteria used for diagnosis. In addition, the PIAMA cohort staff suggested that standardization throughout the cohort could be achieved by adopting an internationally standardized set of diagnosis criteria, if such criteria were available.

The PIAMA cohort staff advised that comparison and cooperation with other cohorts could be better facilitated by adopting a standardized methodology for epidemiological investigation that is used extensively worldwide, such as the International Study of Asthma and Allergies in Childhood (ISAAC), using it also for the contents of questionnaires. Furthermore, it was indicated that in the case of a multicenter cohort, it is important to bring together all field staff responsible for data collection to receive training in one central location.

D. Cohorts and Subcohorts

The Generation R Study was established for the purposes of educational and research institutions, in contrast with the Norwegian and Danish cohorts that were conducted as national projects. At the outset of the Generation R Study, a subcohort comprising around 10% of the overall cohort were chosen as a focus cohort study in order to study supplemental items. One reason for establishing a subcohort was to eliminate possible disparities in child development caused by differences in ethnic background, by focusing on subjects born to two

generations of Dutch-born citizens. In addition, it was decided to designate a single technician to take all measurements, in order to eliminate disparities from having different technicians take ultrasound organ measurements. This decision effectively limited the number of measurements that could be taken and was another reason for establishing a subcohort.

Both the PIAMA Study and the Generation R Study were conducted for research purposes. The PIAMA Study was initially intended as an intervention study and is therefore divided into an intervention study and follow-up study. The intervention study is further divided into an intervention group and placebo group that together comprise approximately 20% of the overall sample size.

The staff of the PIAMA Study and Generation R Study chose to establish subcohorts for focus study within the overall cohort. The staff of these studies indicated that this approach is better for conducting statistical analysis based on the large sample size of the overall cohort, while also obtaining detailed data from the small sample size of the subcohort.

However, there is a strong possibility that the response to the study can be affected by subjects' knowledge of the subcohort. For example, subjects' responses can be affected by their knowledge that the subcohort follows different operational guidelines from the overall cohort, such as a greater volume of questions, examinations, and samples, and different types of questions and examinations. The response can also be affected by subjects knowing that their selection for the subcohort is relevant to their health, such as belonging to a high-risk group for a specific disease. Consequently, the cohort must be carefully designed in order to determine that establishing the subcohort is essential for the purposes of the study, and that the subcohort can be implemented so that it does not confuse the overall study results.

3-2. Cohort Administration

A. Administrative Organization

The Norwegian and Danish cohorts were implemented as national projects with approximately 60,000 subjects. The administration staff involved with these cohorts recommended that daily decision making should be handled by a management body comprising several operational managers working closely together. Due to the nature of the work, the operational managers must work in close physical proximity to each other. In the case of the Norwegian and Danish cohorts, all operational tasks were conducted within one institution.

For the Norwegian and Danish cohorts, a steering committee and/or an advisory board was established in order to advise the operational managers and reflect the opinions of the parties concerned. The steering committee comprises staff such as from study sponsors and government organizations, while the advisory board comprises staff from organizations that conduct the actual field work of recruiting study subjects and taking samples. Of course, all actions relating to the operation of the cohorts are first approved by the ethical committees of the respective organizations and institutions, and with the approval of the state data inspectorate.

All contact and forwarding addresses for the cohort operation are consolidated under the institution to which the operational managers are assigned. This includes telephone help lines for subjects, forwarding addresses for completed questionnaires, and forwarding addresses for physicians to send biological samples.

At the time of the visit by the survey panel, all of the studied cohorts had finished recruiting subjects. Consequently, the cohorts only needed a staff of several working members supervised by operational managers, in order to field calls, enter data, and maintain databases, despite the large scale of the cohorts. When the cohorts were first launched, the staff size was several times larger in order to perform tasks such as conducting phone interviews and asking subjects to return questionnaires that had been forwarded to them.

B. Computer Usage

(The following information applies to cohorts other than the PIAMA Study, since the PIAMA Study is not yet at the phase of collecting detailed information.)

All of the cohorts utilize computer management for operating schedules, operations information, and samples. Computer information management is exclusively conducted using unique ID numbers that are assigned to each participant, in order to facilitate cohort information management. Access to link keys for personal information and registry information is strictly controlled.

The cohorts use computers and peripheral equipment to improve operational efficiency and reduce human error. For example, the Danish cohort uses computers to manage contact information for subjects and work schedules (such as for contacting subjects). Phone interviews are also conducted with the assistance of computers. In addition, the Norwegian and Danish cohorts use scanning equipment to automatically tabulate survey forms.

The Norwegian cohort will give subjects a choice of receiving mailed survey forms or filling out survey forms online, starting from the next survey forms to be implemented at 7 years of age. The Norwegian cohort staff indicate that there are many advantages to using computerized survey forms, since they can be easily tabulated and designed to eliminate errors from illogical answers. Computerized survey forms also reduce the number of unnecessary questions that subjects have to view, by automatically skipping over questions based on answers to previous screening questions. It will be interesting to see how the study subjects respond to this implementation.

3-3. Data Management and Use

A. Information Access

Databases are used to manage all personal information of cohort subjects, in addition to information from survey forms and for biological samples. For the Norwegian and Danish cohorts, researchers can apply to access cohort information. For the Generation R Study, access to cohort information is restricted to joint research projects only.

In all of the above examples, access to information requires the submission of a study planning document and approval through a screening process.

B. Biological Samples

All of the cohorts studied were engaged in sample-taking and storage of blood for use as biological samples.

For the Generation R Study, the actual cohort implementation was done by the staff of hospitals who performed medical examinations on mothers. With the exception of the

Generation R Study, the rest of the cohorts advised that two major precautions had to be observed for taking biological samples. One is to define the procedures for taking and sending samples, and to stress the significance of observing the procedures to ensure the success of the cohort study. The other is to convey these procedures to physicians, nurses, and other staff who actually take samples (blood samples at routine checkups or umbilical cord blood samples after birth), and to gain their cooperation and understanding of the importance of the procedures.

Factors such as the container material used to hold the blood sample, type of reagent added, temperature during transport, and length of time after taking the sample can limit the scope of analyzable items. Furthermore, after samples are received, they must be dispensed and separated according to a later schedule for analysis, and each sample must be stored at an appropriate temperature. Therefore, it was pointed out that it is necessary to draw up detailed and long-term plans for handling of biological samples at the research design phase.

It was also advised that the cohort information database should include information about the history of samples, for storage purposes. This includes information about the length of time in transport, and the timing and frequency when samples are thawed for partial use.

Actual biological samples are almost never provided to outside parties for research purposes. However, in cases of requests by an outside party and backing by research funds, an outside party may be permitted to conduct additional analysis at the institution where the samples are stored. In terms of precedence, samples from the Norwegian cohort were analyzed for a research project by the U.S. National Institute of Environmental Health Sciences (NIEHS).

3-4. Cooperative Framework and Incentives

All of the cohort study staff stressed the need to offer incentives at the initial phases of the study and at each subsequent phase, for all parties involved.

Examples of incentives provided for subjects include the provision of newsletters and birthday gifts, and discount coupons provided by study sponsors. Additional incentives were offered for the Norwegian and Danish cohorts, in the form of a cash prize of 5,000 krone (equivalent to approximately 100,000 yen) for the 10,000th enrollment in the cohort, and prizes in a drawing for a family ski vacation.

For the Norwegian MoBa Study and the Dutch Generation R and PIAMA Studies, subjects were first informed of the cohort study by either a physician or a midwife. Consequently, it was advised that it is important for physicians and midwives to understand the importance of the cohort study, so that they believe that it is worthwhile to recruit subjects for the study. The Norwegian cohort staff led thorough discussions with organizations and unions representing physicians and midwives so that they would embrace the study. They also went to great lengths by visiting extensively with local maternity centers to hold briefing sessions during lunch breaks for physicians and midwives in the field.

Compensation is provided for work involved in implementing the cohort study. For the Norwegian and Danish cohort studies, there are no medical fees to be paid by subjects, but physicians are compensated for taking blood samples for the cohort study. Non-graduate and graduate students who assist the cohort operation can gain access to data, which they can use for their own research or dissertations, by working for the cohort study.

Private companies that sponsor the study realize an advertising benefit by gaining a higher public profile. The benefit for governments is that they gain a scientific base for health care

policies and access to a reference group, information database, and biobank for diverse future uses. Taxpayers benefit directly through the implementation of better government policies for health care that will benefit their own health, while benefitting indirectly from cost reductions that may be achieved.

For the Norwegian and Danish cohorts, the participation rate was observed to decline as the recruitment period progressed. The return rate for questionnaires also continued to decline as the tracking period progressed. Since both Norway and Denmark possess extensive registry systems, the cohorts in those countries can access a wide variety of information about cohort subjects from registries even if the cohorts stop receiving responses from the subjects. This includes information about social status, records of medication, and records of eyewear and hearing aid prescriptions. Moreover, since Norway and Denmark require mandatory military service, all citizens are required to undergo a detailed examination of their physical and mental health at 18 years of age, which can be linked to the cohort data. Norway and Denmark are also able to continue tracking the addresses of subjects.

In contrast, Japan has no such registry systems at this point, so it is not possible to similarly link a cohort to such registry information. Once the cohort loses contact with the participant, it may not be possible to collect further information.

For the PIAMA Study, the participation rate was maintained at rates between 85% and 90% after eight years. The high sustained participation rate is likely due to the large number of mothers participating in the cohort who have a specific interest in the issue of children's allergies.

The cohort staff were of the common opinion that it is essential to maintain the public profile of the cohort by continuing to release the results of the study beginning from the study launch, and to receive regular and continual public exposure such as from scientific papers and media coverage. These initiatives are necessary in order to recruit subjects and keep them participating in the cohort, and to continue securing adequate funding for the cohort.

3-5. Foreseeable Issues

A. Ethical Guidelines and Informed Consent

All of the cohorts studied are operated under the respective ethical guidelines established by the countries and institutions that implement the cohorts. These guidelines cover issues such as respect for human rights, verification of the purposes of research and validity of research methodology, and the framework for approving research plans.

Ethical guidelines typically require that researchers obtain informed consent and take steps to protect personal information from the standpoint of human rights.

All of the cohort staff indicated that they encountered difficulties with gaining consent for participation, due to the particulars of their respective birth cohort studies. These issues center around the prolonged length of the study (which can span several decades if children are tracked into adulthood), and the inability of designating study items that will become critical in the future.

Regarding the prolonged length of the study, the Norwegian cohort requires that the cohort must personally inform children once they reach 15 years of age, in addition to obtaining consent from the mother at initial participation in the study. In addition, new consent forms must also be obtained once the child reaches 18 years of age. For the Danish cohort, data may

be kept until the child turns 20 years of age, and follow-up study using registry information may be conducted based on the mother's consent given at the time of joining the cohort.

For the Dutch Generation R Study, the institution implementing the study divided the cohort into four phases (prenatal, 1–4 years, 4–12 years and 12–20 years) and obtained written consent from the mother at each phase.

In all of the above examples, the subjects and mothers do not have the right to access their personal data. However, by withdrawing their consent to participate in the cohort, they can request that their personal data (information and biological samples) be destroyed.

B. Ethical Guidelines and Study Design

Regarding the inability to designate study items that will become critical in the future, this issue affects the validity of the research (cohort study design). Accordingly, all of the cohort studies except for the PIAMA Study do not outline specific hypotheses in their cohort design, nor do they propose an epidemiological means of study for elucidating the hypotheses. The cohorts only outline general hypotheses and do not venture beyond discussing the need to secure a sufficient sample size in order to verify hypotheses.

For the Norwegian cohort, the research design clearly states that the purpose of the cohort study is "to collect as much data as possible concerning exposures and health outcomes, in order to respond to hypotheses that may arise in the future. The study is not aimed at proving specific etiological hypotheses."

Research projects that use these cohorts are all implemented under the approval of an individual screening process, based on proposals for funding obtained independently from the cohort study.

C. Pros and Cons of Intervention

The biggest ethical issue that is likely to arise from research that uses cohort data is whether or not to inform the participant if a health issue is identified. For all of the cohorts studied, the informed consent for participation in the cohort clearly states that personal data will not be returned.

(The details of informed consent are not known for the PIAMA Study. According to Dr. Bert Brunekreef, the principal investigator of the PIAMA Study, some information must be provided to subjects in order to gain their loyalty to the cohort. However, it was our impression that Dr. Brunekreef did not want to discuss this issue in further detail.)

Regarding this issue, the Norwegian and Danish cohort staff indicated that there was some opposition to the implementation of the cohort study, based on the argument that it was unethical and did not benefit the subjects.

The Norwegian cohort staff indicated that there was a research project in Norway that conducted analysis of risk genes for Type I diabetes as part of the project and proceeded to inform mothers of children in the high-risk group. However, a lawsuit later arose under the claim that informing the subjects had incited fear. The research in question was eventually cancelled due to this pressure.

For the Generation R Study, the focus cohort study specifies that subjects are referred to a specialist if a health issue is discovered.

D. Protection of Personal Information and Information Security

All of the cohorts studied have taken careful steps to protect personal information and implement information security. Subjects are identified only by a unique ID number, and sensitive data including personal information are separately managed. There are also extensive restrictions on linking IDs to data. Similar measures are in place to protect against linking to various registries.

Information security measures are used for maintaining and managing databases and data. Restrictions are in place for both physical and electronic access. Security measures are also in place for the maintenance and management of biobanks and stored biological samples.

3-6. Contributions of Later Cohorts

A. Linking Data to Other Cohorts

All cohort staff pointed out that there were certain possibilities that could be gained from linking data with existing internal and outside cohorts, such as to enable broader statistical analysis and perceive variations by region (ethnicity). It was commonly understood that data must be standardized for this purpose, including standardization of the content of questions, sample types, sample-taking method, items for analysis, and diagnosis. The PIAMA Study staff indicated that one solution is to develop and use a globally standardized methodology for epidemiological investigation, such as ISAAC.

B. Unique Contribution

The prospects of a Japanese cohort were met with strong words of encouragement. It was specifically advised that later cohorts should endeavor to learn from the failures of earlier cohort groups in order to adopt better designs and methodologies, which in turn will deliver greater benefits with less funding and labor.

Regarding the possibility of Japan's making its own unique contribution to the global framework for health care policy, it was advised that Japan should endeavor to design a cohort that addresses the weaknesses of other cohorts, if possible. The specific examples given were as follows:

- Capitalize on advanced analytical technology by taking the initiative to implement measurements such as that of environmental pollutants in biological samples.
- Endeavor to establish a methodology for utilizing a strong track record of environmental monitoring in exposure assessments.
- Endeavor to take and bank RNA samples. Although DNA is easily handled, it is difficult to judge the results of DNA analysis. RNA samples require careful handling but provide direct markers for biological gene expressions. It was also suggested to establish a cDNA bank specifically focusing on developmental periods in order to become aware of the specific expression proteins at each stage of children's development.

Reference I

Report on European Children's and Birth Cohort Studies, Part B
WHO's Programs for Children's Environmental Health

1. Survey Summary

Survey Panel

Manabu, Hasegawa	Ministry of the Environment
Fujio, Kayama	Jichi Medical University
Rie, Masho	Center for Environmental Information Science
Motoyuki, Yuasa	Hokkaido University

Survey Date

November 12, 2007

Purpose of Survey

To interview a medical officer in charge of children's environmental health from the World Health Organization (WHO), in order to understand WHO's initiatives in this area.

Person Interviewed

Dr. Jenny Pronczuk, Medical Officer in Children's Health and the Environment, Public Health and Environment (PHE) Department, WHO

Survey Contents and Results

The survey panel received an overview of WHO's programs for children's environmental health and was provided with relevant documents. The WHO initiatives described to the survey panel were as follows:

- Preparation of national profiles on the status of children's environmental health
  https://www.who.int/ceh/profiles/en/
- Preparation and distribution of training package for health sector
  http://www.who.int/ceh/capacity/trainpackage/en/index.html
- Preparation and distribution of Green Page for recording environmental history
  http://www.who.int/ceh/capacity/paedenvhistory/en/index.html
- Adoption of children's environmental health elements into Integrated Management of Childhood Illness (IMCI) initiatives
- Preparation and provision of guidelines for establishing children's environmental health (CEH) centers

http://www.who.int/ceh/capacity/paedehcentres/en/index.html

- Provision of technical assistance for WHO member countries
- Implementation of joint research

The following documents were provided to the survey panel:

- Environmental Health Criteria 237, "Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals" IPCS, 2006. http://www.who.int/ipcs/publications/ehc/ehc237.pdf
- "Preventing Disease through Healthy Environments—Towards an estimate of the environmental burden of disease" WHO, 2006. http://www.who.int/quantifying_ehimpacts/publications/preventingdisease/en/
- Children's Health and the Environment—A Global Perspective, WHO, 2005. http://whqlibdoc.who.int/publications/2005/9241562927_eng.pdf

2. Survey Results

2.1 WHO's View of Children's Environmental Health

Children are exposed to various kinds of risks depending on the circumstances in their respective countries. These risks include conventional risks such as the impact of industrialization, exposure to unsafe water and food, issues with indoor air quality, and biological-borne infectious disease. They also include known risks such as the use of potentially unsafe chemical substances, effects of traffic and industrialization, and environmental degradation. In addition, there are indeterminate future risks that are just beginning to be understood, such as from persistent organic pollutions (POPs), nanoparticles, climate change, and depletion of the ozone layer.

It is estimated that worldwide, more than three million children under 5 years of age die every year from diseases linked to the environments where they live. This figure includes an estimated 1.6 million deaths from diarrhea, one million deaths from respiratory disease, one million deaths from malaria and other biological-borne infectious diseases, and 300,000 deaths from poisoning and accidents.

The WHO publication *Preventing Disease through Healthy Environments—Towards an estimate of the environmental burden of disease* (2006) reaches the conclusion that the environment has a significant impact on health. The findings of this report including the following data:

- Of 102 major diseases, environmental risk factors contributed to disease burden in 85 categories.
- Globally, an estimated 24% of the disease burden (healthy life years lost) and an estimated 23% all deaths (premature mortality) were attributable to environmental factors. Among children 0–14 years of age, the proportion of deaths attributed to the environment was as high as 36%.

The WHO publication also finds that there are significant disparities in the impact of environmental risk factors on the health of children between developing countries and developed countries. The findings include the following data:

- On average, children in developing countries lose eight times more healthy life years from environmentally caused diseases, per capita, than their counterparts in developed countries.
- In certain very poor regions of the world, the number of healthy life years lost as a result of childhood lower respiratory tract infections is 800 times greater than in developed countries.
- Mental retardation due to lead exposures in general was estimated to be nearly 30 times higher in regions where leaded gasoline was still being used, as compared with regions where leaded gasoline had been completely phased out.

2.2 WHO Initiatives to Address Children's Environmental Health Issues

Following are summaries of WHO projects that were described in detail for the study panel.

A. Preparation and Provision of Guidelines for Establishing Children's Environmental Health Centers

Children's environmental health (CEH) centers are facilities that are able to recognize, assess, and manage environmentally related diseases in children, and provide education and training for medical professionals. They perform the role of hospital, research facility, and educational facility.

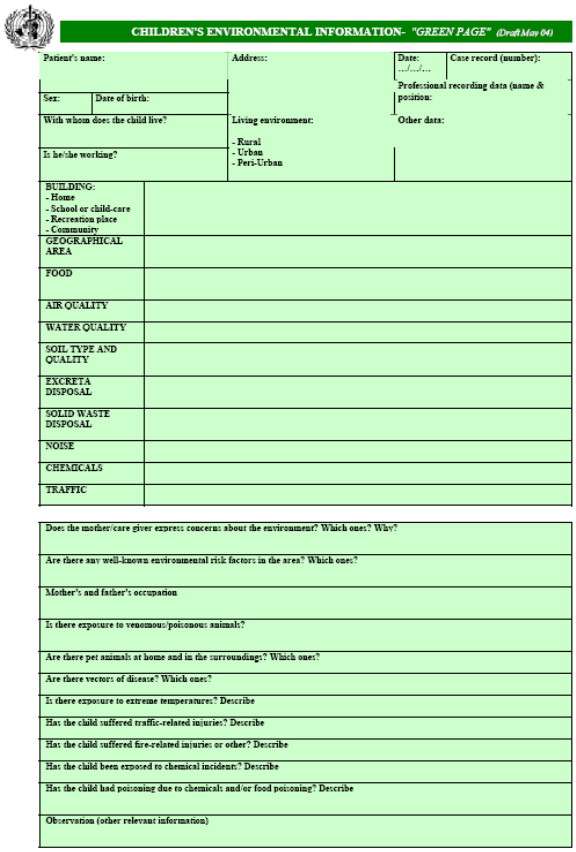
Through the cooperation of WHO, these centers have been established in the United States (Pediatric Environmental Health Specialty Units—PEHSU), Canada, Argentina, Mexico, Uruguay, and Spain.

WHO is currently preparing guidance materials on how to set up and run such centers and to take advantage of networking. The final draft will be published in late 2007.

B. Green Page

The Green Page is a children's environmental record that is designed to be inserted into clinical records in order to record environmental risk factors that may have an impact on a child's health. The purpose of the Green Page is to have physicians record a description of the child's environmental circumstances so that information about past exposures can be obtained if the child develops a future condition that may be linked to environmental factors. Data from Green Pages can be tabulated to provide results that are equivalent to implementing a questionnaire-based study. Green Pages are being used in Armenia and other countries.

Fig. 1 English Green Page Draft



CHILDREN'S ENVIRONMENTAL INFORMATION- *"GREEN PAGE"* (Draft May 04)

Patient's name:	Address:	Date: --/--/---	Case record (number):
Sex: / Date of birth:		Professional recording data (name & position:	
With whom does the child live?	Living environment: - Rural - Urban - Peri-Urban	Other data:	
Is he/she working?			

BUILDING: - Home - School or child-care - Recreation place - Community	
GEOGRAPHICAL AREA	
FOOD	
AIR QUALITY	
WATER QUALITY	
SOIL TYPE AND QUALITY	
EXCRETA DISPOSAL	
SOLID WASTE DISPOSAL	
NOISE	
CHEMICALS	
TRAFFIC	

Does the mother/care giver express concerns about the environment? Which ones? Why?
Are there any well-known environmental risk factors in the area? Which ones?
Mother's and father's occupation
Is there exposure to venomous/poisonous animals?
Are there pet animals at home and in the surroundings? Which ones?
Are there vectors of disease? Which ones?
Is there exposure to extreme temperatures? Describe
Has the child suffered traffic-related injuries? Describe
Has the child suffered fire-related injuries or other? Describe
Has the child been exposed to chemical incidents? Describe
Has the child had poisoning due to chemicals and/or food poisoning? Describe
Observation (other relevant information)

C. Children's Environmental Research Led by WHO

Longitudinal Cohort Study

WHO since 2003 has operated an advisory committee for longitudinal cohort studies with funding from the U.S. National Institutes of Health (NIH), the Environmental Protection Agency (EPA), and the Centers for Disease Control (CDC). The advisory committee promotes mutual exchanges between researchers who are involved in longitudinal cohort studies in various countries, with a particular emphasis on assisting longitudinal cohort studies in developing countries. The aims of the advisory committee are to develop core protocols that can be commonly applied for longitudinal cohort studies to study the effects of the environment on the health and development of children, and to collect data in order to increase the value of information assets in each country.

Following are examples of hypotheses from current longitudinal cohort studies:

- There is a link between environmental exposures during early pregnancy and undesirable pregnancy outcomes such as congenital anomalies.
- Physicochemical and environmental causes have an impact on the sexual maturation of children.
- There is a link between childhood exposures to polluted air and increases in the risk of acute lower respiratory tract infection.
- There is a link between exposures to indoor air pollution and middle ear infections.

- There is a link between fetal exposures and increases in the risk of childhood cancer.
- Fetal and childhood exposures to heavy metals and other environmental pollutants with neurotoxic effects have a negative impact on neurodevelopment.

Following are examples of schemes from current longitudinal cohort studies:

- Sample-taking: Blood (maternal blood, paternal blood, children's blood, umbilical cord blood), amniotic fluid, placenta, meconium, urine (maternal urine, children's urine), sperm, hair, nail, mucous swab samples (oral, vaginal, and cervical), saliva, teeth, feces, and other environmental mediums
- Timing of sample-taking: At the time of enrollment, at second and third trimester, at birth, at 3/6/12 months, at each year of age, other

Use of Biomarkers for Assessing Environmental Exposures in Children

WHO, in collaboration with the Pan American Health Organization (PAHO) and WHO/UNEP/ILO International Programme on Chemical Safety (IPCS), convened an International Workshop on Advances in the Use of Biomarkers in Children in Argentina in the year 2005.

The workshop brought together experts from around the world to discuss the possibility of using biomarkers at each stage of children's development in relation to chemical exposures in the environment. The workshop also stressed the need for banking of biological samples to facilitate biomarker research. Study of new biomarkers for environment exposures in children is currently being conducted with funding mainly provided by the National Institute of Environmental Health Sciences (NIEHS).

WHO plans to convene another workshop in FY2008, and is currently seeking a region to host the next workshop.

Other Research Cooperation

Following are examples of research projects that are being conducted through cooperation between WHO and various countries:

- Research into asthma and respiratory disease (Australia and India)
- Research into the impact of arsenic on pregnancy (Thailand and USA)
- Research into persistent organic pollutants (POPs) in breast milk (Mexico and Canada)

2.3 WHO Outlook for Japan and Programs for Children's Environmental Health

WHO is greatly anticipating the prospect that Japan will implement a new longitudinal cohort study with respect to its programs for children's environmental health.

In addition, WHO is looking forward to Japan's contributions in areas such as the WHO-sponsored workshop on children's environmental health that is scheduled to be convened next year.