

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.

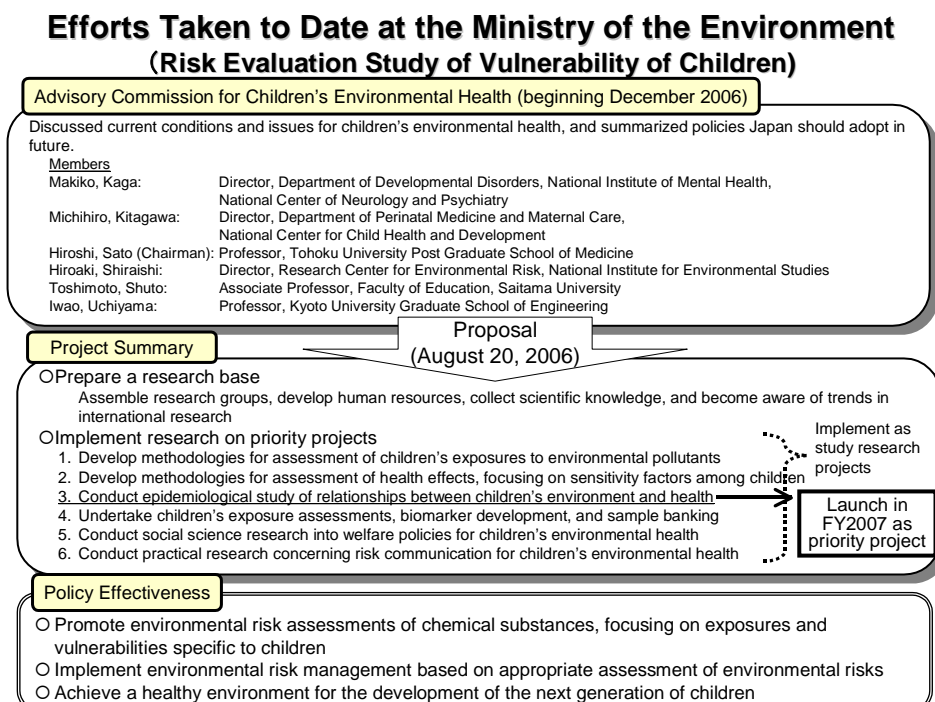
The Advisory Commission for Children’s Environmental Health was established to discuss future efforts for children’s environmental health. From its discussions on issues related to children’s vulnerability to toxic substances and environmental health, it has formulated proposals regarding the direction 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

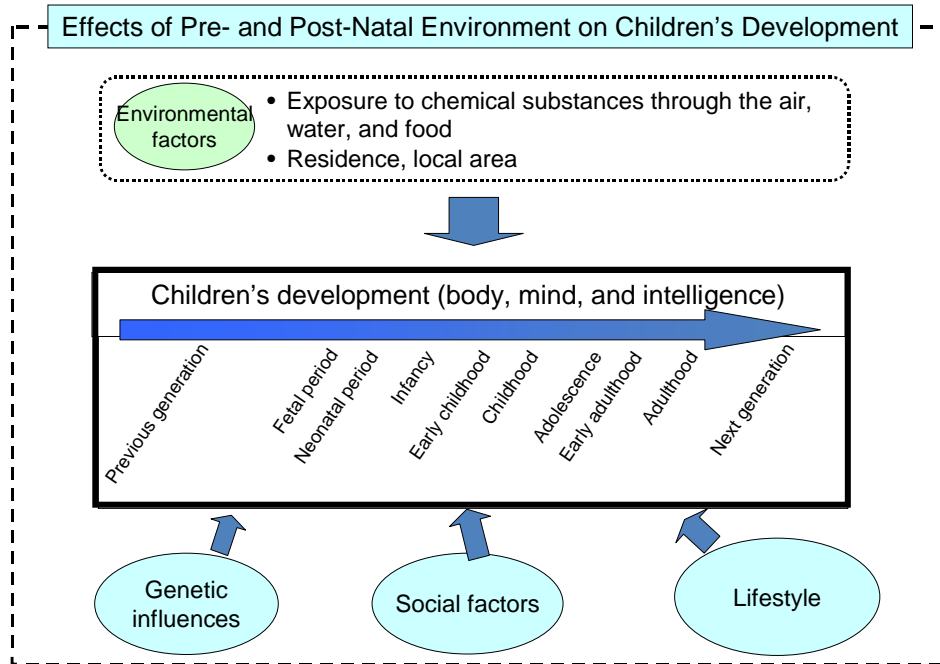
An essential element in the design of an epidemiological study is setting up a hypothesis. The hypothesis for this study has been formulated as follows.

“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)

<p>A. Chemical substance exposure</p> <p>Persistent organic pollutants (POPs), dioxins, polychlorinated biphenyls (PCBs), mercury, lead, arsenic, cadmium, benzene, organofluoric compounds, endocrine disruptors, fire retardants, etc.</p> <p>B. Other factors (confounding factors)</p> <ul style="list-style-type: none"> ■ Genetic influences ■ Social factors and lifestyles <p>Region (address), residence (type, age, air conditioning, etc.)</p> <p>Parents' education, employment history, work conditions, income, smoking, and drinking</p> <p>Diet</p> <p>Family environment (such as number of siblings and pets)</p> <p>Playground environment, school environment, etc.</p>

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)

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

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.

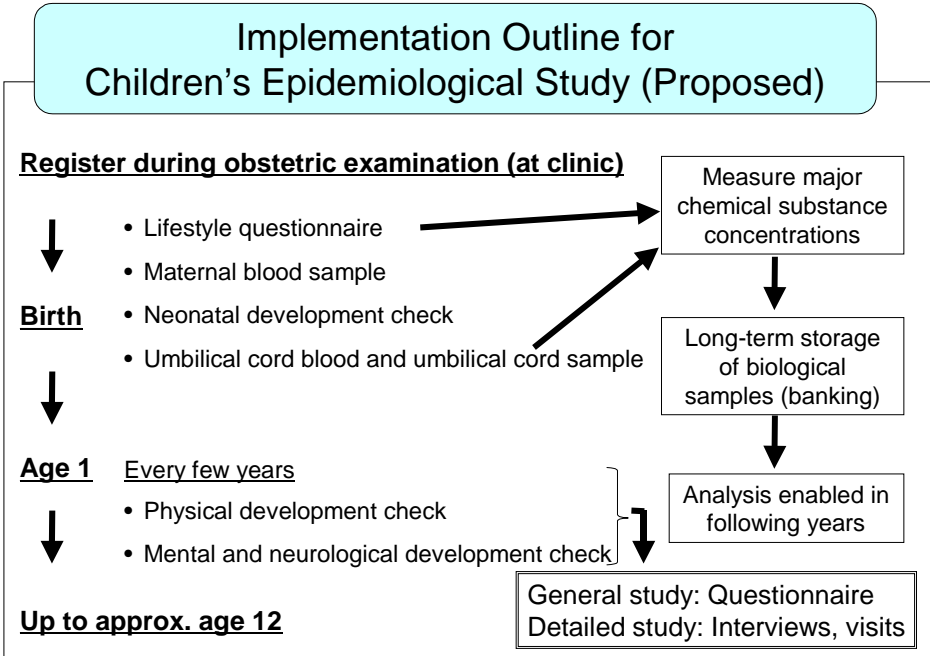
In this epidemiological study, long-term monitoring should be performed for each subject, from the fetal period when body organs are first formed in the womb through to childhood when mental and physical development is most active.

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	<ul style="list-style-type: none">• Planning and adjustment implemented at Core Center.• Study items always implemented in all regions nationwide (at all units).	<ul style="list-style-type: none">• 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.

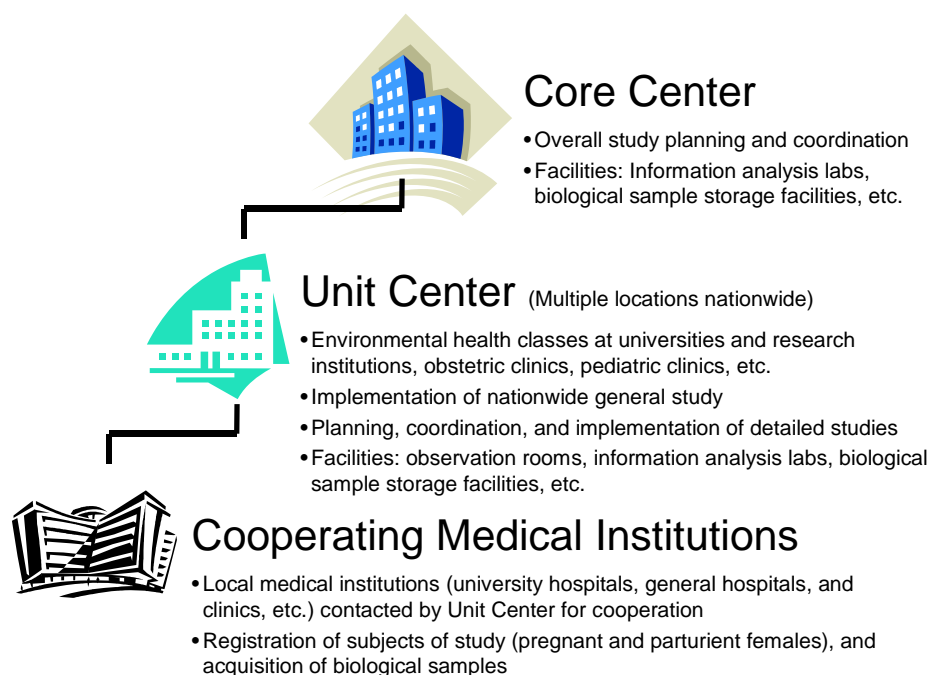
3.4 Registration Period for Subjects of Study (Pregnant and Parturient Women)

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.

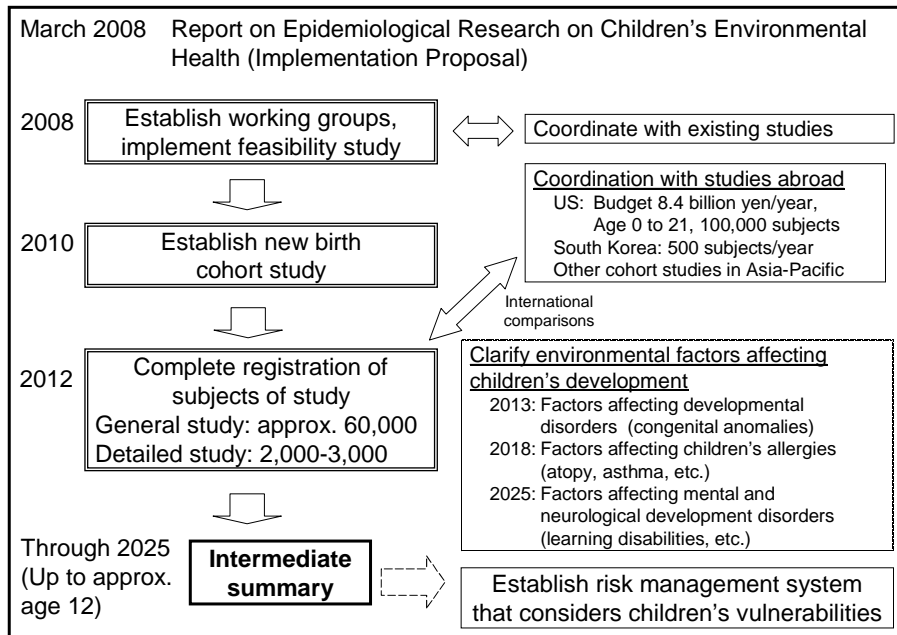
4.1.2 Implementation of Small-Scale Study

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