Japan Environment and Children's Study
(JECS)
Conceptual Plan

Formulated on March 30, 2010

Revised on March 30, 2023

Ministry of the Environment

Introduction

The Japan Environment and Children's Study (JECS) was launched in FY2010 as a large-scale epidemiological survey on 100,000 mother-child pairs across Japan.

As the first project funded by the Ministry of the Environment in the field of life sciences, the JECS received a Superior rating in the assessment of priority for science and technology measures for the FY2010 budget request in the Council for Science, Technology and Innovation. This rating secured the necessary funding to conduct a large-scale epidemiological study on 100,000 children based on the Conceptual Plan, leading to the decision to launch the JECS.

The JECS is launched based on plans and study design drawn up by the Ministry of the Environment. The Programme Office is established under the National Institute for Environmental Studies to undertake the overall management and operation of the study, while the Medical Support Centre established in the National Centre for Child Health and Development provides support through their medical expertise. Fifteen Regional Centres, established in universities and research institutes nationwide selected through an open call for entries, are responsible for the recruitment and follow-up of participants in the respective regions.

With the continuation of the JECS until participant children reach about 40 years of age, this Conceptual Plan outlines the survey's implementation structure and basic principles until participant children reach 18 years old. A review is planed around FY2028 when the oldest participant children reach 17 years of age.

Research implementing institutions are required to prepare their Study Protocol and standard operating procedures separately based on this Conceptual Plan.

Environmental Health Department, Minister's Secretariat, Ministry of the Environment

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1. Background

The G8 Environment Ministers' Meeting held in Miami, U.S., in 1997 recognized that children worldwide were facing the threat of toxic substances in the environment and declared the need to prioritize initiatives addressing issues regarding the environmental health of children. During the same period, large-scale epidemiological studies involving 100,000 children launched in Denmark, Norway, and the U.S. [1] In 2002, Delegations at the World Summit on Sustainable Development (WSSD) agreed to "aim to achieve, by 2020, that chemicals are used and produced in ways that lead to the minimization of significant adverse effects on human health and the environment." In 2006, the Strategic Approach on International Chemical Management (SAICM) was adopted as an international agreement outlining measures to achieve the WSSD commitment. These measures include risk reduction based on scientific risk assessments, the collection and dissemination of information, capacity building, and technical collaboration. Furthermore, at the G8 Environment Ministers' Meeting on Children's Health and the Environment in Syracuse, Italy, in 2009, countries agreed to cooperate in conducting large-scale epidemiological studies.

In Japan, the 2006 "Report of the Advisory Commission for Children's Environmental Health" proposed a direction for future policies addressing issues related to the vulnerability of children and environmental health. The report highlighted the need to conduct epidemiological studies on the relationship between environment and health in children while promoting experimental studies to elucidate mechanisms to clarify the impact that environmental factors such as exposure to chemicals and living environment on children's growth and development.

To clarify the impact that environmental risks have on human health, efforts have long focused on animal experiments and fundamental research aiming to elucidate mechanisms. However, due to morphological and physiological differences between animal and human species, it is difficult to apply the results of animal experiments directly to humans. Therefore, it is important to adopt an epidemiological approach to observe the impact of environmental risks on actual human populations.

In light of that, a proposal was made in 2008 to launch a new, large-scale

[1] The National Children's Study in the U.S. was closed later.

epidemiological cohort study on newborns to identify the impact of environmental chemicals (Report by of the Conference on the Epidemiological Study of Children's Environmental Health). This led to the formulation of the Conceptual Plan for the Japan Environment and Children's Study (JECS) in 2010. Based on this Conceptual Plan, the JECS was launched as a large-scale epidemiological study to elucidate the impact of environmental factors, including chemicals, on children's health. Approximately 100,000 expectant mothers, 50,000 fathers, and 100,000 newborns, recruited between January 2011 and March 2014, have participated in the study, with follow-up surveys scheduled until participants children reach 13 years of age.

At the initial stages of the formulation of the Conceptual Plan (2010), it was considered ideal to study the impact of environmental factors on human health throughout the participant' lifetime by continuing follow-up surveys even after they reach 13 years of age, while it was deemed appropriate to make a decision whether to continue beyond 13 years, based on a review of the research outcomes, social needs, retention rates, and other factors at some point in time. Since the participant children will reach 13 years of age in 2024, the Health and Environment Epidemiological Study Working Group, established in 2021, summarized the findings of the JECS to date and decided in March 2022 to continue the JECS until the participants are about 40 years old. In response, a review was conducted by the FY2022 JECS Project Evaluation Committee to revise the Conceptual Plan.

As a result of the review, it was decided that the Conceptual Plan to include plans serving as the study's guiding principles until the participant children reach 18 years of age, with the anticipation of conducting long-term follow-up until they are about 40 years old to study the impact of the environment on human health, including future generations.

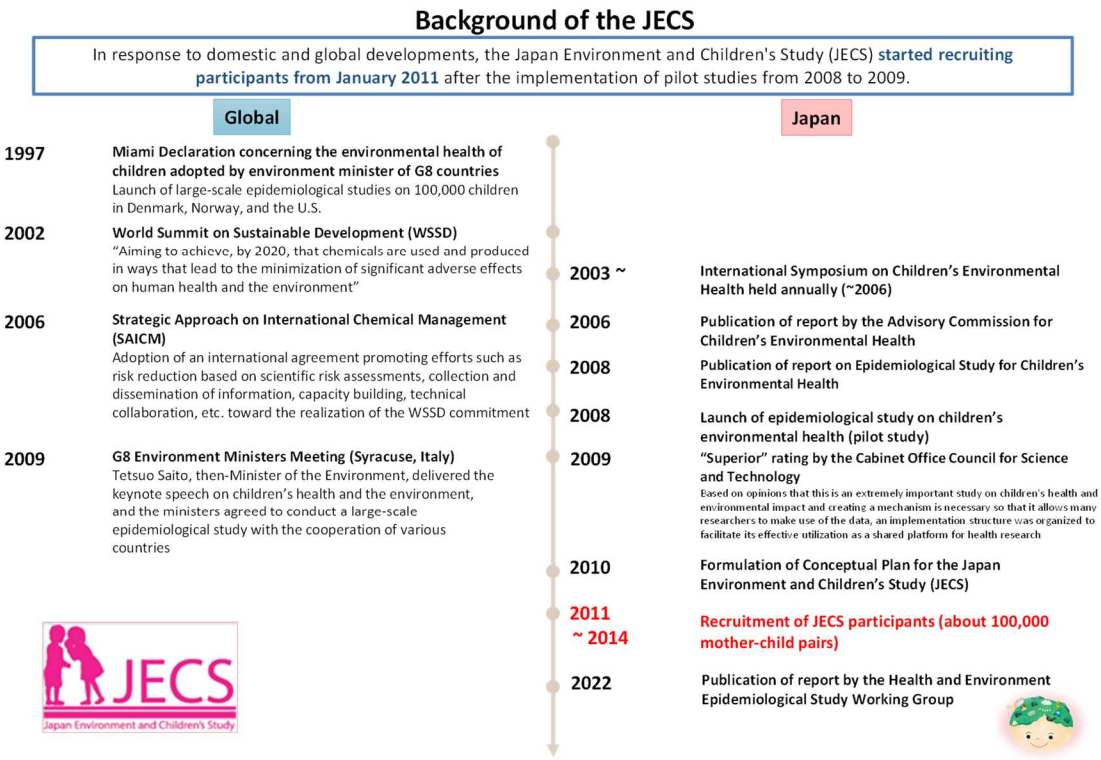

Figure 1　Background of the Japan Environment and Children's Study

2. Formulation of the Conceptual Plan and Revised Structure

The Conceptual Plan was formulated in 2010 following discussions by the Working Group of the Epidemiological Research for Children's Environmental Health and several other working groups.

For the FY2022 revision, the JECS Project Evaluation Committee conducted reviews starting in July 2022, based on the Report of the Health and Environment Epidemiological Study Working Group (March 2022).

3. Title of This Study

This study is titled “Japan Environment and Children’s Study,” abbreviated as “JECS.”

4. Aims of the Study

The JECS aims to elucidate the impact of environmental factors on human health from the fetal period through early childhood and later in life. Specifically, the study was initiated to clarify the effects of exposure to chemicals and living environments on children’s health from the fetal period through to early childhood, so as to support the development of an appropriate risk management system by providing information to risk management authorities and industry, thereby informing voluntary initiatives and the revision of examination standards for chemical regulations and environmental standards. Due to extremely low incidence of events such as congenital anomalies, which have been reported to be associated by environmental chemicals, it is necessary to have at least 100,000 study participants. This large sample size also ensures that the involvement of chemicals, even at low concentrations, can be sufficiently detected for events with relatively high incidence. Thus, the JECS was designed to accumulate data from100,000 participants.

The JECS will continue to follow up with the participant children even after they reach 13 years of age. Additionally, the study aims to observe the relationship between living environments and chemical exposure with the development of diseases after adolescence, adopting a life course approach.

5. Issues that Should be Elucidated Through This Study

The JECS is conducted based on the central hypothesis that environmental factors, including chemical exposure from the fetal period to early childhood, may affect pregnancy/reproduction, congenital anomalies, neuropsychiatric development, the immune system/allergy, and metabolism/endocrine system. Moreover, as the study continues beyond the participants' age of 13 years, it will examine the relationship between chemical exposure during the fetal period and long-term health impact such as the development of age-dependent diseases after adolescence. The specific research hypotheses will be outlined in the Study Protocol.

To thoroughly investigate various hypotheses based on this central hypothesis, it is essential to also examine confounding factors besides chemical exposure. Therefore, this study also considers factors such as genetics, social conditions, and lifestyle-related factors.

Pediatric cancer is not included as a hypothesis in this study due to difficulty in securing the number of cases required. However, research in this area will be advanced through participation in international frameworks, such as the International Childhood Cancer Cohort Consortium (I4C).

6. Environmental Factors and Health Outcomes and Endpoints Studied in This Study

6-1 Environmental Factors Studied in This Study

The primary factors to be examined in this study are exposure to environmental chemicals and other confounding factors. The candidate substances for analyses (Table 2) were selected considering the following points (Table 1). However, the substances to be analyzed will be determined during the study implementation.

Table 1. Points considered when selecting the candidate substances for analyses

- Substances that accumulate easily in the body (e.g., persistent organic pollutants (POPs))
- Substances that pass through the placenta easily (e.g., methyl mercury)
- Substances that children have increased opportunities for exposure to (e.g., various volatile organic compounds (VOC) that are related to the sick building syndrome)
- Substances that are of great public concern (e.g., pesticides)
- Substances that are useful for examining the central hypothesis

Sample collection and storage methods that enable the appropriate analysis of these substances shall be prescribed in the standard operating procedures. The chemical analyses of biological samples shall be carried out considering the latest research developments and the advancements in analytical methods. Analyses shall be conducted in phases, with the substances for analyses determined based on the analytical methods, types and volume required, costs, and storage stability of the samples. It is also needed to consider improving work efficiency on the processes until the results of analyses are obtained, including improvements to the operational system.

Table 2. List of Candidate Substances for Analyses (2010)

a	Inorganic substances	Mercury	
		Lead, cadmium, etc.	
		Arsenic	
			By chemical form: Arsenic acid, arsenous acid, dimethylarsinic acid, arsenobetaine, etc.
		Selenium, aluminum, etc.	
		Iodide, perchlorate, nitrate, etc.	
b	Chlorine-based POPs (excluding agricultural chemicals)	Dioxins (PCDDs、PCDFs、Co-PCBs)	
		PCBs (polychlorinated biphenyl) and metabolites (hydroxylated PCB)	
		HCB (hexachlorobenzene), PeCB (pentachlorobenzene)	
		Others	
c	Bromine-based POPs	Brominated flame retardants	
			PBDE (Polybrominated diphenyl ethers: PeBDE, OBDE, etc.)
			PBB (Polybrominated biphenyl: HBB, PeBB, etc.)
			Others
		Brominated dioxins (PBDDs、PBDFs)	
d	Agricultural chemicals	POPs-Organochlorine Pesticides	
			Chlordane (cis-,trans-chlordane、cis-, trans-nonachlor、oxychlordane)
			DDTs (p,p'-, o,p'-DDT、p,p'-, o,p'-DDE、p,p'-, o,p'-DDD)
			Drins dieldrin, etc.

			Heptachlors heptachlor, cis-, trans-heptachlorepoxide
			HCH (alpha, beta, gamma, delta) hexachlorocyclohexane
			Mirex
			Toxaphene (representative isomers)
			Chlordecone
		Organophosphorus pesticides (OP)	
			OP metabolites: dimethylphosphate, diethylphosphate, dimethylthiophosphate, diethylthiophosphate, etc.
			3-methyl-4-nitrophenol (Fenitrothion metabolite), p-nitrophenol (parathion metabolite)
			Acephate or methamidophos
			Dichlorvos (DDVP) or metabolite (DMP)
			3,5,6-trichloro-2-pyridinol (chlorpyrifos metabolite)
		Pyrethroid pesticides	
			3-phenoxybenzoic acid, 2,2-dimethylcyclopropane-1-carboxylic acids (Pyrethroid metabolites), etc.
		Carbamate / dithiocarbamate pesticides	
			Analysis of urinary metabolites such as ethylthiourea, etc.
		Neonicotinoid (Acetamiprid, Imidacloprid)	
			6-Chloronicotinic acid (Imidacloprid metabolite)
		Herbicides	
			PCP and other chlorophenols, Atrazine, Bentazone, Diuron, Bromobutide, Glyphosate, etc.
		Antimicrobials	
			Flutolanil, Carpropamid, Iprodione, Flusulfamide, etc.
		Others	
e	Organofluorine compounds	Perfluorinated chemicals (PFCs)	
			PFOA, PFOS (perfluorooctane sulfonic acid), etc.
f	Phthalic acid ester	Phthalates	
			Mono (2-ethylhexyl) phthalate (DEHP metabolite), etc.
g	Aromatics	Nitro musk	
		Polycyclic musk	
h	Phenols		Parabens (methyl-, ethyl-, propyl-, butyl-, benzyl-hydroxybenzoate, etc.)
			Bisphenol A, Bisphenol F, etc.
			Nonylphenol, etc.
i	PAHs	Polycyclic aromatic hydrocarbons	
			BaP (benzo(a)pyrene), pyrene, phenanthrene, etc.
			Related metabolites (1-OH-pyrene、1-,2/9-,3-,3-OH-phenanthrene, etc.)
			Ames test/umu test
j	Smoking		Cotinine, thiocyanate
k	Air pollutants	VOC (volatile organic compounds)	
	Indoor pollutants		Benzene, toluene, xylene, etc.
			Formaldehyde, acetaldehyde, acrolein, crotonaldehyde

		General items	
			NO_2, SO_2, SPM, $PM_{2.5}$, CO, ozone, allergen
			p-dichlorobenzene
l	Others		Phytoestrogens
			Caffeine
			Triclosan
			Deet (N,N-diethyl-3-methylbenzamide)
			Pyridine
			Acrylamide
			Tributoxyethyl phosphate (TBEP), Tributyl phosphate (TBP), etc.
			Other chemical substances and metabolites
m	Early impact indicators		8-hydroxydeoxyguanosine (8-OHdG), etc.

6-2 Main Health Outcomes and Endpoints

In addition to the main health outcomes that should be observed during childhood, outcomes, including the examples shown in Table 3, shall be evaluated in order to examine the relationship between chemical exposure during the fetal period and the development of age-dependent diseases after adolescence as the study continues beyond 13 years,.

Table 3. Health Impact Indicators (Outcomes/Endpoints) (Examples)

- Physical growth: Such as low birth weight, physical growth and development after birth
- Congenital abnormalities: Such as hypospadias, cryptorchidism, cleft lip and palate, intestinal atresia, ventricular septal defect and Down's syndrome
- Differences in sex development: Such as sex ratio, genital dysplasia, sex differentiation of the brain
- Neuropsychiatric development: Such as autism disorder, learning disorders (LD), attention deficit hyperactivity disorder (ADHD)
- Immune system: Such as allergies, atopic dermatitis and asthma
- Metabolism/Endocrine systems: Such as abnormal glucose tolerance, obesity and effects on reproductive organs
- Development of age-dependent diseases after adolescence *13 years old and after

Regarding health outcomes that require longitudinal examination, repeated measurement over time shall be planned appropriately. It is particularly necessary

to evaluate the relationship between health effects determined in childhood and those determined at or after 13 years of age, based on closely tracked data. Comprehensive studies are also necessary, such as comparisons with existing knowledge about the mechanisms by which the concerned effects occur.

Details related to the assessment of outcomes, such as standards and assessment methods, are standardized nationwide by the standard operating procedures.

Note: Genetic factors

To infer causality in the relationship between environmental factors and health impact, it is possible to examine this relationship while considering genetic factors in observation studies (Mendelian randomization studies), similar to randomized intervention trials. Genetic analysis will be conducted in the JECS, and studies will be conducted considering genetic factors. As various environmental factors impact gene expression and the subsequent biological reactions, as well as health effects, epigenome and omics analysis will also be considered.

As data on genetic abnormalities contain especially sensitive information, full consideration will be given to data handling and the use of the analytic results. Scaling up the study size may benefit to obtain highly reproducible results and collaborative analyses with other cohort studies within and outside Japan will be a future option, while careful attention must be given to handling personal information.

7. Pilot Study

Ahead of the JECS conducting the study on 100,000 mother-child pairs across Japan, a Pilot Study has been conducted on a small-scale population since 2008.

The Pilot Study, conducted about two years ahead of the Main Study, consists of survey items that should be studied in the Main Study and targets a small-scale participant population registered with informed consent. The Pilot Study plays an important role in testing the feasibility of the study methods and making appropriate revisions before the Main Study begins. This Pilot Study will continue to be conducted at Jichi Medical University, the University of Occupational and Environmental Health, Japan, Kyushu University, and Kumamoto University.

Additionally, another small-scale cohort study has also been established to test the analysis methods for environmental chemicals present in biological samples. This is being conducted at Tohoku University and contributes to establishing methods for assessing exposure from biological samples.

8. Study Organization Structure

The JECS is launched based on plans and study design drawn up by the Ministry of the Environment. The Programme Office, established in the National Institute for Environmental Studies, is responsible for the overall management and operation of the study, while the Medical Support Centre, established in the National Center for Child Health and Development, provides support through their medical expertise. Fifteen Regional Centres, established in universities and research institutes nationwide selected through an open call for entries, are tasked with the recruitment and follow-up of participants in the respective regions. (Figure 2)

This system will, in principle, remain in place for the continuation of the study after participant children reach 13 years of age. Considering the possibility that participants may relocate across the country for studies or employment, the organizational structure will be reviewed to enable a flexible response corresponding to the participants' ages. Specifically, by FY2029, when the oldest participant children reach 18 years of age, reviews are expected to establish an operational structure that is effective, efficient, and sustainable.

This study is conducted according to the Conceptual Plan, and the Study Protocol and standard operating procedures that are formulated in accordance with the Conceptual Plan. The Programme Office will mainly review the Study Protocol and standard operating procedures. The Study Protocol is undergo a research ethics review and, upon the approval of the President of the National Institute for Environmental Studies, where the Programme Office is based, the study is conducted with the approval of the heads of the universities or research institutes where the Regional Centres are located. The operation systems for the JECS is set out in Figure 3, but this structure is subject to change.

A mechanism will be established to facilitate wider JECS data sharing, aiming to expedite data analysis and in turn the publication study findings, thereby accelerating the contribution to society through these findings.

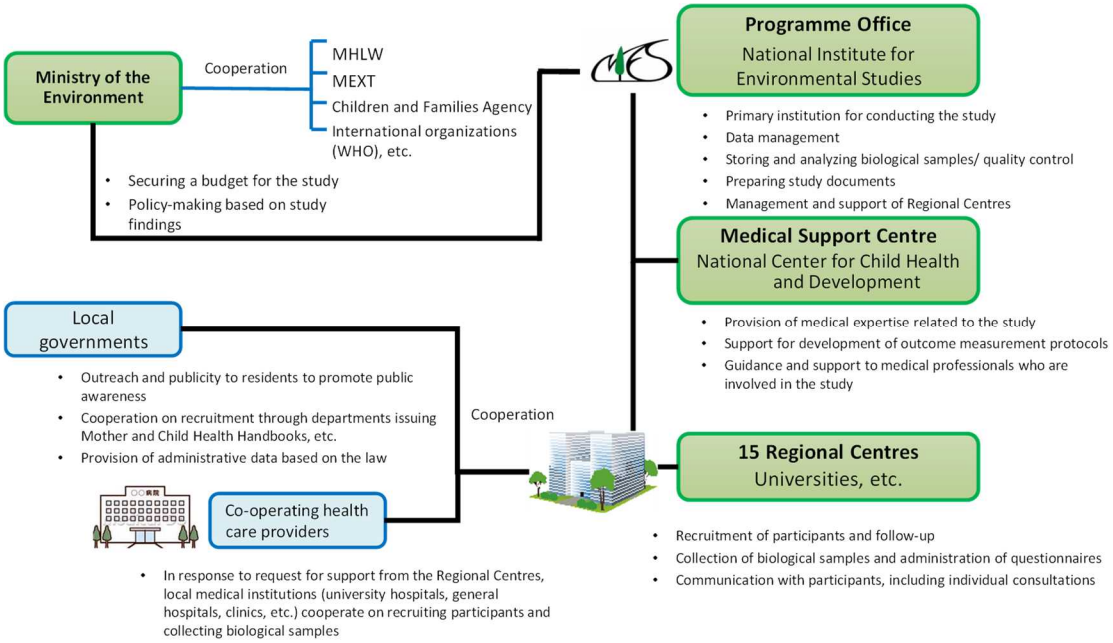

Figure 2 Organizational Structure of the JECS

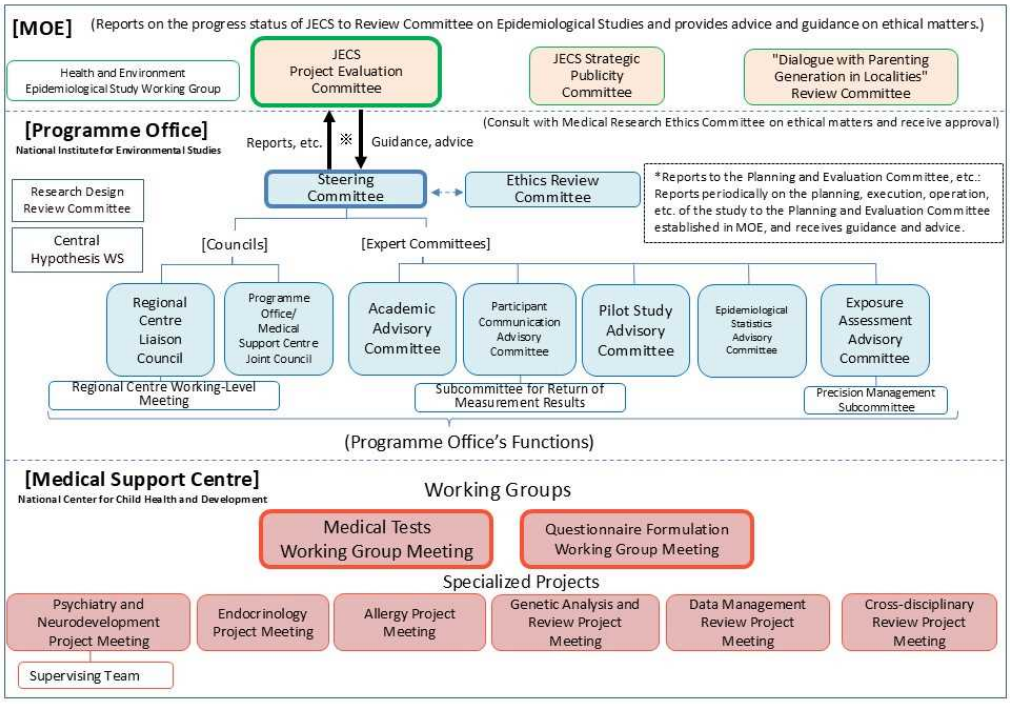

Figure 3 Operational System of the JECS

8-1 Ministry of the Environment

The Ministry of the Environment sets the basic principle, secures the funding, and evaluates the JECS project. In setting the basic principle, preliminary findings from the Pilot Study are utilized, and reviews are conducted with expert committees. To ensure the smooth conduct of the study and effective contribution to society through the study findings, the Ministry of the Environment coordinates with the relevant ministries, agencies, and international organizations. The Ministry of the Environment is also responsible for returning study findings to society by publicizing the project to a wide range of audiences and disseminating information.

8-2 Programme Office

The Programme Office, established in the National Institute for Environmental Studies, is the central organization responsible for the conduct of the JECS. It undertakes the overall management and operation of the study.

The Programme Office operates a data management system that consolidates and stores data related to the study (excluding genetic information), develops systems

for sharing data, stores and analyzes biological samples and environmental specimens, and develops protocols and standard operating procedures related to the study. It also cooperates with the Regional Centres to carry out publicity and communication activities related to participant follow-ups. Alongside managing the overall progress of the study, the Programme Office establishes the risk management policy, manages and supports the Regional Centres, and serves as a secretariat for the study as a whole. Additionally, it serves as a liaison office for academic collaboration within Japan and overseas and reports on activities related to this study to the Ministry of the Environment.

8-3 Medical Support Centre

The Medical Support Centre is established in the National Center for Child Health and Development to provide medical support related to the JECS.

With its medical expertise, the Medical Support Centre supports the Programme Office and cooperates to ensure the smooth conduct of the study. It leads research on genome and genetic analysis and undertakes the analysis, storage, and management of data related to genome and genetic analysis.

The Medical Support Centre takes on a leadership role in measuring health outcomes. It standardizes the selection of outcome measurement methods, outcome diagnosis and determination methods, develops protocols and standard operating procedures related to measurement, provides guidance on outcome measurement, trains staff responsible for outcome measurement, manages the precision of outcome measurements, and oversees the medical consultations related to these activities.

8-4 Regional Centres

The Regional Centres are established in 15 locations across Japan selected through an open call for entries when the JECS was launched, with the aim of recruiting approximately 100,000 people for this study. They are composed mainly of universities and research institutes. Each Regional Centre recruits participants in its respective designated Study Area and is responsible for conducting follow-up surveys until participant children reach 18 years of age.

Table 4. List of Regional Centres (2022)

NO	Regional Centres	Study Areas	University name (Joint research organization)
1	Hokkaido	Sapporo (Kita-ku and Toyohira-ku), Asahikawa, part of Kitami, Oketo, Kunneppu, Tsubetsu, and Bihoro	Hokkaido University
			Sapporo Medical university
			Asahikawa Medical University
			The Japanese Red Cross, Hokkaido College of Nursing
2	Miyagi	Kesennuma, Minamisanriku, Ishinomaki, Onagawa, Osaki, Wakuya, Misato, Kami, Shikama, Kurihara, Tome, Iwanuma, Watari, and Yamamoto	Tohoku University
3	Fukushima	Fukushima Prefecture	Fukushima Medical University
4	Chiba	Kamogawa, Minamiboso, Tateyama, Kyonan, Katsuura, Isumi, Onjuku, Ootaki, Kisarazu, Sodegaura, Futtsu, Kimitsu, Chiba (Midori-ku), and Ichimiya	Chiba University
5	Kanagawa	Yokohama (Kanazawa-ku), Yamato, and Odawara	Yokohama City University
6	Koshin	Kofu, Chuo, Koshu, Yamanashi, Fujiyoshida, Ina, Komagane, Tatsuno, Minowa, Iijima, Minamiminowa, Nakagawa, and Miyada	University of Yamanashi
			Shinshu University
7	Toyama	Toyama, Kurobe, Uozu, Namerikawa, Asahi, and Nyuzen	University of Toyama
8	Aichi	Ichinomiya and Nagoya (Kita-ku)	Nagoya City University
9	Kyoto	Kyoto (Sakyou-ku and Kita-ku), Kizugawa, and Nagahama	Kyoto University
			Doshisha University
10	Osaka	Kishiwada, Kaizuka, Kumatori, Izumisano, Tajiri, Sennan, Hannan, Misaki, and Izumi	Osaka University
			Osaka Medical Centre Research Institute for Maternal and Child Health
11	Hyogo	Amagasaki	Hyogo College of Medicine
12	Tottori	Yonago, Sakaiminato, Daisen, Houki, Nanbu, Kofu, Hino, Nichinan, and Hiezu	Tottori University
13	Kochi	Kochi, Nankoku, Shimanto, Yusuhara, Kohnan, Kami, Sukumo, Tosashimizu, Kuroshio, Ohtsuki, and Mihara	Kochi University
14	Fukuoka	Kitakyushu (Yahatanishi-ku) and Fukuoka (Higashi-ku)	University of Occupational and Environmental Health
			Kyushu University
15	South Kyushu/ Okinawa	Minamata, Tsunagi, Ashikita, Amakusa, Reihoku, Kami-Amakusa, Hitoyoshi, Nishiki, Asagiri, Taragi, Yunomae, Mizukami, Sagara, Itsuki, Yamae, Kuma, Nobeoka, and Miyakojima	Kumamoto University
			University of Miyazaki
			University of the Ryukyu

The roles of the Regional Centres for the immediate future are as follows.

A. Roles of the Regional Centres

1) Until the participant children reach 13 years of age

1. In principle, one Regional Centre recruits about 2,000 to 9,000 people over a three-year period and follows up with the participants. Regional Centres are not allowed to drop out of the study midway through the study period.
2. Regional Centres will conduct the Main Study and Sub-Cohort Study in accordance with the Study Protocol and standard operating procedures prepared by the Programme Office, while receiving instructions from the Medical Support Centre where necessary.
3. Regional Centres establish local conferences to ensure a cooperative relationship with local governments and medical institutions in the study area, and plan and operate the conferences.

[Items that Regional Centres should ensure in cooperation with local communities]

- Cooperation with the prefectures or municipalities in the Study Area
- Permission to look up the Basic Resident Register
- Consent of field staff (divisions in charge of children)
- Cooperation of medical associations (medical associations that are strongly related to this study)
- Cooperation with nursery school associations, kindergarten associations, Boards of Education, heads of neighborhood associations, welfare commissioners, etc.
- Establishment of local conferences (the following is an example of the members)
  - ✧ Head of Regional Centre (Chairperson)
  - ✧ Co-operating health care providers, medical associations, nursing associations, etc.
  - ✧ Person-in-charge of perinatal pediatrics (municipal level)
  - ✧ Person-in-charge of health (municipal level)
  - ✧ Person-in-charge of the environment (municipal level)
  - ✧ Public health center
  - ✧ Person-in-charge of education, such as Boards of Education, nursery school associations, kindergarten associations, elementary school principals, etc.

4. Regional Centres ensure an appropriate mechanism to obtain informed consent from participants. The consent forms should be paper-based and stored at the Regional Centre during the study period.
5. The following should be undertaken for expectant mothers who have given informed consent: (1) Registration in the data system; (2) Completion and submission of dedicated JECS checklist by doctors; (3) Administration of questionnaires; and, (4) Collection of blood and urine samples. The first collection of blood and urine samples should be carried out after receiving informed consent, and the second collection should be carried out at the end of the second trimester or start of the third trimester of the pregnancy.
6. During childbirth, cord blood and umbilical cord are collected and quickly handed over to the designated logistics service provider.
7. After childbirth, in accordance with the standard operating procedures prepared separately, biological samples are collected and handed over to the designated logistics service provider quickly or after cryopreservation.
8. Regional Centres conduct self-administered questionnaires about twice a year on participant children until they reach 13 years of age. In addition, face-to-face interviews are conducted, environmental specimens are collected, and biological samples (such as blood, urine and hair) are collected. The frequency of interviews and sample collection and the specific contents of questionnaires follow the standard operating procedures prepared separately.
9. Before participant children reach 13 years of age, Regional Centres obtain informed consent from their legal representatives (including informed assent of the children) for their continued participation in the study from age 13 to 18.
10. Regional Centres conduct a Sub-Cohort Study on selected participants. The contents of the Sub-Cohort Study follow the Study Protocol drawn up separately.
11. The Regional Centres are responsible for securing retention rates. Regional Centres with poor retention rates may have their funding reduced.
12. The Programme Office collectively provides newsletters and other information materials to participants, while each Regional Centre is expected to continue putting efforts to improve their retention rates.
13. The regular expenses (operating expenses for Regional Centres, comprising mainly of personnel expenses) disbursed to a standard Regional Centre with about 6,000 people is approximately 100 million yen per year. (This does not

include token of appreciation to participants) (Note: These figures are subject to change depending on the future funding situation.)

14. Regional Centres register the personal information of participants onto the database managed by the Programme Office. All information obtained through the Main Study and Sub-Cohort Study is managed centrally by the Programme Office, and the necessary data access rights are granted to the respective Regional Centres.
15. Regional Centres assign full-time risk managers and full-time information managers and secure a system that enables communication with the Programme Office and the Ministry of the Environment at all times.
16. Regional Centres provide a contact number/e-mail for participants, working together with the Programme Office.
17. Where necessary, the Regional Centres undergo research ethics reviews by the ethics committees of their affiliated institutions and obtain approval from the head of the institution for the study.
18. Recruitment is carried out based on the methods according to the standard operating procedures prescribed separately. Explanation to potential participants must include their possibility of participation in the Sub-Cohort Study in addition to the Main Study.
19. Regional Centres work together with the Medical Support Centre to conduct face-to-face interviews and other assessments based on standardized methods. The relevant staff are invited to participate in training sessions organized by the Medical Support Centre for such standardized methods.
20. Regional Centres conduct field surveys during predetermined periods. In principle, field surveys are conducted by a pair of nurse or public health nurse with another staff member. During these surveys, separately defined items are conducted. On these survey methods, the staff members are required to undergo training offered by the Medical Support Centre.
21. Other specific procedures for the Main Study and Sub-Cohort Study follow the standard operating procedures.

2) When the participant children are 13 to 18 years of age

(Including contents that will continue to be implemented from *1)

1. Regional Centres will follow up with participants. They will conduct follow-up surveys in accordance with the Study Protocol and standard operating procedures prepared by the Programme Office, while receiving instructions

from the Medical Support Centre where necessary.

2. Regional Centres establish local conferences to ensure that a cooperative relationship with local governments and medical institutions is set up in the Study Area, and plan and operate the conferences.
3. In accordance with the standard operating procedures prepared separately, biological samples are collected and handed over to the designated logistics service providers quickly or after cryopreservation.
4. Regional Centres encourage participant children to complete self-administered questionnaires until they reach 18 years of age. In addition, face-to face interviews are conducted and biological samples (such as blood, urine and hair) are collected. The frequency of face-to-face interviews and sample collection and the specific contents of questionnaires follow the standard operating procedures prepared separately. When participant children reach 16 years of age, Regional Centres will obtain informed consent from them for their continued participation in the study after age 16.
5. Regional Centres conduct a Sub-Cohort Study on selected participants. The contents of the Sub-Cohort Study follow the research proposals drawn up separately.
6. The Regional Centres are responsible for securing retention rates. Regional Centres with poor retention rates may have their funding reduced.
7. The Programme Office collectively send newsletters or other information materials to participants, while each Regional Centre is expected to continue putting efforts to improve their retention rates.
8. The regular expenses (operating expenses for Regional Centres, comprising mainly of personnel expenses) disbursed to a standard Regional Centre with about 6,000 people is approximately 100 million yen per year. (This does not include token of appreciation to participants) (Note: These figures are subject to changes depending on the future funding situation.)
9. Regional Centres register the personal information of participants onto the database managed by the Programme Office. All information obtained through the study (excluding Adjunct Studies) is managed centrally by the Programme Office, and the necessary data access rights are granted to the respective Regional Centres.
10. Regional Centres assign full-time risk managers and full-time information managers and secure a system that enables communication with the Programme Office and the Ministry of the Environment at all times.

11. Regional Centres work together with the Programme Office to establish contact offices for participants.
12. Where necessary, the Regional Centres of this study will undergo an examination by the ethics committees of the institutions they are affiliated with. Permission is obtained from the head of the institution for the implantation of the study.
13. Regional Centres work together with the Medical Support Centre to conduct face-to-face interviews and other assessments. based on standardized methods. To that end, the relevant staff participate in training organized by the Medical Support Centre to conduct face-to-face interviews and other assessments based on standardized methods.
14. Other specific procedures for the study (excluding Adjunct Studies) follow the standard operating procedures.

B. Benefits for Regional Centres

1. Access to data
   (a) Access to data collected by their own Regional Centres
   For specimens and questionnaires collected by Regional Centres, access rights to the data are granted to each Regional Centre once the Programme Office has completed the analysis and aggregation.
   (b) Rights to access full JECS data and publish papers
   Access to full JECS data and the right to publish papers is granted in accordance with the separately prescribed "Basic Rules on the Use of Data Collected through the JECS and Publication of Results."
2. Proposal rights to biological sample analysis and questionnaire contents
   Regional Centres can present proposals on the contents of the Main Study and Sub-Cohort Study for future analyses, such as how to analyze the biological samples stored at the Programme Office and items to be included in the questionnaires during the follow-up period.
3. Adjunct Studies
   Regional Centres may use their own funds to conduct adjunct studies, in addition to the Main Study/Sub-Cohort Study as far as that does not impact on these studies.

C. Operation of Regional Centres

1. Regional Centres should be able to fulfill all the "Roles of the Regional Centres." They are required to continue their operation until FY2032 when all participant children reach 18 years of age.
2. Regional Centres are required to have a system that enables them to communicate with participants, such as facilitating responses to questionnaires.
3. Regional Centres are required to have a system that facilitate the participant retainment and management of personal information.
4. Regional Centres are required to coordinate systems to conduct face-to-face interviews.
5. Regional Centres are required to disseminate study findings.

Reference: Selection criteria for Regional Centres (during the open recruitment conducted in 2010)

1. To be able to fulfill all the "Roles of the Regional Centres." Specific conditions, efforts, and schemes that allow them to better fulfill the respective criteria will be considered an advantage.
2. As a selection criterion, particular emphasis is placed on whether the recruitment method is appropriate for the population base.
3. As a selection criterion, particular emphasis is placed on the ability to designate areas where potential participants have characteristic exposures, as target areas for the study.
4. As a selection criterion, particular emphasis is placed on the ability to reduce the operational costs of the Regional Centre through creative efforts.
5. Particular emphasis is placed on previous successful experience of conducting epidemiological studies. Possessing research capabilities, systems, efforts, and schemes that can contribute in particular to examining the central hypotheses will be considered an advantage.
6. Within a Regional Centre, in principle, a system should be established for collaboration and cooperation between relevant departments such as obstetrics, pediatrics, and environmental science, while focusing on the environmental health and public health departments.
7. A system for collaborating and cooperating with Co-operating health care providers has been established or is expected to be established (if already established, it will be considered an advantage).

8. A system for collaborating and cooperating with local medical and educational organizations (for example, medical associations, nursing associations, kindergarten/nursery school associations, neighborhood associations and educational organizations) has been established or is expected to be established (if already established, it will be considered an advantage).
9. A system for collaboration and full-scale cooperation with the local governments of planned recruitment areas has been established or is expected to be established (if already established through agreements, it will be considered an advantage).
10. To have coordinated beforehand with other Regional Centre candidates on planned recruitment areas.
11. To have the personnel and organizational infrastructure to function as a stable Regional Centre for 16 years.
12. To be able to have systems and prepare physical spaces, etc. to ensure information security.
13. To be able to prepare technically and organizationally to enable access to the JECS database managed by the Programme Office, via the Internet and using the protocols specified by the Programme Office.

8-5 Co-operating Health Care Providers

Local medical institutions that register expectant mothers as study participants and collect biological samples at the request of the Regional Centre are referred to as "Co-operating health care providers."

Medical institutions that are anticipated to serve as Co-operating health care providers include clinics, general hospitals, the obstetric and pediatric departments of university hospitals, perinatal medical centers, where expectant mothers and participant children in the Study Areas are likely to visit for medical consultations.

8-6 Local Governments

Local governments are in the Study Areas are expected to cooperate in the following ways:

- Participation in local conferences
- Cooperation on outreach and publicity to the local community to promote

public awareness (including circular notices)
- Cooperation on recruitment through departments issuing Mother and Child Health Handbooks, etc. (during recruitment)
- Collaboration on health checkups for infants, etc. (for the study phases during infancy, early childhood, and schooling age)
- Permission to look up the Basic Resident Register

8-7 Outsourcing

The Ministry of the Environment, Programme Office, Medical Support Centre, and Regional Centres may outsource some of the work required for the study to external contractors or organizations, where necessary. The contracting entity is responsible for overseeing and managing contractors to ensure that outsourcing does not compromise the study's quality as per defined standards.

8-8 Study Organizations for the Pilot Study

The respective organizations are responsible for conducting the Pilot Study, which precedes the Main Study. Detailed study plans are coordinated with the Programme Office.

9. Study Implementation Procedures

9-1 Overview of Implementation

The JECS is a birth cohort study in which expectant mothers are enrolled during their first visit to obstetrics facilities, and the children born are longitudinally tracked until the participant children reach about 40 years of age.

This study involves gathering information from participants through self-administered questionnaires and collecting biological samples. Where necessary, information is obtained from public institutions and other organizations through data-sharing cooperation. Self-administered questionnaires are mailed until participants reach 12 years of age, while a participant portal system will primarily be used to conduct online questionnaires from age 13 onward. Biological samples are necessary to enable the objective measurement of health outcomes and exposure, and the JECS aims to collect samples at appropriate timings during the study period (for example, once between the ages of 13 and 18, and several times

between the ages of 18 and 40). With the anticipated advancement of digitalization of health and medical information in the future, obtaining individual identification numbers, with participant consent, may be considered for linking health data.

As this is a nationwide study, study procedures are standardized nationwide, except under exceptional circumstances.

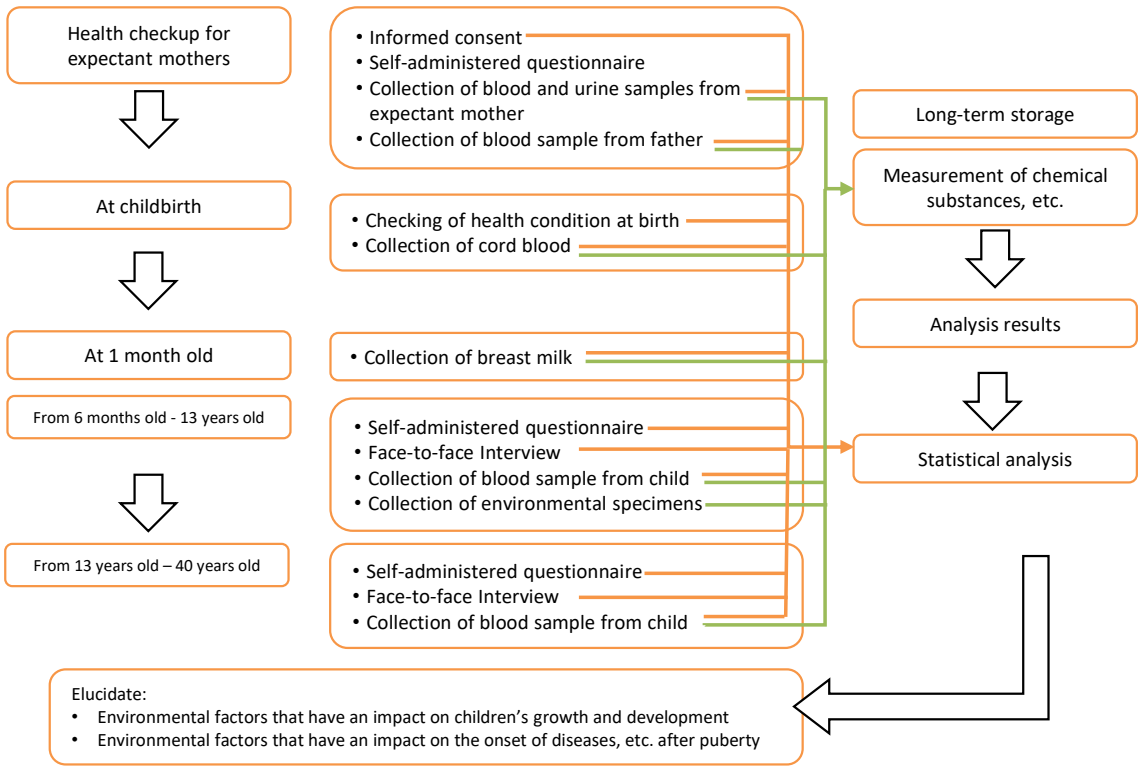

Figure 4 Overview of the Implementation of JECS

9-2 Study Participants

The JECS follows children born to expectant mothers enrolled in the study, with follow-up surveys continuing until the participant children reach about 40 years of age.

Expectant mothers were recruited over three years from January 2011 at Regional Centres across Japan. At Co-operating health care providers (obstetrics facilities) affiliate with Regional Centres, all potentially eligible expectant mothers were invited to participate. Detailed explanations were provided during their visits to the medical institutions (during their first visit as far as possible) before obtaining their informed consent to participate in the study. While the first trimester of pregnancy

(less than 14 weeks) was considered to be ideal, registration up to before birth were not excluded.

As the participant children will be followed up from childhood to adulthood in the study for age 13 and after, informed consent will be obtained from the legal representatives of the participant children for the study plan from ages 13 to 18. Furthermore, informed consent for follow-up surveys will be obtained from the participant children themselves after they reach 16 years of age.

9-3 Overview of Study Items, and Schedule

The proposed study schedule is outlined in Table 5. Specific study items based on this schedule shall be detailed in the Study Protocol and other documents. These documents will be periodically updated based on future funding availability, study progress, and other pertinent factors.

Table 5. Overview of Study Plan

Timing	Main Study	Sub-cohort Study
At recruitment (first trimester)	Filling in of medical record Self-administered questionnaires for father/mother Mother: Collection of blood and urine samples Father: Collection of blood samples	
Second – Third trimesters	Self-administered questionnaire Mother: Collection of blood and urine samples	
At delivery	Filling in of medical record Collection of cord blood	
During hospital stay after delivery	Collection of blood (mother), filter paper blood sample (child), hair sample (mother)	
1 month after birth	Filling in of medical record Self-administered questionnaire Collection of mother's and child's hair samples	

6 months – 6 years after birth	Self-administered questionnaire	At 1.5 years old: Environmental measurement At 2 years old: Psychoneurological development examination (interview) Medical examination (blood tests, physical measurements, etc.) At 3 years old: Environmental measurement At 4 years old: Psychoneurological development examination (interview), medical examination (blood tests, physical measurements, etc.)
6 – 12 years old	Self-administered questionnaire Collection of information from school medical records Collection of deciduous teeth that have fallen off At 8 years old: Psychoneurological development examination, physical measurements, collection of urine sample At 12 years old: Pediatric examination, psychoneurological development examination, physical measurements, collection of blood and urine samples	At 6, 8, 10, and 12 years old: Individual exposure monitoring (about 2 times) At 8, 10, and 12 years old: Psychoneurological development examination, medical examination (blood tests, physical measurements, etc.)
13 – 15 years old	Self-administered questionnaire	
16 years old	Self-administered questionnaire Physical measurements, collection of blood and urine samples	
17 years old	Self-administered questionnaire	
~ about 40 years old	(Study contents will be reviewed in the future)	

9-4 Self-administered Questionnaires

Self-administered questionnaires are conducted through post until the participants are 12 years old, and primarily through an online questionnaire format from age 13 and after. The Study Protocol will be prepared with consideration given to participant retention and burden on participants.

Standardized methods are needed for conducting self-administered questionnaires to ensure response validity and reliability, while full consideration also needs to be given to the receptivity of participants.

9-5 Collection, Transportation, Analysis, and Storage of Specimens

In this study, biological samples are provided by participating mothers, children, and fathers.

1) Collection of Biological Samples

Biological samples (hair, urine, blood, breast milk, milk teeth, and other samples) are collected. The type of samples, collection period, and collection method are specified in the standard operating procedures and the procedures are carried out in a standardized manner nationwide.

2) Transportation, Analysis, and Storage of Biological Samples

The Programme Office oversees the transportation, analysis, and storage of biological samples. Quality management of biological samples is fundamental for the study data, and quality management measures are needed in an efficient manner.

It is necessary to consider storage in the separate forms of temporary storage for interim analysis which needs putting in and taking out samples, and long-term storage for stale preservation for a long period of time. Please refer to “11. Long-term Storage of Biological Samples” for the details for long-term storage facilities.

3) Collection, Analysis, and Storage of Environmental Specimens

Collection, analysis and long-term storage of environmental specimens are effective to assess chemical exposure in the living environment, such as household environment and analyze their impact on children’s health. Analysis and storage are planned for the environmental specimens that have been collected.

4) Quality Control

The Programme Office plays a central role in quality control related to analyses for this study. It is necessary to employ the latest measurement techniques to ensure the quality of measurement data. An efficient management system needs to be established, including a medium- to long-term development of research facility development plan.

9-6 Linkage with Health and Medical Information

While prioritizing personal information protection, consideration is need for advancing coordination with the relevant organizations on linkage of the JECS data

with other health and medical information. Building trust with participants is crucial in collecting health and medical information. Initiatives to alleviate participant concerns shall be established including about future data usage.

9-7 Follow-up

Given the multi-decade duration of follow-up period, maintaining a stable research operation structure is imperative. Through various creative efforts, the aim is to achieve an 80% or higher retention rate until participant children reach 13 years of age, with continued high retention rate thereafter. In particular, with the extension of the study period, it is necessary to further strengthen efforts for higher retention rate.

Regional Centres, under the management and support by the Programme Office and Medical Support Centre, conduct follow-up of participants primarily through their environmental health and public health departments, as well as in cooperation with departments related to pediatrics, environmental science, and other relevant departments.

With regard to ongoing efforts to obtain the long-term participation mainly by each Regional Centre, it is necessary to consider establishing an operating structure for following up with participants, as they may relocate to various parts in the country for further studies or employment.

1) The following are examples of matters that need for the follow-up;

(a) Maintenance of retention rate

- Participants' satisfaction and understanding should be prioritized.
- Continuous communication is needed with participants to conduct self-administered questionnaires and physical examinations at different timings.

(b) Understanding reasons for case censoring and outcomes

- Each Regional Centre is responsible for the Main Study and Sub-cohort Study for the participants they recruited.
- Participants' relocation to areas outside the Study Areas results in missing data such as face-to-face interviews, but self-administered questionnaires continue to follow-up such participants.
- In case of relocation to a study area that is under another Regional Centre,

the study case may be passed on to the Regional Centre of the area that the participant relocate under agreement.

- Regional Centres constantly need to know the response rate for follow-up questionnaires and put efforts into maintaining a high retention rate.
- With the use of population demographic statistics, the Basic Resident Register, and other data sources, follow-up should be conducted on disease infection or death (causes of death) of participants (children, fathers, mothers).
- For participants who have become uncontactable, information about their situation should be obtained through phone calls, home visits, accessing administrative data, or other means.

(c) Obtaining information about the situation for participants with particular diseases

- Information should be obtained from the medical institution/physician the participant registered.

2) The following are examples of efforts to maintain retention rate;

- Timely and appropriate information provision/exchange to participants (e.g., newsletters, websites, portal sites for participants)
- Keeping track of their places of residence

9-8 Quality Assurance for the Study, and National Standards

To ensure the quality of data from the large-scale Main Study and Sub-Cohort Study, which are conducted according to standardized specifications, standard operating procedures are established for each study. Personnel training is conducted, supplemented by e-learning tools and other relevant resources as needed.

Standard operating procedures shall be prepared for each of the following items.

- Survey procedures
- Biological sample related processes, including collection period and methods, transportation, analysis and measurement items, and analysis and measurement methods
- Standards for outcome evaluation and corresponding evaluation methods
- Data management and data sharing protocols

- Risk management and communication practices etc.

10. Data Management

Management of study data is conducted in compliance with the “Ethical Guidelines for Medical and Biological Research Involving Human Subjects” (MEXT, MHLW, METI). Data must be properly prepared, managed, processed, recorded, and stored.

Data handled in the JECS includes paper-based records such as questionnaires and consent forms, encoded text and image data, clinical data and other existing information, digital records for biological sample storage and management, as well as analysis data for chemicals substances. All materials used in this study (e.g. cooperation request forms, consent forms, questionnaires, biological sample storage containers) are assigned unique material category codes and serial numbers that remain consistent throughout the study period.

1) Data storage and management

All the data collected in this study are stored and managed in databases operated by data centers that comply with the Information system Security Management and Assessment Program (ISMAP). Access to these databases is strictly controlled. Data is continuously backed up at the data centers and stored remotely at a separate site to safeguard against potential caused by disasters.

Long-term storage of the data obtained in this study is supervised by the Programme Office. During the period between follow-up and data analysis, the data is processed to prevent easy identification of individual subjects. Correspondence tables are created to enable identification information, and the data and these tables are stored separately. After this period, the plan is to store and utilize the information for an indefinite long period of time by removing identifying information from the data and obtaining consent of participants.

2) Data management system

A progress management system is established to monitor and support study operations, including participant recruitment, registration, consent acquisition; the status of self-administered questionnaires (data entry, distribution, receipt and storage); acquisition of clinical information; monetary token disbursement; and

handling inquiries. Additionally, a system is in place to manage biological sample collection, transport, analysis and storage.

Access rights to collected data in this study is strictly controlled. All system users are registered with the Programme Office, and their access rights are assigned based on the user's affiliated organization (Programme Office, Medical Support Centre, Regional Centre), the user level, and database attributes. User authentication involves appropriate methods, such as biometric verification, to ensure secure access to the data management system.

3) System security

The data management system is secured according to the information security policy of the National Institute for Environmental Studies. Organizational, personnel, physical, and technological measures are implemented to ensure an appropriate level of security, with consideration also given to consistency with relevant regulations such as the Ethical Guidelines for Medical and Biological Research Involving Human Subjects, Guidelines for Safety Management of Medical Information by Providers of Information Systems and Services, and the Act on the Protection of Personal Information.

4) Other matters

To facilitate the smooth execution of the study, tools are employed such as document management systems for basic documentation and standard operating procedures, web conferencing systems, as well as websites (for the general public, for study participants) and portal sites (for study participants, for study stakeholders).

11. Long-term Storage of Biological Samples

Certain biological samples provided by participants (e.g. blood, urine, breast milk) are planned to be stored long-term in storage facilities managed by the Programme Office. These samples may utilized for future analysis, including those not initially planned during the study design phase. In addition, blood and other biological samples are stored for long-term for potential genetic analysis.

Biological samples stored long-term serve as a snapshot of exposure information at

the time of collection (or integral values such as POPs in breast milk), and long-term storage facilities act as “time capsules” storing biological samples for the future. Long-term biological sample storages ensures the potential to obtain valuable insights into effects that were unknown at the time of sample collection and cannot be acquired through other means.

1) Period, etc. of long-term storage required for the JECS

Storage facilities store biological samples (e.g. blood, urine, breast milk) collected from mothers, children, and fathers who participated in the study, over the long-term. Since the study involves recruiting expectant mothers and tracking their children until they reach about 40 years of age, consent will be obtained to store the biological samples beyond the completion of the study.

Efforts should be made to secure consent for the longest possible duration and broadest scope to accommodate future needs, such as the analysis of emerging chemicals, biomarkers, disease-related genes and causative genes, or requests from other studies on children’s health.

Given that certain substances exhibit toxicity after more than 20 years from exposure, as observed in carcinogens and substances with endocrine disruptor effects, it is essential to establish a storage system capable of storing samples for several decades to enable the comparison of long-term effects of such substances with past exposure information. With regard to the continued storage of samples after the completion of the study, periodic reviews should be carried out on policies on facility maintenance, management, and renovation, as well as the extension of storage period.

2) Management of biological samples

Proper management of biological samples is critical to ensure their effective use over the medium- to long-term. Management procedures must ensure that the location and condition of stored samples are continuously monitored. In the management of samples, particular emphasis is placed on stable and reliable long-term storage, ensuring anonymity, and preventing the spread of infectious pathogenic microbes and viruses. Particularly from an analytical chemistry perspective, it is extremely important to ensure traceability from sample collection through transportation and storage, as well as preventing contamination and quality

degradation.

Inventory management: Receipt, storage, disposal of biological samples and history of provision for analysis.

History management: Condition during collection and storage, temperature, freezing/defrosting/dispensation

Tracking: Date and time samples are sent, their destination, confirmation of receipt

Safety management: Implementation of robust safety management measures

Consideration for infection prevention

Backups for power outages, decentralized and redundant storage

Information management: Assignment of personal information managers

Education for staff handling the samples

3) Facilities and equipment for long-term storage

Since the primary objective is the analysis of chemicals, samples should be processed as little as possible before storage (out of concerns that information may be lost due to contamination, quality degradation, and removal as a result of preprocessing procedures). It is preferable to store them under refrigerated conditions at low temperatures as possible, away from light and oxygen.

12. Risk Management

1) Responding to health risks that participants can avoid

During the study, if it is determined that participants face health risks and there are viable methods to migrate these risks, or if the circumstances outlined in relevant standard operating procedures are applicable, the participants and their guardians must be contacted immediately. The situation should be explained, and appropriate medical advice provided, including referrals to specialist physicians if needed. Regional Centres may seek advice from the Programme Office and the Medical Support Centre when making these determinations. Once participants have been contacted in this context, Regional Centres should report the details to the Programme Office.

2) Responding to accidents related to the study

To address potential accidents related to the study, standard operating procedures for risk and crisis management must be established and implemented in

cooperation with all research implementing organizations. Each research implementing organization is required to appoint a risk manager, conduct risk evaluations, and take proactive measures to prevent foreseeable risks. In the event of an accidents, it must be reported swiftly to the risk manager, and dealt with through prompt cooperation with the risk manager of the Programme Office.

Potential accidents include technical errors, adverse health effects on participants, and breaches of personal information confidentiality.

3) Insurance coverage for the JECS (compensation for research-related incidents)

It is necessary to take up accident and liability insurance coverage in case of any research-related harm that may occur to participants.

In the event of harm to participants, compensation is not limited to financial reimbursement; it may also include providing necessary medical treatment at an appropriate medical institution.

4) Risk management for data and biological sample storage and utilization

Designated personnel responsible for data and biological sample management are appointed at the Programme Office to oversee these processes. Business continuity plans (BCP) are drawn up for data and sample management respectively, and data and samples are managed so as to prevent their loss even during emergencies such as natural disasters or large-scale power outages.

To mitigate risks of data or sample loss in the course of usage, management is carried out by appropriately entering into usage agreements and joint research agreements.

5) Risk management related to publication and utilization of study results

Study results are expected to be published as academic papers and through various media channels, including press releases. It is desirable to appoint a person-in-charge to manage public responses to press releases and to respond to inaccurate or misleading comments circulated on social media platforms.

13. Protection of Participants and Communication

1) Establishment of contact offices

A call center is established to handle inquiries from participants during the study. Responses are provided immediately by using periodically updated FAQ databases. Depending on the contents of the inquiry, responses may also be provided independently according to the standard operating procedures. For inquiries that cannot be resolved via the FAQ, participants are given the contact number of the appropriate Regional Centre. In case where calls are received outside of office hour of the Programme Office or Regional Centres, or the inquiry cannot be resolved immediatedly, the call center records the inquiry and contacts the Programme Office or Regional Centres on the next working day.

Apart from study-related inquiries, participants may seek assistance for matters such as childrearing difficulties, medical consultations, or other matters. The call center is encouraged to address such peripheral needs as far as possible. User-friendly inquiry methods, including online inquiry forms, are also considered to improve accessibility for participants.

2) Reporting measures required

Standard operating procedures outline the procedures to be taken in the event that cases of child abuse, domestic violence, bullying, or similar concerns are uncovered. Such incidents are handled in accordance with the standard operating procedures.

3) Protection of personal information

Requests from participants for information disclosure are processed by the National Institute for Environmental Studies, where the Programme Office is based, following the institute's established regulations. To ensure information security, the study complys with the information security policy of the National Institute for Environmental Studies.

From the viewpoint of personal information protection, access rights to personal information databases, as well as correspondence tables linking personal information data with study data, are held by the Programme Office and Regional Centres under strict management. This principle is maintained even in situations

where direct contact with participants is required for the Programme office for progress management or follow-up purposes.

4) Communication with participants

Effective information provision and communication are carried out to encourage participants' long-term involvement in the study, even beyond adolescence. Participants receive tailored explanations, appropriate to their age, about the personal, societal, and international significance of their participation. Efforts are made to instill a sense of pride in contributing to the study.

With regard to communication, it is also necessary to maintain a system that facilitates direct involvement through the Regional Centres while making use of information and communication technology (ICT) and developing applications. Regular surveys, consistent information sharing, and communication via the participants portal are carried out periodically to strengthen trust between participants and researchers. Models from previous research projects, such as the Avon Longitudinal Study of Parents and Children (ALSPAC) in the United Kingdom, are reviewed to promote the study while engaging participants.

As for the analysis results for biological samples and self-administered questionnaires, efforts are made to proactively share information and take effective communication with participants based on the intention of participants as confirmed when obtaining their consent.

5) Reporting of study results

When analysis results are deemed beneficial to participants, efforts are made to proactively provide this information individually. During the consent process, participants are given the options to choose whether they wish to be informed of such results and their wishes are respected.

General and well-established findings, such as dietary assessment results, are provided to all participants. Careful consideration is given to the manner in which information is conveyed to prevent causing unnecessary anxiety.

6) Genetic analysis and genetic counselling

As a general rule, participants are not informed of the results of genetic analyses.

However, significant findings that should be provided to the participants, such as incidental findings that have been found during the genetic analysis process, are continuously reviewed in consultation with experts.

7) Token of appreciation and benefits

While valuing protection of participants and communication with them, they are recognized for their contributions to the study through a predetermined monetary token of appreciation for tasks such as completing questionnaires and providing biological samples. In addition, mechanisms to support participants on their consultations on matters such as health and childrearing, are developed as additional benefits of participation.

14. Consideration for Ethics and Informed Consent

This study, led by the Programme Office based in the National Institute for Environmental Studies as the primary research institute, is subject to research ethics reviews through the centralized research ethics review method, and receives approval for the study from the head of the institution (President of the National Institute for Environmental Studies). Subsequently, approval is also obtained from the heads of organizations comprising the Regional Centres, which serves as joint research organizations. Reports on the progress status of this study are periodically submitted to the Review Committee for Epidemiological Research, established under the auspices of the Ministry of the Environment, and feedback is provided by the Committee as necessary.

1) Ethical guidelines and ethics committees

This study, including the handling of personal data and biological samples, adheres the Act on the Protection of Personal Information and the Ethical Guidelines for Medical and Biological Research Involving Human Subjects (MEXT, MHLW, METI). Application forms for research ethics review for this study are prepared accordingly, consultations are held with the Medical Research Ethics Committee of the National Institute for Environmental Studies for the Main Study and Sub-Cohort Study, and approval is granted by the President of the National Institute for Environmental Studies. Thereafter, when ethics reviews are required by the ethics committees of affiliated organizations (such as universities, research institutes, and medical institutions) of the Regional Centres, which are joint research

organizations, approval for the study is granted by the respective heads of these organizations following institutional ethics committee reviews. If a separate ethics review is necessary within a joint research organization, it is conducted by the respective organization's institutional review board before the research is implemented.

Adjunct studies are conducted independently by the Regional Centres with approval for research implementation from the head of the organization, after a review has been completed by the Institutional Review Board of the organization that the Regional Centre is affiliated with.

2) Informed consent

Informed consent is obtained directly from mothers and fathers for the participation in this study. For participant children, since long-term follow-up is required from childhood through adulthood, consent is obtained at different stages using appropriate methods. Specifically, consent for the study until 13 years of age is obtained from the child's mother at the time of her recruitment. For the study between the ages of 13 and 18, consent is obtained from their legal representatives before the child reaches age 13. From age 16 and onward, consent is obtained from the participant children themselves. Additionally, until participants reach 16 years of age, efforts are made to provide information directly to participating children and confirm their informed assent.

Explanatory documents and consent forms for the Main Study and Sub-Cohort Study are standardized across all the Regional Centres. During the consent process, research staff carefully explain the purpose of the study, procedures including biological sample analysis and long-term storage, and other information using clear, accessible language to ensure participants understand before they consent.

For items planned from the outset, consent is obtained during recruitment. If a new study component is later added that was not part of the original plan, separate consent is obtained for that specific component. However, for self-administered questionnaires, participants are not required to provide additional consent, as they may decline to answer any specific question. Specifically, for mailed self-administered questionnaires, participants are instructed at the beginning of the questionnaire: "If you do not wish to answer a question, please indicate your

intention by placing a cross (x) in the response field." For online self-administered questionnaire, a mechanism is implemented that allows participants to skip questions they do not wish to answer.

Refer to sections 10.1 and 11.1 for further information on consent related to the long-term storage of data and biological samples.

During the recruitment process, participants are also informed about and asked to consent to the use of local government data to verify their status when they become uncontactable by other means.

Consent forms are retained and securely managed at Regional Centres for the long-term, ensuring that participants can be followed up with throughout the study.

15. Use, Analysis, and Sharing of Data and Biological Samples Obtained Through the Study

In the analysis of data obtained through the study, the greatest priority is given to the study objective, which is to elucidate the relationship between environmental factors and the health of children.

The data collected through this study is highly valuable, encompassing environmental, genetic, social, and lifestyle factors. To maximize the study's scientific contributions, data sharing is encouraged across diverse research disciplines, including social sciences and economics. This approach aims to broaden the scope of research outcomes and foster solutions to biopsychosocial challenges faced by children. Mechanisms for the appropriate provision of biological samples to researchers, with the consent of participants, will also be reviewed and implemented.

Data sharing will be carried out in accordance with a separately defined data sharing implementation plan. By actively promoting data sharing with researchers, the study seeks to enhance data analysis efforts and promote the publication of findings. For each research proposal involving shared data, participants will be informed, and mechanisms will be in place to allow participants to express their intentions should they not wish to have their data included in shared data analysis.

The overall and general statistical analysis conducted as part of this study will include, but are not limited to, the following categories: (1) Analysis of exposure; (2) Analysis of self-administered questionnaires; (3) Analysis of outcomes (diseases/symptoms); (4) Testing hypotheses combining the above elements.

16. Conveying the Benefit of Study Findings to Society, and Information Dissemination

The JECS is a pioneering cohort study on the healthy development of children, conducted at an unprecedented scale and level of quality in Japan. One of its primary aims is to enhance and strengthen public health countermeasures related to chemicals, with a commitment to proactively returning the study outcomes to society. Findings from the JECS are required to actively shared through presentations at scientific conferences and publications in academic journals, both domestically and internationally. To ensure scientific rigor and consistency in the dissemination of study findings, any publication of academic papers must follow the established procedures outlined in the study's basic rules. In addition to national-level data analysis, regional analyses of environmental and health issues are also expected as valuable study outcomes. Furthermore, the JECS plays a critical role in publishing research findings that confirm the absence of significant health impacts.

A key focus of the study in public outreach. To facilitate this, user-friendly materials will be created and widely distributed to the general public. For academic papers, simplified summaries written in plain language will also be prepared for the general public. These public dissemination efforts aim to foster societal benefits through the study findings and encourage behavioral changes among the general public and consumers who are the target audience. These public dissemination strategy will be made through collaboration with various stakeholders, such as future generations of parents, expectant mothers, influencers with significant reach among parenting communities, policymakers from relevant ministries and agencies, and product manufacturers interested in consumer behavior and awareness. Specific initiatives, such as symposiums and dialogue sessions, will be organized to promote awareness and understanding of the JECS. Where applicable, study findings will be shared with government bodies, local governments, and other organizations to support policy formulation including development and revision of guidelines and projects, while also considering prior research findings and both domestic and international contexts. In particular, emphasis should be placed on collaboration with the school health and

educational sectors to reach future generations, ensuring broad dissemination of study findings. In addition, information about the study will continue to be shared with the news media, administrative organizations, healthcare institutions, academia, industries, and citizen organizations.

Efforts will also made to maintain participant involvement by providing regular updates on study progress. This includes a dedicated website for participants, sending e-mail newsletters, and promoting two-way communication through organizing events and other outreach activities. To sustain long-term public interest and ensure the continued relevance of the study, information about its findings and progress will be disseminated periodically and broadly.

Since this study has garnered international attention, efforts will also be made to disseminate information in English.

17. Implementation of Human Biomonitoring

To effectively assess chemical risks, it is essential to gain a comprehensive understanding of exposure levels to target chemicals, even if JECS findings indicate potential toxicity. It is important to conduct a human biomonitoring project alongside the JECS to enhance and maximize the study's overall outcomes.

18. International Collaboration

Particularly with regard to the analysis of rare diseases, an international collaborative research framework will be established, with careful consideration given to safeguarding personal information. Collaboration with relevant organizations will also be pursued to ensure the knowledge and technologies developed through JECS can contribute to technical support to developing countries. Efforts will be made to keep pace with global trends in chemical management and to incorporate JECS findings into international initiatives. In addition, JECS aims to strengthen partnerships with international organizations, including information sharing with the World Health Organization and other international agencies.

19. Costs of the Study

The costs associated with conducting the Main Study and the Sub-Cohort Study are covered by the project budget of the Ministry of the Environment.

For Adjunct Studies, the Programme Office, Medical Support Centre, and Regional Centres are responsible for independently securing necessary funding. This can be achieved by applying for competitive grants from the Ministry of Environment and other governmental agencies, as well as obtaining research funding from private-sector organizations.

20. Contracts for This Study

This study is conducted using the project fund provided by the Ministry of the Environment. As this is a nationwide study, all involved parties, including the Programme Office, Medical Support Centre, Regional Centres, Co-operating health care providers, individual researchers, and research staff members, must prioritize the validation of the study's central hypotheses as a national project over their own individual research goals. Contracts must be entered into with a shared understanding of this foundational principle.

21. Review of the Conceptual Plan

By FY2028 when the first cohort of participant children reaches the age of 17, a comprehensive review of the Conceptual Plan will be conducted. This review will assess and revise the operational structure to ensure the long-term continuation of the study in an effective, efficient, and sustainable manner.

Reference Materials: Review Organizations

Members of the FY2022 JECS Project Evaluation Committee

(Titles omitted, in order of the Japanese syllabary)

Name	Affiliation/Designation
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Health and Environment Epidemiological Study Review Committee
(Convened from July 2023 – March 2022)
Members

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Kichiro MATSUMOTO	Executive Director, Japan Medical Association
Akihiro YONEDA	Vice President, The Japanese Society of Pediatric Hematology/Oncology

Observers to the Health and Environment Epidemiological Study Review Committee

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Glossary

The terminology used in this Conceptual Plan are defined as follows.

Outcome (Consequences)	Changes resulting from causative factors (exposure, etc.), all changes observed in the health condition.
Informed assent	Refers to the expression of assent by research subjects who have been assessed objectively to be lacking in the ability to grant informed consent, who are given explanations about research to be conducted or continued in easy-to-understand terms corresponding to their comprehension ability, and who indicate their understanding of and assent to the conduct or continuation of the research in question.
Informed consent	Refers to consent granted by persons invited to be research subjects to become research subjects and on the handling of materials, etc. This consent is granted based on their own free will, and upon receiving adequate explanations from researchers, etc. beforehand about epidemiological research and acquiring understanding about the significance, purpose, methods, expected outcomes, and disadvantages, etc. of the epidemiological study in question.
Censor/censored	Dropping out from the follow-up studies. The state in which the resulting event has not yet occurred, and that of being unable to verify the occurrence of the said event after the final confirmation. (Censored due to relocation, death, etc.)
End point	Illness, symptoms, or other conditions that should be measured as the impact of causative factors (exposure, etc.) on health in the process of validating the hypotheses.
Chemicals in the environment	The study targets all chemical substances that we are exposed to, or at risk of being exposed to, in life in typical environments. The sources of exposure cover almost all the things that we come into contact with, including the air, indoor air, buildings, drinking water and domestic water, food, river basin water, soil, toys, furniture, etc.
Environmental factor	Environmental factors that have an impact of health in the adopted hypotheses. Primary factors.
Co-operating health care providers	Local medical institutions participating in the study in response to calls for cooperation from Regional Centres.
Conceptual Plan	Basic policy for JECS set out by the Ministry of the Environment.

Programme Office	The organization responsible for the overall coordination of this study.
Confounder/Confounding factor	Of the factors that have an impact on health, those that have an impact on the validation of the hypotheses adopted in this study.
Cohort study	In epidemiological studies, populations that share certain common characteristics are called “cohorts.” A cohort study follows up with these subjects, observes the health events that are occurring (disease, death, etc.), and elucidate the relationship between these health events and the causes.
Contamination	The contamination of biospecimens and environmental specimens from chemical substances in the environment or in containers, etc., during the processes of collection, transportation, analysis, and storage of biospecimens, and the processes of transportation, analysis, and storage of environmental specimens.
Participants	Persons participating continuously in this study.
Self-rating questionnaire Self-administered questionnaire	Questionnaires completed by the study subjects on their own.
Standard operating procedure	Describes the details and procedures for the execution of the Conceptual Plan and the Study Protocol in the implementation of this study. The standard operating procedures include manuals on system building, study procedures, support for local governments, support for Co-operating health care providers, risk management communication, analysis methods, precision management, data management, and study staff education.
Sub-Cohort Study	A study conducted on a part (5,000 people) of the 100,000-person cohort under the budget of the Ministry of the Environment.
Symptom	Physical or mental manifestations or signs that are characteristic of a disease- or health-related condition.
Checklist	A form for the investigators in the study to fill in the results of diagnosis and interviews.
Diagnosis	Processes or results that determine a health- or disease-related condition.
Biospecimen	Specimens collected from the body for the purpose of analysis and storage, such as blood, urine, nails, hair, saliva, buccal mucous membrane, umbilical cord, umbilical cord blood, placenta, vernix, meconium, breast milk, etc.

Main Study	A study conducted on a target cohort of 100,000 subjects under the budget of the Ministry of the Environment.
Congenital abnormality Congenital anomalies Congenital malformations	Congenital external and visceral abnormalities.
Consultation center	The primary consultation center for study subjects is the Regional Centre. Depending on the contents of the consultation, the inquiry may be handed over to the person-in-charge of consultations/emergency response of the Programme Office (nationwide), and the person-in-charge of consultations/emergency response of the Regional Centre (cases that are unique to a Regional Centre or related to a specific Co-operating health care provider, etc.)
Fetal period	Period from 10 weeks of pregnancy till birth.
Long-term storage	Refers to the long-term storage of biospecimens, environmental specimens, etc.
End of the study	Refers to the point when the study ends. Specifically, it is the point when follow-up has been completed for all study subjects (children), and the data (results of self-administered questionnaires, diagnosis results, analysis results, etc.) has been aggregated by the Programme Office. However, for study items that have been segmented from the Main Study, it refers to the point when the data for these items have been aggregated by the Programme Office or the Regional Centres. E.g.: When the study on ○○ has ended.
Participants (Mother)/ (Parturient) Participants (Child) Participants (Father)	Expectant mothers, husbands, and children (fetuses at the point of recruitment) registered in this study and continuously participating in data collection or specimen collection.
Study Area	Refers to the areas where recruitment of study participants (parturients) is carried out for this study. Comprises administrative units such as towns and villages, regional cities, wards, and areas under the jurisdiction of health centers. Regional Centres select one or more Study Areas with consideration given to factors such as number of births, regional representation, exposure to chemical substances, etc.
Adjunct Study	A study conducted with a limited number of participants under the independent budget of Regional Centres.
Follow-up	The implementation of diagnosis, face-to-face interviews, questionnaires, biospecimen collection, etc. on study subjects over

	time, to collect data and specimens.
Lost to follow-up	Continuously obtaining information related to exposure and results from the target population. Not necessarily limited to conditions where direct contact can be made with the subject. (includes follow-up of public information only) Cases where the subjects are unable to participate until the end of the research, for some reason or other.
Retention (participation rate)	The number of study participants for whom follow-up information can be (could be) obtained over time, divided by the number of study participants at the start of the study.
Registration	Disease registration refers to the work of gathering people who are afflicted by disease, in accordance with a certain set of criteria. However, in this study, registration refers to registration to participate in the study, upon receipt by the Programme Office or Regional Centres of the first questionnaire (registration form including letter of consent) filled in by participants who have agreed to participate in the study. Note that enrollment refers to the "registration work" itself.
Biomarker	Indicators that show the chemical substances and metabolites in biospecimens, as well as early biological effects. Used to assess the exposure to, and health impact of, chemical substances in the environment.
Biomonitoring	Refers to the assessment of exposure to chemical substances by measuring the indicators that show the chemical substances and metabolites in biospecimens, as well as early biological effects.
Pilot study	A preliminary study implemented on a small scale ahead of the Main Study.
Exposure	The exposure of an individual to the primary factors, and the extent of exposure.
Guardian	A person who has charge of/protects a minor's personal position/assets. Includes their birth parents, adoptive parents, relatives, head of a children's institution, etc.
Medical Support Centre	An organization that takes a leading role in measuring the indicators (outcomes) of health impact, etc. Also analyzes, stores, and manages data related to genomic/genetic analyses, among other work.
Face-to-face interview	A survey conducted in person by a doctor or trained expert.
Regional Centre	An organization that consolidates the Main Study in a region. Established in 15 locations across Japan.

Recruitment	Recruitment refers to the series of work of looking for study participants, inviting them to participate in the study, obtaining their consent, and registering them as participants.