

NIMD Annual Report
2010
(April 2010 - March 2011)

National Institute for Minamata Disease
Ministry of the Environment
Japan

Preface for Annual Report of Fiscal year 2010

Fiscal year 2010 was witness to a historical and catastrophic disaster in Japan. On March 11, 2011, an unprecedented disastrous earthquake struck eastern Japan, followed by a massive tsunami; approximately 20,000 people lost their lives or were reported missing as a result of this tragedy. The earthquake disaster caused a major accident at a nuclear plant, and the ensuing radioactive contamination continues to cause problems for the Fukushima area. I pray that the disaster survivors can avoid or recover from illness and disability and for the quickest possible recovery from this tragedy.

The budgetary demands of earthquake restoration have hampered the finances of both the Diet and local governments. Research organizations that are also private corporations have always been required to provide managerial efficiency, a wide range of services, and evaluations. However, in both private and public national research organizations, budgetary efficiency based on objective evaluations is now demanded. In view of this situation, we engaged an outside organization to evaluate our research institute and created a research evaluation committee and a conventional research evaluation committee for fiscal year 2010. Furthermore, we determined that the newly established research assessment committee should carry out an annual research evaluation, produce an evaluation of the mid-term plan every five years, and create a proposal for the following mid-term five-year plan. The fiscal year 2010 Research Assessment Committee was held on February 21, 2011. Although the organization assessment committee, which meets every three years, was due to meet in fiscal year 2010, the meeting was held on April 15, 2011, to finalize the renovation of the Minamata Disease Archives. Part of the second floor of the Minamata Disease Archives was updated based on recommendations from the external committee and from a previous Minamata Disease Archives administrative review meeting. We began planning in September 2010, and construction began in December and was completed in March 2011.

A significant event at the research institute during fiscal year 2010 was the completion of repair work on the rehabilitation facility. The rehabilitation facility did not receive the same earthquake-proofing repair work that the research center's main building received in fiscal year 2009. Because electronic devices such as lighting equipment had become faulty, and because water leakage occurred owing to an aging roof and outer wall fittings, the entire facility was reconstructed, beginning in December 2010. At this time, we moved a rehabilitation room and a research room (from the section undergoing renovations) to the main building of the research center. For this reason, patient rehabilitation was carried out in the main building conference room during the construction period. Construction was not completed before the end of 2010 for a number of reasons including design changes; the estimated completion time was extended to 2011. Construction was finally completed in July 2011. The rehabilitation room and research room were promptly reinstated in the rehabilitation facility after completion, and we resumed conducting patient rehabilitation in the rehabilitation facility.

A major topic of discussion concerns a study regarding the possibility of an objective evaluation system using magnetoencephalography (MEG) that has shown stable progress. Currently, the diagnosis of Minamata disease is made by a combination of epidemiological conditions and neurologic symptoms, and the lack of an objective index for diagnosis often causes confusion. If an objective rating system of brain dysfunction as a result of methylmercury poisoning—including Minamata disease—is established, it is expected to help health care workers to rehabilitate and provide a better environment for Minamata disease patients through the evaluation

of their brain functioning over time. In the future, we aim to establish an objective MEG-based rating system of brain dysfunction as a result of methylmercury poisoning, because a noninvasive measurement technique to visualize brain functioning without craniotomy would be quickly adopted. In 2010, we began to produce a new air puff device and develop an analytical method (areal mean signal method). We established an evaluation system consisting of a two-point distinction using MEG and an evaluation system utilizing the spread of sense stimulation from the peripheral to the central nervous system. In addition, we built a network for securing disease control (cerebrovascular disorders, Parkinson's disease, spinocerebellar degeneration, diabetes) in which a lesion necessary to identify the condition of a Minamata disease patient was obvious.

In terms of international collaboration, we held a workshop in Slovenia in cooperation with the Jozef Stefan Institute of the Republic of Slovenia. Furthermore, 14 specialists from outside the country were invited to the NIMD forum, promoting the exchange of knowledge research capabilities regarding mercury, the environment, and health.

An assistive technology class was held to offer rehabilitation services and information to local Minamata disease patients. Then, we started the "Community development project for home-care support and health care practice" and supported the independent management of the Izumi Rehabilitation Center. In the Minamata district, taking into consideration personnel training for occupational therapists, we held a "leader class" and performed instruction in all districts.

Moreover, aiming to revive Minamata and revitalize the town, we fostered talented social science researchers and strengthened the organization of research.

Because of the enforcement of the Special Measures Law and other provisions, Minamata has at last begun to recover from its extensive health issues and environmental pollution. Considerable amounts of time, money, and effort will be needed in the future for our country to recover from this serious disaster. With this annual report, we hope to obtain your opinion and counsel so that the activities of this research institute may continue, and so that its teachings on Minamata can help to eradicate the ill health resulting from the Minamata disaster and contribute to the recovery and promotion of the area.

October 2011

Director General
National Institute for Minamata Disease
Ministry of Environment
Japan
Juichi Abe

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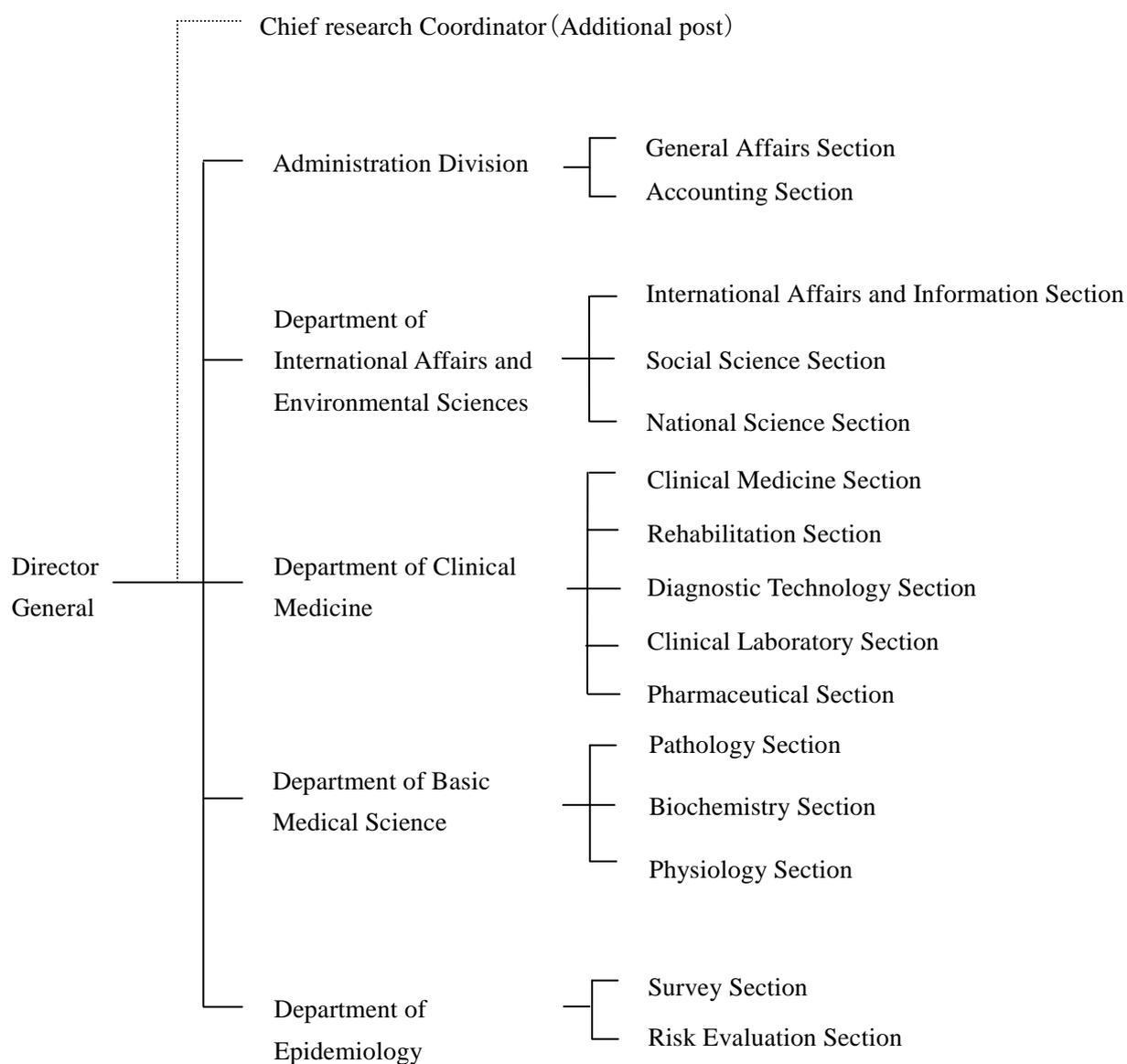
General Information

1. Organization and Operation

(1) Organization

The National Institute for Minamata Disease is divided into the following departments: Department of International Affairs and Environmental Sciences, Department of Clinical Medicine, Department of Basic Medical Science, Department of Epidemiology, and the Administration Division. In total, the organization consists of 4 departments, 1 division, and 13 sections, employing 30 people.

In addition, we have installed a chief research coordinator, who controls important matters regarding office work at the center.



(As of March 31, 2011)

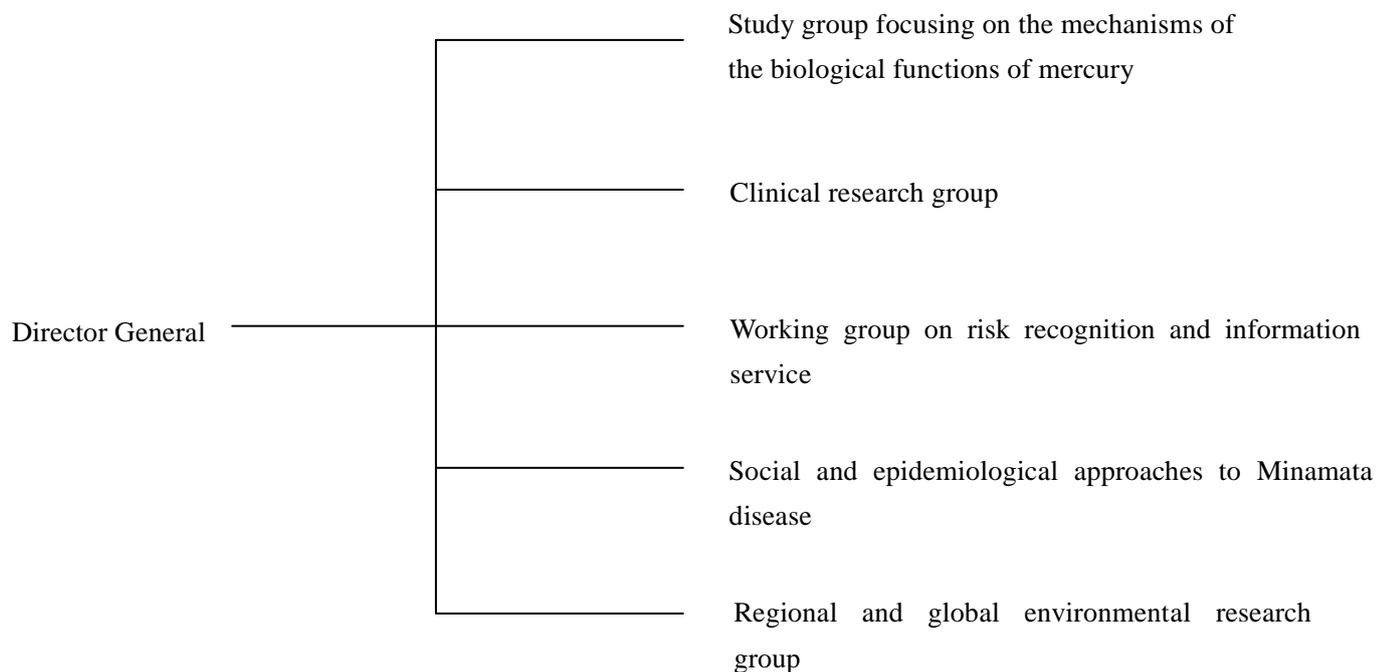
(3) Operation

The following is a classification of the research activities and duties of NIMD based on its mid-term five-year plan:

- 1) Project research: Surveys and research in key research fields are carried out by teams formed across departments.
- 2) Fundamental research: Efforts are made to improve research potential at NIMD and to develop human resources from a long-term perspective.
- 3) Other activities: Efforts are made to clarify tasks associated with research, and they are undertaken by the organization as a whole.

Moreover, we classify project research, fundamental research, and other activities into five groups described below by their purposes, and we promote interdepartmental collaborations on investigations, research, and other activities. We share information between groups and progress together to enable flexible correspondence that is not bound by the framework of the organization.

The current medium-term five-year plan is for fiscal years 2010–2014.



2. Budget, Employees, and Institutional maintenance

(1) Budget

(Unit: 1000 yen)

| Expense type | FY 2010 | FY 2009 | FY 2008 | FY 2007 | FY 2006 |
|------------------------------------|---------|---------|---------|---------|---------|
| Total expenses | 573,118 | 772,317 | 739,929 | 757,585 | 865,385 |
| Office expenses | 67,670 | 68,400 | 72,677 | 74,442 | 116,295 |
| Research expenses | 455,911 | 469,267 | 441,377 | 496,926 | 463,338 |
| Institutional maintenance expenses | 49,537 | 234,650 | 225,875 | 186,217 | 285,752 |

(2) Employees

| Department | FY 2010 | FY 2009 | FY 2008 | FY 2007 | FY 2006 |
|--|---------|---------|---------|---------|---------|
| Administration division | 4 | 4 | 4 | 4 | 4 |
| International Affairs and Environmental Sciences | 8 | 8 | 8 | 8 | 8 |
| Clinical Medicine | 8 | 8 | 8 | 7 | 7 |
| Basic Medical Science | 7 | 7 | 7 | 7 | 7 |
| Epidemiology | 3 | 3 | 3 | 3 | 3 |
| Total | 30 | 30 | 30 | 29 | 29 |

(3) Institutional maintenance

A major part of our institutional maintenance in fiscal year 2010 consisted of repair work to the rehabilitation facility.

Rehabilitation facility repair work

The rehabilitation facility, built at the same time as the research center's main building, did not undergo the anti-earthquake retrofitting that occurred on the main building in fiscal year 2009. The entire facility was renovated in December 2010 because of faulty electronic devices and water damage caused by a leaking roof and outer wall fittings. A rehabilitation room and research room were moved into the main building of the research center while the upgrade was carried out. In the meantime, patient rehabilitation was carried out in the main building conference room. Construction was not completed as expected because of various design changes and the project was extended and completed in July 2011. The rehabilitation room and research room were promptly returned to the rehabilitation facility after completion, and we resumed conducting patient rehabilitation in the rehabilitation facility.



Report on research and other activities in
fiscal year 2010

1. Study group focusing on the mechanisms of the biological functions of mercury

The aim of this group is to solve the molecular mechanisms underlying mercury toxicity to humans by studying the biological effect of mercury. Our goal is to develop the methods for the following projects based on the understanding of the mechanisms of toxicity: to understand the initial disease state of methylmercury (MeHg) poisoning, the evaluation of MeHg toxicity, protection against disorders, and new treatments to repair damage. Our approach stands on biochemical, molecular biological, and pathological viewpoints, using cultured cell systems and animal modeling. Our studies include investigations into differences in stress responses and changes in the activation of cellular signal transduction systems caused by MeHg exposure to determine differences in MeHg sensitivity among organs and individuals. We have also investigated nerve cell death and regeneration after damage caused by MeHg, as well as aquaporin molecules to clarify the relationship between brain edema and MeHg.

In this way, we try to uncover the mechanism of MeHg toxicity. Further, we are working to discover drugs that suppress MeHg toxicity and correct the defect of nerve regeneration caused by MeHg.

The fiscal year 2010 outline of this group's research is as follows:

[Research theme and summary]

(1) Research on selective cytotoxicity and factors determining individual sensitivity of methylmercury (Project research)

Masatake Fujimura

(Department of Basic Medical Science)

The MeHg poisoning model (drinking water containing 20 ppm of methylmercury for 0, 1, 2, 3, or 4 weeks) was utilized in an experiment using an animal model (rat). This regimen produces a pathological change to cerebellar granule cells akin to that observed in methylmercury poisoning patients. I made cryosections for cutting into micro-die sections. After confirming that nerve cell death specific to cerebellar granule cells occurred after four weeks of drinking contaminated water, each class (a Purkinje cell layer, a granule cell layer, and a molecular layer) of neurons in the cerebellum was separated, and a technique of collecting mRNA from them was established. Furthermore, I have continued the project "Research on neurological action and tissue change after exposure to methylmercury during the fetal stage," which I researched last year, discovering a neurotrophic factor connective material that decreased in the brain when fetal animals were exposed to a 5-ppm dose of methylmercury. It reacts with brain-derived neurotrophic factor (BDNF) antibody, but its molecular weight is greater than 27 kD (the molecular weight of BDNF). In addition, in September 2010, I presented my results at the world Japanese Society of Neuropathology meeting (Cerebral cortex and methylmercury, nerve pathology change in the hippocampus, and difference in tau protein phosphorylation characteristics).

(2) Study on the molecular genetic and biochemical factors causing differences of stress responses to methylmercury (Fundamental research)

Fusako Usuki

(Department of Clinical Medicine)

The differences in cellular responses to MeHg between MeHg-susceptible and non-susceptible cell lines were examined. First, upregulation of glutathione (TrxR1) mRNAs was observed in both cell lines earlier than an increase in intracellular reactive oxygen species (ROS) 3 hours after MeHg exposure. GPx1 and TrxR1 are selenoenzymes of the two major redox systems—glutathione and thioredoxin systems. However, the increase in ROS occurred later in MeHg-non-susceptible cell lines than susceptible cell lines. Furthermore, the change in selenoenzymes was suppressed earlier in MeHg-non-susceptible cell lines than MeHg-susceptible cell lines. These facts suggest that MeHg-non-susceptible cell lines may have some inhibitory factors other than the antioxidant enzymes under investigation.

Regarding the mechanism of oxidative stress caused by MeHg, I summarized the data indicating that MeHg-induced relative selenium-deficient condition affects the major antioxidant selenoenzymes GPx1 and TrxR1 through a posttranscriptional effect, resulting in the disturbance of cellular redox systems and the incidence of oxidative stress. These findings were submitted to the *Journal of Biological Chemistry*, a peer-reviewed general biochemical journal, and my paper was accepted for publication (Usuki F, Yamashita A, Fujimura M: Post-transcriptional defects of antioxidant selenoenzymes cause oxidative stress under methylmercury exposure. *J Biol Chem*, 2010 Nov 24 [Epub ahead of print]).

(3) Research on effect of methylmercury to neurite outgrowth and relief of toxicity (Fundamental research)

Masatake Fujimura

(Department of Basic Medical Science)

An experiment regarding axonal degeneration and neuronal death used environmental poisons other than methylmercury (inorganic mercury, lead, rotenone, amyloid) and was conducted using cultured nerve cells.

The study revealed that inorganic mercury and rotenone (a candidate for causing Parkinson's disease), like methylmercury, caused axon denaturation and a decrease in Rac1 prior to nerve cell death. Moreover, to clarify the roles of Rac1 and RhoA in methylmercury toxicity, particularly their roles in axonal degeneration and neuronal death, expression control of Rac1 or the RhoA was carried out using siRNA. Inhibition of Rac1 blocked axonal degeneration and neuron death by itself, and inhibition of RhoA blocked axonal degeneration and neuronal death due to methylmercury. Furthermore, an *in vivo* examination in which rats drank water containing 20 ppm of methylmercury for four weeks was conducted to ascertain the effects of ROCK inhibitor (Fasudil) on methylmercury toxicity. Fasudil (3 mg/kg/day) restrained the tendency of methylmercury to denature the hind leg intersection and the posterior root nerve in the spinal cord. Last year, I published the findings of my experiment using cultured nerve cells, which concerned the action of the ROCK repressor in methylmercury toxicity. (Fujimura M, Usuki F, Kawamura M, Izumo S: Inhibition of the Rho/ROCK pathway prevents neuronal degeneration *in vitro* and *in vivo* acute poisoning exposure experiment following methylmercury exposure. *Toxicol. Appl. Pharmacol*, 2011; 250: 1–9.)

(4) Involvement of aquaporins in methylmercury toxicity (Fundamental research)

Megumi Yamamoto

(Department of Basic Medical Science)

To clarify the involvement of aquaporins in methylmercury neurotoxicity, preliminary acute methylmercury exposure experiments using a marmoset were conducted twice. Based on data regarding neurological symptoms, body weight change, and total mercury concentration of tissues in preliminary experiments, final examination was carried out using three control animals and three methylmercury-exposed animals. As a result, assumed neurological symptoms from pre-examinations results were observed. In two of the three animals to which methylmercury was administrated, an increase in size of the white matter was (edema) observed. Detailed analysis (immunohistochemistry, mRNA expression analysis, protein expression analysis) of each aquaporin are currently in progress.

2. Clinical research group

§ Research

With the aging of Minamata disease victims, symptoms due to cervical spondylosis or metabolic syndrome occur along with a central nerve disorder associated with Minamata disease. Thus, it becomes difficult to diagnose Minamata disease solely using clinical neurological data. The establishment of an objective method for the diagnosis of methylmercury poisoning (including useful discrimination of Minamata disease from other diseases) is desired.

Moreover, there is an increasing need for improved conditions for Minamata disease patients including health care administration, advanced rehabilitation for Minamata disease patients, and the development of treatment for the sequelae of congenital and infantile Minamata disease.

Therefore, in this research group, we perform research on the objective evaluations of the neurological functions of Minamata disease sufferers using MEG and the improvement of activities of daily living (ADL) of intractable neurologic disease patients including congenital and infantile Minamata disease by functional neurosurgery.

The following is an outline of all research by this group in fiscal year 2010:

[Research theme and summary]

(1) Clinical research on the of Minamata Disease
–focus on the establishment of the objective assessment by magnetoencephalography– (Project research)

Masaaki Nakamura
(Department of Clinical Medicine)

Minamata disease is diagnosed by a combination of epidemiological conditions and neurologic symptoms, but the lack of an objective diagnosis index makes diagnosis difficult. If an objective evaluation of brain dysfunction due to methylmercury poisoning, including Minamata disease, is established, it is expected to be useful to create better conditions for Minamata disease patients by evaluating their brain function over time. A noninvasive measurement to visualize brain function without craniotomy has recently developed. In this study, we aim to establish an objective evaluation of brain dysfunction due to methylmercury poisoning. In 2010, we established a MEG-based method assessing two-point discrimination and the transmission of somatic sensory stimuli from the periphery to the somatosensory cortex. In addition, we built a network for securing disease control (cerebrovascular disorders, Parkinson's disease, spinocerebellar degeneration, diabetes) to clarify the clinical condition of Minamata disease.

(2) Development of treatment for subsequent complications of congenital and infantile Minamata disease (Fundamental research)

Masaaki Nakamura
(Department of Clinical Medicine)

Involuntary movements such as dystonia and chronic intractable pain are sequelae of congenital and infantile Minamata disease. There was no effective cure until now, and sequelae resulted in the decrease of ADL of patients. Functional neurosurgery has rapidly developed as an effective treatment for the symptoms described above. It is expected that the

medical cost can be significantly decreased and the effects of rehabilitation increased. We set up a functional neurosurgery research group in fiscal year 2010 to explore the possibility of medical treatment using functional neurosurgery for the sequelae of congenital and infantile Minamata disease. In 2011, we explained meal instructions based on a deglutition function inspection to a congenital Minamata disease patient and his caretaker. Because the patient and his caretaker had a good understanding of the meal instructions, accidental swallowing was avoided. In addition, after discussions with the staff of a cooperative workshop and its director (Dr. Masazumi Harada), we assist congenital Minamata disease patients while sharing information. In the future, we plan to look at various test results including X-rays and MRIs to better understand lower limb pain and numbness of both hands in six congenital Minamata disease patients. In addition, we are going to discuss diagnosis and cure regarding these cases at a group meeting of a functional surgery research group.

§ Activities

In recent years, Minamata disease has begun to move toward a political resolution. The Department of Clinical Medicine is responsible for the administration of Minamata disease in active cooperation with a related organization. In addition to conventional rehabilitation including day-stay care for congenital and infantile Minamata disease patients, we perform educational rehabilitation activities (a rehabilitation technical school and a care technical school). To examine effective home care support for Minamata disease victims and their families, we initiated a project, the “Community development project for

home care support including health care practice” followed by a project titled “Home support model study including care prevention” (Fiscal year 2006—2009). Furthermore, through health seminars, we are working to improve the health of residents in methylmercury contamination areas.

The fiscal year 2010 outline of this group’s research is as follows:

[Activities theme and summary]

(3) Practice of rehabilitation for patients with Minamata disease and transmission of information on care and rehabilitation (Other activities)

Fusako Usuki

(Department of Clinical Medicine)

We continued to provide outpatients with rehabilitation in the form of day-stay care twice a week. The principal object is to improve their quality of life. We found that vibration therapy undertaken to relieve severe pain of the enthesitis of the sole was useful not only for the reduction of severe pain of the sole but also to relieve spasticity. The findings were reported at an academic conference and submitted to a research journal. Repetitive facilitation exercises for neuronal circuit strengthening (the KAWAHIRA method) were performed for cases with spasticity or deep sensory disturbance; it was useful in improving their motor function. In addition, a training program for the practice of basic actions for daily life and dysphagia was performed. As a result, improvements in activities of daily life ADL were acquired.

We hold annual workshops for rehabilitation and specialized staff to improve their techniques and to pass on these skills to residents. This year, in July 2010, the third workshop on assistance techniques was

held under the theme of “True understanding of dementia”. According to the results of a questionnaire given to attendees, the workshop was well received. We consider workshops as useful forums in which to share information on care and rehabilitation techniques and to then transfer these to the community.

(4) Community development project for home care support including health care practice (Other activities)

Masaaki Nakamura

(Department of Clinical Medicine)

Beginning in fiscal year 2006, I carried out a study titled “Home support model study including care prevention” to examine methods of support, including rehabilitation, that lead to improvements in ADL for aging Minamata disease victims and their families. After this project, we started a project titled “Community development project for home care support including health care practice” so that these concepts would take root in the area. As a result, much attention has been given to the community-based social welfare system and rehabilitation using an improved gaming machine for the elderly. In addition, we conducted educational activities in the Minamata district for the improvement of occupational therapy in this area.

(5) Health seminars (Other activities)

Koji Murao

(Department of Clinical Medicine)

We have been sharing knowledge regarding various illnesses with the Minamata Ashikita-gun Medical Association since fiscal year 2003, and we held a

health seminar in areas surrounding Minamata to support “*Moyainaoshi*”. In fiscal year 2010 we presented seminars on the following topics: “Thirty ideas to lose weight,” “Diabetes,” and “Mental health care”. There was a considerable reaction from citizens. We have been co-sponsors of the Dental Association since 2010 and we are cooperating with the Pharmacists’ Association beginning this fiscal year. We intend to give seminars on health promotion in the Minamata area together with the Medical Association, the Dental Association, and the Pharmacists’ Association.

3. Working group on risk recognition and information services

There is increasing interest worldwide in the low levels of methylmercury ingested via fish consumption. There are also various rumors circulating on a number of topics, and some of these are clearly biased interpretations. In this research group, the current situation and the present risk level associated with methylmercury intake are recognized, and we aim to disseminate accurate and detailed information.

The fiscal year 2010 outline of this group's research is as follows:

§ Research

[Research theme and summary]

(1) Studies on methylmercury exposure in whale-eating district (Project research)

Akira Yasutake

(Department of Basic Medical Science)

Between June and August 2010, 728 hair samples (349 men, 379 women) and 111 blood samples (48 men, 63 women) were collected and mercury concentration was analyzed. The mean hair mercury content in men decreased 9% from 2009, and the value for women decreased 6% from 2009. Selenium analyses of the blood samples are currently underway at the University of Tokyo. We secured the cooperation of Wakayama Medical College in September and November and performed a neurology medical examination on 137 subjects (84 men, 53 women). We performed EMG inspections (18 people), head MRIs (7 people), cervical vertebrae MRIs (8 people), and lumbar vertebrae MRIs (8 people). We are adjusting the start date of pediatric medical examinations from fiscal year 2011.

We have measured the total mercury content of the fish and shellfish samples offered by the Taiji-cho Fishermen's Cooperative Association, and mercury, methylmercury, and selenium analyses are in progress for whale and dolphin samples (RS-10-06). In addition, we reported our findings in fiscal year 2009, including our investigation from winter 2009, published on the National Institute for Minamata Disease website, and we held a briefing session for Taiji-cho and the media.

(2) Global Center of Excellence Project on Mercury Research and Investigation (Project research)

Masanori Sasaki

(Chief Research Coordinator)

The National Institute for Minamata Disease is a worldwide research institute specializing in mercury poisoning, and our mission and role is to promote the research of mercury worldwide.

The institute, taking advantage of past investigations that have yielded valuable results, promotes mercury research within and outside of Japan, archival functions, review and database functions, and training functions. With the development of these functions, the institute is now recognized as the global center of world mercury-related research and investigation.

However, the expected research has not been produced because of the fragmented basis of the functions. From now on, we will promote the development of these functions in an integrative and cross-sectional fashion, as is demanded of the National Institute for Minamata Disease and as only we can do.

(3) Exposure assessment of methylmercury and other heavy metals in pregnant women and fetuses (Fundamental research)

Mineshi Sakamoto
(Department of International Affairs and Environmental Sciences)

The developing brain in late gestation and/or early-lactation periods is especially susceptible to environmental toxicants. Fetuses and breast-feeding infants depend on their mothers for their nutrition, being also exposed through their mothers to heavy metals such as methylmercury, lead, arsenic, cadmium, and selenium. The developing brains of both fetuses and infants are susceptible to environmental contaminants. However, the contribution of breast-feeding on the metal body burden in infants remains unclear. The main objective of this study was to investigate the changes in body burden of metals such as methylmercury, lead, arsenic, cadmium, and selenium in infants during a 3-month breast-feeding period compared with placental transfer of the metals. Metal concentrations were measured in maternal and cord (fetus) red blood cells (RBCs) at parturition and in infant RBCs at 3 months of age. Most mercury in RBCs is in methyl form, and total mercury concentration in RBCs reflects methylmercury exposure. The mercury level in cord RBCs was approximately 1.5 times higher than that in mothers ($p < 0.01$), while in infants it declined by approximately 60% after 3 months of breast-feeding ($p < 0.01$). The changes in selenium level in RBCs showed a similar trend to those in mercury, but the cord selenium level was not significantly different from the maternal level. Lead and arsenic concentrations in cord RBCs were approximately 60% of the maternal levels and did not

show significant differences after 3 months. The cadmium level in cord RBCs was approximately 20% of that in maternal RBCs, remaining low until 3 months of age. These results suggest that methylmercury transfer through the placenta is exceptionally high among the examined metals. However, concentration in infants decreased to the maternal level after 3 months of lactation. The placenta barrier appears to act strongly against cadmium, but only to some degree against lead and arsenic, being at a similar level after 3 months of lactation. In conclusion, while pregnant women should take care to avoid high methylmercury exposure, metal exposure through breast-feeding does not pose any great risk.

(4) Protective effect of selenium against methylmercury toxicity and co-existence of mercury and selenium in human and sea-mammals (Fundamental research)

Mineshi Sakamoto
(Department of International Affairs and Environmental Sciences)

Subject 1: “Direct protective effects of selenomethionine (SeMet) against neuronal degeneration by methylmercury (MeHg) in developing rat brains”

Our goal in this study was to demonstrate the direct protective effects of SeMet against the neuronal degeneration caused by MeHg in developing brains, which are vulnerable to MeHg exposure. We used a rat model of fetal-type Minamata disease, which causes neuronal degeneration in the cerebrum. Wistar rats at postnatal day 14 (PD14) were orally administered MeHg, either MeHg (8 mg Hg/kg/day in a solution containing L-cysteine and condensed milk),

SeMet (2 mg/kg/day) alone or MeHg and SeMet co-exposure (MeHg was administered 30 min after SeMet) for 10 consecutive days. 24 hours after the final administration the effects of the different treatments were investigated. Decreases in body weights were observed in MeHg groups, but this was negated by co-exposure to SeMet. Total mercury concentration in the cerebrum was higher in the co-exposed group than MeHg group. Decreased GSH-Px activity was observed in the cerebrum in the MeHg group, and co-exposure to SeMet prevented these effects. Neuronal degeneration and reactive astrocytosis were caused in the cerebral cortex by MeHg exposure, and were prevented by co-exposure to SeMet.

Subject 2: “Research on mercury and selenium levels in inhabitants who eat a large amount of whale”

The blood mercury concentration of males was twice that of females residing in Taiji-cho. In contrast, selenium density was almost the same in males and females, showing slightly higher levels than the average values for the Japanese population. Blood mercury concentrations and selenium concentrations for males and females showed positive correlations with each other. These results indicate that the higher the blood mercury concentrations of Taiji-cho inhabitants, the higher the blood selenium levels.

Subject 3: “Total mercury concentrations in eight species of fish and shellfish consumed in Taiji-cho”

Mercury levels in fish and shellfish were similar to the level reported by the Ministry of Health, Labour and Welfare; there were no particularly characteristic patterns in mercury levels. Fish species with the highest mercury levels were bonito and *Thunnus alalunga*, which exceeded 0.3 µg/g.

(5) Information service using hair mercury analysis (Fundamental research)

Akira Yasutake

(Department of Basic Medical Science)

In fiscal year 2010, more than 1,600 hair samples were analyzed for mercury; the samples were collected from visitors at NIMD, Minamata Disease Archives, and from other organizations. The analytical results were sent to each individual. For information services on methylmercury, a brochure “Mercury and Health” (Japanese and English versions) was revised. To compare the appearance of mercury in hair (via the consumption of methylmercury-containing food) for both genders, hair and blood samples were collected from 50 student volunteers (25 males and 25 females) in Kumamoto City before and after the ingestion of big-eye tuna. However, the mercury analyses of the samples (blood, plasma, and hair) provided no clear evidence to explain the gender difference in hair mercury levels.

(6) Quantitative evaluation on the association of methylmercury concentration in cord blood and health effects in mother and infant (Fundamental research)

Noriyuki Hachiya

(Department of International Affairs and Environmental Sciences)

The risk of infectious diseases for infants was quantitatively analyzed for associations with methylmercury concentrations in umbilical cord blood using data obtained from mother-child pairs in a Tokyo/Sado cohort. A multiple regression analysis revealed that concentrations of methylmercury in umbilical cord blood, the use of day nurseries and child care facilities, and the exposure of 1-year-old

infants to passive smoking were found to show significant positive associations with the frequency of infants' fevers. In contrast, having no siblings and the annual income of the father showed a significant negative correlation. A benchmark analysis was performed on the relation between the frequency of infants' fevers, after adjustments for confounding, and methylmercury concentrations using a statistical package SPBS of Prof. Murata, Akita Univ. No contradictory results were obtained on the benchmark dose (BMD) and its lowest confidence limit (BMDL) comparing to the pre-existing estimations using semi-quantitative analysis. Furthermore, the adjusted frequency of infants' fevers showed a linear dose-response curve against the methylmercury concentration without any apparent threshold.

(7) Study on information transmission and risk perception on health risk of low level exposure to methylmercury (Fundamental research)

Noriyuki Hachiya

(Department of International Affairs
and environmental Sciences)

An experience-based risk communication including hair mercury measurement was conducted on attendants at an environmental event in Tokyo—408 attendants participated in the risk communication program. At the time of hair sampling, an attitude survey was carried out on issues on the health risks associated with low-level exposure to methylmercury. Results for the hair mercury measurement were mailed to participants along with a second questionnaire. The answers to the second questionnaire were analyzed to determine how participants accepted their own hair mercury level and to investigate participants'

cognizance of the health risk information after providing an epidemiological evidence list on the health effects of low-level methylmercury. The experience-based risk communication was confirmed as useful by summarizing the results on risk perception obtained by a series of surveys conducted in this study.

(8) Experimental research on influence of human health in French Guiana river pollution (Fundamental research)

Masatake Fujimura

(Department of Basic Medical Science)

I performed an experiment on the influence of polluted fish on pregnant rats during this fiscal year. As a target for comparison, we measured the actions (quantity of motion, short-term memory, coordinated movement) of fish and tuna in French Guiana that had high mercury densities and those of fish (such as salmon) that had low mercury densities. No significant differences were observed between the polluted group and the untreated control group. In addition, a collaborator is conducting an analysis of the toxic outbreak mechanism that involves, for example, mitochondrial functions as a toxic index. I performed an analysis of all materials except for known environmental pollutants. I also performed a literature review and consulted with outside researchers. However, no enforcement is possible without the consent of experts in the field of analysis (the probability of success is low, and enforcement takes an enormous amount of time).

Moreover, a manuscript on an experiment on the exposure of adult mice that I carried out in fiscal year 2009 was accepted for publication.

(Bourdineaud JP, Fujimura M, Laclau M, Sawada M, Yasutake A: Deleterious effects in mice of fish-associated methylmercury contained in a diet mimicking the Western populations' average fish consumption. Environ. Int., in press.)

§ Activities

[Activities theme and summary]

(9) Organization of documents and materials on Minamata disease, and information providing in Minamata Disease Archives (Other activities)

Noriyuki Hachiya

(Department of International Affairs
and Environmental Sciences)

As an administrative institution that holds and manages documents and materials on Minamata disease for academic research and other purposes, the Minamata Disease Archives conforms with all applicable rules and regulations, and a contents list and search system have been consolidated. The exhibits displayed in the exhibition hall at the Minamata Disease Archives were updated after scientific and specialized examination and also in consideration of visitors' needs. The facilities were renovated (they were old and deteriorating); a competitive bidding process was used to determine the renovation contract.

(10) Hair mercury examination of areas concerning for mercury pollution around the world (Other activities)

Masatake Fujimura

(Department of Basic Medical Science)

This fiscal year, we obtained hair samples from four nations: Indonesia (31 men, 14 women), Brazil (65 men, 97 women), French Guiana (14 men, 15 women),

and South Korea (661 men, 635 women). We measured mercury quantities in each hair sample, and mercury density data were reported to the donors.

1) Indonesian hair samples were collected from inhabitants of an area containing a gold mining company. The total average level of mercury in men was 29.9 ppm, and the average in women was 10.6 ppm. It is thought that these hair mercury levels reflect external exposure by the adhesion of mercury vapor to the hair while gold mining, because the total amount of mercury in the sample was more than 10 ppm, but methylmercury was just 10.0% or less of the total.

2) Brazilian hair samples were obtained from the indigenous population living in Amazonia. Men averaged 9.7 ppm of mercury and women 7.9 ppm. Although gold mining is carried out in this area, the indigenous population does not mine for gold. Therefore, it was thought that the hair mercury levels reflected internal mercury exposure via mercury contamination from fish close to the gold mining operation.

3) Hair samples from French Guiana were obtained from an indigenous population from a lower part of the river near a gold mine (the upper Maloney district). Men averaged 8.9 ppm of mercury and women 10.0 ppm. Because the total amount of mercury in the sample was more than 10 ppm, and the amount of methylmercury was 90% or higher, it is thought that these hair mercury levels reflect internal mercury exposure via mercury contamination from fish close to the gold mining operation.

4) Korean hair samples were obtained from inhabitants in the outskirts of Seoul. Men averaged 1.4 ppm and women 1.3 ppm. Gold mining is not performed in this area, and pollution by chemical

factories is not reported either. Therefore, it is thought that these hair mercury levels reflect the normal consumption of regular fish.

(11) Digitization of histopathological slides of Minamata disease patients for permanent preservation
(Other activities)

Masumi Marumoto

(Department of Basic Medical Science)

I carry out these duties with two purposes. The first is to permanently preserve examples of tissue affected by Minamata disease by digitizing pathological specimens. These data will be handed down to future generations. The second purpose is to exhibit the digitized specimens on the Internet to enable researchers and students around the world to use the Minamata disease pathology specimens as curricular material. In this fiscal year, I created a case report in the form of an atlas of two examples each of fetal and puerile Minamata disease. In addition, I carried out the digitization of pathological specimens from five cases of puerile Minamata disease and two adult cases of Minamata disease for public presentation in virtual slide form. I also carried out the digitization of pathology specimens of five cases of puerile Minamata disease for permanent preservation.

4. Social and epidemiological approaches to Minamata disease

More than half a century has passed since the official discovery of Minamata disease. While the significant environmental pollution caused by methylmercury is now considered a historical event, the effects of the Minamata disease episode still remain in the regional communities. In this research group, historical validations were carried out on risk management problems for environmental pollution from methylmercury, which caused such terrible harm, and local reproduction in the affected areas was sociologically analyzed.

The outline of this group's research in fiscal year 2010 is as follows:

[Research theme and summary]

(1) Study on risk management in Minamata disease history (Fundamental research)

Noriyuki Hachiya
(Department of International Affairs
and Environmental Sciences)

As a starting point to discuss the issue of the risk management of the harm to health that occurred from the environmental pollution by methylmercury, documents were collected dated from the first occurrence of Minamata disease, and the issues of concern are now being summarized as a review of epidemiology research on Minamata disease. The review is titled "Epidemiological Update of Methylmercury and Minamata Disease" and may contain discussions from a viewpoint of risk governance, environmental and toxicological considerations, background to Minamata disease outbreaks, investigations of early epidemiological

research and recent achievements, information regarding the onset threshold of Niigata Minamata disease patients, and follow-up studies on the inhabitants of the contaminated site.

(2) Research on regeneration in Minamata disease area (Fundamental research)

Tazusa Arakaki
(Department of International Affairs
and Environmental Sciences)

Regarding the community renewal project "Environmental creation and development project in Minamata," I performed investigations and literature research regarding recognized changes in Minamata disease and emotional confrontations via *Moyainaoshi*. In the hearing investigation, the 10-year-old issue of industrial waste disposal during field construction was pointed out. In addition, the opinion was expressed that the ill feelings between citizens and patients had passed because civic investigation techniques had been adopted. By working together to solve common problems, all involved parties came to understand each other's viewpoints.

Regarding the local action on *Moyainaoshi*, it was used as a base for community-based welfare (including care prevention) when I examined the business summary of the Minamata City Moyai Naoshi Center (Moyai-kan). The South Moyai Naoshi Center (Orange-kan), an event that focused on Minamata disease, and *Moyainaoshi* have decreased in magnitude year-by-year. Based on these results, I have planned a questionnaire for the next fiscal year.

During the joint project exhibition with the

Minamata Disease Municipal Museum, we presented exhibition panels entitled “*Moyainaoshi* in the past and in the future”.

5. Regional and global environmental research group

Because Minamata disease was caused by environmental methylmercury exposure, we focus on so-called environmental changes and perform comprehensive research that classifies fieldwork into fields of vision.

Mercury circulates through land, water, and the atmosphere, and its chemical form changes in each domain. In other words, mercury released as a metal becomes methylmercury and circulates to arrive in people's bodies via the food chain. I investigate the movement of methylmercury in the atmosphere, rain, seawater, and study mercury circulation as an ecosystemic field. Each primary researcher exchanges information with other researchers, establishing joint ownership of the results because all of these elements are mutually related; this helps each individual research project.

The fiscal year 2010 outline of this group's research is as follows:

§ Research

[Research theme and summary]

(1) Mercury behavior in marine environment
–Comparative study of mercury distribution and influence to benthos community constitution between the surface sediment of intertidal zone and the terrestrial environments– (Fundamental research)

Yoshiaki Yasuda

(Department of International Affairs
and Environmental Sciences)

Despite this topic being our primary focus (because many of the mercury analyses on the samples collected during the periodic investigations of

intertidal zone benthos required completion), we could not determine the circumstances of the measurement environment. However, we were almost able to find a correlation between the distribution of mercury at the bottom of the sea and the total internal mercury density in *Turbo (Lunella) cornatus coreensis*, the natural herbivore that we chose as an indicator organism. In contrast, in our distribution investigation of the Indonesia Talawaan River Basin mercury, we found a new flow channel of mercury while studying the change in the distribution of the small-scale gold ore smelters that I researched from 2004. This research will be continued in the future by my successor.

(2) Marine ecosystem and mercury behavior in Yatsushiro Sea.-Quantitative survey of marine benthic community in Yatsushiro Sea and mercury concentration of several fishes through food web- (Fundamental research)

Keisuke Mori

(Department of Epidemiology)

Around the Gulf of Minamata, I investigated the distribution of benthos in the Yatsushiro Sea. I elucidated the distribution and diffusion of mercury from a biological viewpoint.

I took up my position during this fiscal year, and as such, much of my time was spent learning about the field, making appeals to collaborators, and drafting my research plan. I also learned various mercury analysis techniques from a predecessor.

(3) Research on its influences and behaviors of mercury in an aquatic environment of Minamata Bay (Fundamental research)

Akito Matsuyama
(Department of Epidemiology)

I carried out research titled “Continuation of periodic water quality monitoring in Minamata Bay and summer concentration observation to understand water quality change during the summer” and “Fish cage experiment in Minamata Bay.”

In the former project, I found that there are differences in the seasonal variation tendencies of total dissolved mercury and methylmercury. In particular, concentrations of dissolved mercury around the bottom of the sea are high regardless of season; this is likely caused by elution from bottom material. In the latter study, I carried out a fish cage experiment in the Minamata Bay area using sea bream for 2 years (2009–2010). Methylmercury concentration in seawater increased in 2010, as expected in an average year. However, an accumulation of mercury in the fish was not observed as a result. The two-year fish cage experiment has revealed that there is almost no possibility that the mercury that exists in seawater will be absorbed through the gills of fish. Instead, it will accumulate inside of the general body of the ocean.

(4) Research on chemical reactions, transport and deposition of atmospheric mercury (Fundamental research)

Koji Marumoto
(Department of International Affairs
and Environmental Sciences)

In this study, speciation analysis was carried out on mercury in the air and wet depositions collected at the

rooftop of the Minamata Disease Archives. In addition, preliminary research on monitoring for methylmercury in the air was performed.

In the former study, strong positive correlations were found among total mercury, dissolved mercury, particulate mercury, and dissolved reactive mercury in the wet depositions. Thus, it was clear that dissolved methylmercury concentrations in wet depositions were higher in winter than in summer. However, regarding the speciation on mercury in the air, the analytical equipment for gaseous divalent mercury experienced some problems. Therefore, the equipment was repaired.

In the latter study, the pilot unit of the standard gas generation system for low concentrations of gaseous divalent mercury and gaseous methylmercury was created and its operation monitored. However, it was found that further improvements were necessary.

(5) Study on natural emission sources of atmospheric mercury (Fundamental research)

Koji Marumoto
(Department of International Affairs
and Environmental Sciences)

A sampling unit for volatile mercury (dissolved gaseous mercury, DGM) in seawater was designed. This unit is able to collect DGM without disturbing seawater to avoid the loss of DGM in seawater sampling. Furthermore, this unit was made using a number of ready-made components to cut costs. In the following year (2011), the sampling conditions of this unit will be investigated.

(6) Research on food web in Minamata Bay as for mercury pollution by using an ultratrace analysis on mercury and a molecular- biology technique (Fundamental research)

Akito Matsuyama
(Department of Epidemiology)

I carried out a mercury analysis of the muscle of *Sebastes marmoratus* that I gathered in Minamata Bay. I identified their stomach contents, and performed a DNA amplification experiment via PCR.

Mercury concentration was correlated with *Sebastes marmoratus* weight. The stomach contents were similar to previous findings; the main contaminants were crustaceans and small shells. In addition, I succeeded in the amplification of 16S mitochondrial rRNA gene domains by PCR.

§ Activities

[Activities theme and summary]

(7) Cooperation of research in the international organization (Other activities)

Mineshi Sakamoto
(Department of International Affairs and
Environmental Sciences)

Four invitations were sent to foreign researchers and researchers from the National Institute for Minamata Disease were dispatched on 12 occasions. Their main activities were technology transfers (for example, teaching mercury analysis techniques to foreign researchers), research presentations at international conferences, and investigations into the health effects in mercury polluted areas. Moreover, we gave 12 training lectures summarizing Minamata disease, mercury, and health issues, attended by a total of 116 people.

(8) The JICA project for strengthening the health vigilance system on methylmercury in the Tapajos River Basin, Amazon (Other activities)

Mineshi Sakamoto
(Department of International Affairs and
Environmental Sciences)

The Japanese Final Evaluation Team (hereinafter referred to as “the team”), organized by the Japan International Cooperation Agency (JICA) and the National Institute for Minamata Disease (NIMD), visited the Federative Republic of Brazil (hereafter Brazil) from September 17 to 28, 2009, and the team considers that the project purpose has been largely achieved. However, at the request of our Brazilian counterparts, a technical transfer of clinical diagnosis of methylmercury intoxication was undertaken as part of a project extension from June 27 to July 7, 2010 in a town along the Tapajos River Basin. The international workshop was jointly conducted with Brazilian counterpart organizations, and this project was successfully completed.

(9) NIMD Forum and International Workshop (Other activities)

Mineshi Sakamoto
(Department of International Affairs and
Environmental Sciences)

From January 25 to 28, 2011, we held an NIMD forum on the mechanism of methylmercury toxicity, and we invited 14 domestic and international specialists to attend. From October 10 to 14, 2010, we held an international workshop in the Republic of Slovenia. The workshop was organized in cooperation with the Jozef Stefan Institute. The theme was “International workshop on the mercury

contamination area: Its characteristics, influence, and purification.” Approximately 60 researchers, including the presenters, participated in the workshop.

6. Publications and Scientific meetings

[Scientific publications (English)]

Retrospective study on temporal and regional variations of methylmercury concentrations in preserved umbilical cords collected from inhabitants of the Minamata area, Japan.

Sakamoto M, Murata K, Tsuruta K, Miyamoto K, Akagi H. *Ecotoxicol Environ Saf*. 2010;73:1144-1449.

Mercury deposit distribution in Minamata Bay.

Yasuda Y, Mori K. *Coastal Mar Sci*. 2010;34:223-229.

Effect of methylmercury administration on choroid plexus function in rats.

Nakamura M, Yasutake A, Fujimura M, Hachiya N, Marumoto M. *Arch Toxicol*. 2011;85:911-918.

Post-transcriptional defects of antioxidant selenoenzymes cause oxidative stress under methylmercury exposure.

Usuki F, Yamashita A, Fujimura M. *J Biol Chem*. 2011;286:6641-6649.

Inhibition of the Rho/ROCK pathway prevents neuronal degeneration *in vitro* and *in vivo* following methylmercury exposure.

Fujimura M, Usuki F, Kawamura M, Izumo S. *Toxicol Appl Pharmacol*. 2011;250:1-9.

Deleterious effects in mice of fish-associated methylmercury contained in a diet mimicking the Western populations' average fish consumption.

Bourdineaud JP, Fujimura M, Laclau M, Sawada M, Yasutake A. *Environ Int*. 2011;37:303-313.

Induction by mercury compounds of metallothioneins in mouse tissues: inorganic mercury accumulation is not a dominant factor for metallothionein induction in the liver.

Yasutake A, Nakamura M. *J Toxicol Sci*. 2011;36:365-372.

Mercury distribution in seawater of Kagoshima Bay near the active Volcano, Mt. Sakurajima in Japan.

Ando T, Yamamoto M, Tomiyasu T, Tsuji M, Akiba S. *Bull Environ Contam Toxicol*. 2010;84:477-481.

Head hair total mercury and methylmercury levels in some Ghanaian individuals for the estimation of their exposure to mercury: preliminary studies.

Voegborlo RB, Matsuyama A, Adimado AA, Akagi H. *Bull Environ Contam Toxicol*. 2010;84:34-38.

Mercury Speciation in the water of Minamata Bay, Japan.

Matsuyama A, Eguchi T, Sonoda I, Tada A, Yano S, Tai A, Marumoto K, Tomiyasu T, Akagi H. *Water, Air, and Soil Pollut*. 2010;218:399-412.

Toxicokinetics of mercury in children : Children's Exposure to Mercury Compounds.

Adler R, Barbosa F Jr., Domingo J, Flegal R, GardenerR, Goldman L, Nyland J, Sakamoto M, Silbergeld E, Stern A, Wells E, Yamamoto M. *World Health Organization*. 2010;59-64.

[Scientific publications (Japanese)]

Noriyuki Hachiya, Akira Yasutake (2010) Risk of low level methylmercury exposure through consumption of fishery products. (9) Perception of risk information among participants of hair mercury analysis program. Proceedings of the SRA Japan 23rd Annual Meeting, 23: 147-152.

Akio Yamashita, Fusako Usuki (2010) mRNA surveillance: molecular mechanism and function. In extra edition of Jikken Igaku (eds. Haruhiko Shiomi, Mikiko Shiomi, Toshifumi Inada, and Tetsuro Hirose), YODOSHA, Japan 134-141.

Tomio Tanigawa, Satoko Yamada, Satomi Sakaguchi, Shin-ichi Iwashita, Ken-ichiro Miyamoto (2010) A pharmacological effect of essential oils to pain stimulation: the clinical and basic study on brain pain-related. AROMA RESEARCH 11: 312-319.

Satsuki Tohyama, Kiyoka Miyamoto, Fusako Usuki (2011) One case of Minamata disease patient with mild mental retardation who improved social skill by rehabilitation. Occupational Therapy 30: 213-218.

[Scientific meeting (Abroad)]

Usuki F, Yamashita A, Fujimura M. Methylmercury causes oxidative stress through its posttranscriptional effect on antioxidant selenoenzymes. XVIIth International Congress of Neuropathology, Salzburg, 2010. 9.

Fujimura M, Usuki F, Takashima A. Methylmercury induces neuropathological changes with tau hyperphosphorylation mainly through the activation of

the c-jun N-terminal kinase pathway in the cerebral cortex, but not in the hippocampus of the mouse brain. 17th International Congress of Neuropathology, Salzburg, 2010. 9.

[Scientific meeting (Domestic)]

Keisuke Mori: The distribution situation of the Benthos in the Ariake Sea –Mainly on gammarus–. Zoological Soc. of Japan•Botanical Soc. of Japan•Ecological Society of Japan Joint meeting of the Kyushu region, Fukuoka, 2010. 5.

Tazusa Arakaki: Hearing investigation of the hygiene person in charge at the time of a Minamata disease official confirmation. The 80th Annual Meeting of The Japanese Society for Hygiene, Sendai, 2010. 5.

Noriyuki Hachiya, Akira Yasutake: The hair mercury level and its determinants in general population of Japan (2). The 80th Annual Meeting of the Japanese Society for Hygiene, Sendai, 2010. 5.

Kohji Marumoto, Akito Matsuyama: Factors affecting the seasonal variation of methyl mercury in wet depositions collected at Minamata city. The 51th Annual Meeting of The Japanese Society for Atmospheric Environment, Osaka, 2010.9.

Keisuke Mori: About rare benthos discovered in the Gulf of Minamata peripheral sea area. Joint meeting of The Plankton Society of Japan and Japanese Association of Benthology in 2010, Kashiwa, 2010. 10.

Noriyuki Hachiya, Akira Yasutake: Risk of low level methylmercury exposure through consumption of fishery products (9) Perception of risk information among participants of hair mercury analysis program. SRA Japan the 23rd Annual Meeting, Tokyo, 2010. 11.

Satsuki Tohyama, Fusako Usuki : One case of fetal-type Minamata disease patient whose pain and spasticity relieved by vibratory stimulation led to improvement of ADL. p.61: In Proceedings of the 32nd Joint Meeting of Physical Therapists and Occupational Therapists in Kyushu, Okinawa, 2010.11.

Sakamoto M. Protective effects of selenomethionine against methylmercury-induced neuronal degeneration in developing rat brain. NIMD FORUM 2011, Minamata, 2011. 1.

Usuki F. Posttranscriptional defects of antioxidant selenoenzymes cause oxidative stress undermethylmercury exposure. NIMD FORUM 2011, Minamata, 2011. 1.

Fujimura M. Neuritic degeneration contributes to MeHg-induced neuronal cell death. NIMD FORUM 2011, Minamata, 2011. 1.

Keisuke Mori: The benthos distribution situation in the Gulf of Minamata sand mud tideland – After getting over mercury contamination –. 58th Annual Meeting of Ecological Society of Japan, Sapporo, 2011. 3.

Masanori Sasaki: About a recent topic about the healthy influence with mercury. The 151st meeting of the Japanese Society of Veterinary Science, symposium” The latest knowledge of deleterious effects of methylmercury and the toxic expression mechanism,” Tokyo, 2011. 3.

7. International joint research projects [Dispatches]

| Country and event location Name of institution | Name | Project/Meeting | Event | Dispatch period |
|---|---|--|--|------------------------------|
| Republic of Slovenia Sosa River estuary | Department of Epidemiology Akito Matsuyama | Analysis and measurement of mercury density according to the form of residual mercury in sea-floor mud in the Adriatic Sea | Last year I visited the field as a researcher in charge of the project “Influence of density stratification on changes in the highly concentrated residual mercury of the northern Adriatic Sea Sosa River estuary”, and I carried out water sampling, bottom sampling, and performed various analyses and analytical studies. | May 5–11, 2010 |
| People’s Republic of China Guangzhou | Department of International Affairs and Environmental Sciences Department of Epidemiology Mineshi Sakamoto | SETAC Asia-Pacific Summit | I presented the results of the project “Methylmercury investigation of the cord blood of Shiranui sea inhabitants born at the time of Minamata disease emergence.” This conference is a major international environmental conference held in China, and participation was essential. This is an important source of international collaboration for the National Institute for Minamata Disease. | June 3–8, 2010 |
| United States Tennessee | Department of International Affairs and Environmental Sciences Department of Epidemiology Mineshi Sakamoto | Lecture during a special session on mercury, given at the Goldschmidt Conference | I gave a lecture on mercury toxicity at a special session on mercury at the Geochemical Society’s Goldschmidt Conference. | June 11–21, 2010 |
| Brazil Rio Tapajos Basin | Department of International Affairs and Environmental Sciences Department of Epidemiology Mineshi Sakamoto Department of Clinical Medicine Masaaki Nakamura | Fieldwork on the JICA project (health monitoring system reinforcement project concerning methylmercury in Brazil) | Local collaborative enforcement and the dispatch of a doctor by JICA were necessary for a survey on Tapajos Basin inhabitants by the JICA. I gave a local lecture seminar on the last day of dispatch, and this project is now finished. | June 25— July 11, 2010 |

| Country and event location Name of institution | Name | Project/Meeting | Event | Dispatch period |
|---|--|---|--|------------------------|
| Spain Barcelona | Department of International Affairs and Environmental Sciences Department of Epidemiology Mineshi Sakamoto | International Union of Toxicology (IUTOX), the XII International Congress of Toxicology | I presented the results of the project “Methylmercury exposure evaluation of a pregnant woman and a fetus.” I exchanged the latest information regarding the risks and benefits of eating fish with Dr. Jose L. Domingo of Spain at this conference. | July 17–25, 2010 |
| Indonesia Manado | Department of International Affairs and Environmental Sciences Yoshiaki Yasuda | Investigation of the distribution of methylmercury in the inland water environment | Change in the marine ecosystem due to mercury in Manado, Indonesia—the distribution of chemical forms of mercury at the bottom of the intertidal zone’s surface and an investigation into its influence on the crowd structure of benthos; tests to compare this environment with an inland water environment were performed. | Aug. 21 – Sep. 2, 2010 |
| | Department of Epidemiology Keisuke Mori | | | |
| Republic of Slovenia Ljubljana | Department of Epidemiology Akito Matsuyama | Field observations of mercury in Slovenia’s Soča coastal zone | Mercury waste from a Slovenian mine is known to flow into the Soča River, and the mercury density of the river water is known to be high. In this work, I compared the water in this river with the water environment of the Minamata Gulf by going into the field, gathering real field samples, and carrying out various analyses. | Aug. 26 – Sep. 1, 2010 |
| Austria Salzburg | Department of Clinical Medicine Fusako Usuki | Research presentation at the 17th Japanese Society of Neuropathology | I published the results of research on the outbreak mechanism of oxidative stress and cells’ stress response to methylmercury. | Sep. 9–17, 2010 |
| | Department of Basic Medical Science Masatake Fujimura | | I presented the results of research on the relationship between pathological change and tau protein phosphorylation in the methylmercury exposure model. | |

| Country and event location Name of institution | Name | Project/Meeting | Event | Dispatch period |
|--|--|--|---|------------------|
| Republic of Kazakhstan Karagandy Province | Department of Epidemiology Akito Matsuyama | Follow-up investigation on the environmental monitoring of mercury in the Nura Basin | In the Nura River, it was revealed that mercury pollution was caused by discharge from an acetaldehyde manufacturing facility. I received this news and was dispatched as a short-term dispatch expert for the JICA technical cooperation project “Republic of Kazakhstan Nura Sea Basin mercury environment monitoring project” in fiscal year 2008. Although the project was only planned for one year, I received a request for a follow-up investigation after the technology transfer. | Sep. 13–25, 2010 |
| Republic of Slovenia Pyran | Dispatched personnel | Participation in fiscal year 2010 Slovenian mercury workshop | We held a workshop about mercury pollution in cooperation with the Jožef Stefan Institute. I participated in its administration as an executive chairperson. I performed information collection on world mercury research and presented our center’s research results. | Oct. 8–16, 2010 |
| Republic of Slovenia Pyran Republic of Slovenia Pyran Idrija Ljubljana | Department of International Affairs and Environmental Sciences Department of Epidemiology Mineshi Sakamoto | Participation in fiscal year 2010 Slovenian mercury workshop | We held a workshop on mercury pollution in cooperation with the Jožef Stefan Institute. I participated as a general administrator so that the administration of the workshop would run smoothly. I performed information collection concerning world mercury research. | Oct. 8–17, 2010 |
| | Department of Basic Medical Science Masanori Sasaki | Participation in fiscal year 2010 Slovenian mercury workshop and the field observation of mercury in Soča coastal zone | We held a workshop about mercury pollution in cooperation with the Jožef Stefan Institute. I performed information collection concerning world mercury levels and presented the results of our center’s research thereof. In addition, I gathered soil samples in cooperation with the Jožef Stefan Institute and performed a comparison with the water environment of the Gulf of Minamata. | |

| Country and event location Name of institution | Name | Project/Meeting | Event | Dispatch period |
|---|--|--|---|------------------|
| Italy Rome | Department of International Affairs and Environmental Sciences Department of Epidemiology Koji Marumoto | Attendance at the inaugural meeting of the Global Mercury Observation System | Inaugural meeting of the Global Mercury Observation System (GMOS), which is a worldwide atmospheric mercury monitoring network. I attended the meeting to introduce an observation site and its contents, and to make arrangements for future plans with a researcher at the international environmental laboratory in GMOS. | Nov. 15–21, 2010 |
| Indonesia Jakarta | Department of Epidemiology Akito Matsuyama | Investigation of mercury contamination at a small-scale gold mine site in suburbs of Jakarta | Areas surrounding suburbs in Jakarta, Indonesia are dotted with small-scale gold mine sites, and mercury is used for gold refinement. There are reports that the surrounding environment is highly polluted by mercury. In this investigation, I ascertained the general pollution status and performed mercury analysis on soil and river water. I collected samples locally and held hearings with inhabitants of Jakarta's outskirts. | Jan. 17–24, 2011 |
| Canada Halifax | Department of International Affairs and Environmental Sciences Department of Epidemiology Mineshi Sakamoto | The 10th International Conference on Mercury as a Global Pollutant (ICMGP) Second meeting | The international conference on mercury held in Halifax, Canada, enabled the exchange of information about the overall problem of mercury. Researchers from various countries brought the results of their field research on mercury, such as atmospheric, environmental, health-related, and gold-mining-related data, and presented them at the meeting. I attended the preparatory committee for the international conference on mercury in June, and planned final adjustments. | Mar. 6–13, 2011 |

8. International joint research projects [Invitation]

| Name | Organization | Position | Research theme | Invitation period | Person in charge of acceptance |
|--------------------------|---|--------------------------|--|-------------------------|--------------------------------|
| Ying Tian | Shanghai Jiao Tong University | Professor | Mercury exposure and infant health | June 15–16, 2010 | Masatake Fujimura |
| Yu Gao | | Doctor of Medicine | | | |
| Markus Talintukan Lasut | Sam Ratulangi University | Professor | Collaborative investigation about “Circulation of mercury in the quality of Indonesia Indonesia Tarawa Ann River Basin” | Sep. 7–19, 2010 | Yoshiaki Yasuda |
| Hee-Ung Chung | South Korean National Institute for Environmental Studies | Researcher | Japan-Korea collaborative investigation business “Research on environmental pollution material exposure and healthy influence on humans” | Oct. 18–29, 2010 | Mineshi Sakamoto |
| Young-Min Kwon | South Korean National Institute for Environmental Studies | Researcher | Japan-Korea collaborative investigation business “Research on environmental pollution material exposure and healthy influence on humans” | Nov. 29 – Dec. 10, 2010 | Mineshi Sakamoto |
| Sandra Ceccatelli | Karolinska Institutet | Professor | NIMD Forum | Jan. 23–29, 2011 | Fusako Usuki |
| Roshan Tohighi | Karolinska Institutet | Executive chief engineer | NIMD Forum | Jan. 23–29, 2011 | Fusako Usuki |
| William Rostene | French National Institute for Medical | Professor | NIMD Forum | Jan. 23–29, 2011 | Masatake Fujimura |
| Jean-Paul Bourdineaud | University of Bordeaux | Professor | NIMD Forum | Jan. 23–30, 2011 | Masatake Fujimura |
| Michael Aschner | Vanderbilt University Medical center | Professor | NIMD Forum | Jan. 22–29, 2011 | Masatake Fujimura |
| Chris Newland | Auburn University | Professor | NIMD Forum | Jan. 22–Feb. 2, 2011 | Masatake Fujimura |
| Ebany J. Martinez-Finley | Vanderbilt University Medical Center | Postdoctoral fellow | NIMD Forum | Jan. 22–29, 2011 | Masatake Fujimura |

| Name | Organization | Position | Research theme | Invitation period | Person in charge of acceptance |
|-----------------|-----------------------------|---------------------|----------------|-------------------|--------------------------------|
| Yoshito Kumagai | University of Tsukuba | Professor | NIMD Forum | Jan. 25–28, 2011 | Koji Okamoto |
| Shuji Izumo | Kagoshima University | Professor | NIMD Forum | Jan. 27–28, 2011 | Koji Okamoto |
| Hwang Gi Wook | Tohoku University | Lecture | NIMD Forum | Jan. 26–28, 2011 | Koji Okamoto |
| Takashi Toyama | University of Tsukuba | Doctoral course | NIMD Forum | Jan. 25–28, 2011 | Koji Okamoto |
| Akira Naganuma | Tohoku University | Professor | NIMD Forum | Jan. 26–28, 2011 | Koji Okamoto |
| Toshiyuki Kaji | Tokyo University of Science | Professor | NIMD Forum | Jan. 24–28, 2011 | Koji Okamoto |
| Takashi Hirooka | Tokyo University of Science | Assistant professor | NIMD Forum | Jan. 24–28, 2011 | Koji Okamoto |

9. Visitor for training

| Day | Training course name | Organization |
|-------------|--|--|
| Jun.3,2010 | The risk management and Residue Analysis of Chemicals for Environmental safet | Japan International Cooperation Agency |
| Jul.7,2010 | The JICA group training On Pollution Control for Hazardous Substances in the Environment | Grobal Environment centre Foundation |
| Jul.29,2010 | Kumamoto University Summer program 2010 | Kumamoto University Center for Globalization |
| Aug.27,2010 | Industrial waste water treatment technique | Kitakyusyu Internaional Techno-cooperative Association |
| Sep.10,2010 | Circulation society creation in Asia (China) | Kitakyusyu Internaional Techno-cooperative Association |
| Oct.6,2010 | The JICA group training Occupational health and preventive medicine for workers | Kitakyusyu Internaional Techno-cooperative Association |
| Oct.8,2010 | The JICA group training Eco-ModelCity- Sustainable City through Community Participation- | Eco-Model City promotion section in Minamata city |
| Oct.14,2010 | The JICA group training Water environment monitoring | Japan Environmental Sanitation Center |
| Oct.25,2010 | China Building a compensation system of environmental pollution and health damage | Japan International Cooperation Agency |
| Nov.25,2010 | The JICA training the Area Focused Training Course on Effluent Pollution Contorol Caused by Mining and Manufacturing Industries for Central and South America | Global Environment Centre Fundation |
| Nov.26,2010 | Minamata disease spread education seminar | Ministry of Environment |

| Day | Training course name | Organaization |
|-------------|--|--|
| Dec.10,2010 | Circulation society creation in Asia (ASEAN•Indian) | Kitakyusyu Internaional Techno-cooperative Association |
| Feb.2,2011 | The JICA training In Food Sanitation administration | Kitakyusyu Internaional Techno-cooperative Association |
| Fev.16,2011 | Training Course In Establishment Of Sound Material Cycle Society For ASEAN Countries | Kitakyusyu Internaional Techno-cooperative Association |
| Mar.25,2011 | Industrial Pollution Control Management For Middle East Countries | Kitakyusyu Internaional Techno-cooperative Association |

10. Research and other activities in fiscal year 2011

As of July, 2011

1. Promotion of project-type research

(1) [Study group focusing on the mechanism of biological functions of mercury]

| Research subject | Chief researcher |
|--|-------------------|
| Research on selective cytotoxicity and factors determining individual sensitivity of methylmercury | Masatake Fujimura |

(2) [Clinical research group]

| Research subject | Chief researcher |
|--|------------------|
| Clinical research on the of Minamata Disease –focus on the establishment of the objective assessment by magnetoencephalography– | Masaaki Nakamura |

(3) [Working group on risk recognition and information service]

| Research subject | Chief researcher |
|---|------------------|
| Studies on methylmercury exposure in whale-eating district | Masaaki Nakamura |
| Global Center of Excellence Project on Mercury Research and Investigation | Masanori Sasaki |

2. Promotion of fundamental research

(1) [Study group focusing on the mechanism of biological functions of mercury]

| Research subject | Chief researcher |
|---|-------------------|
| Study on the molecular genetic and biochemical factors causing differences of stress responses to methylmercury | FusakoUsuki |
| Research on effect of methylmercury to neurite outgrowth and relief of toxicity | Masatake Fujimura |
| Involvement of aquaporins in methylmercury toxicity | Megumi Yamamoto |
| Role of microglia and macrophage in methylmercury toxicity | Megumi Yamamoto |

(2) [Clinical research group]

| Research subject | Chief researcher |
|--|------------------|
| Development of treatment for subsequent complications of congenital and infantile Minamata disease | Masaaki Nakamura |

(3) [Working group on risk recognition and information service]

| Research subject | Chief researcher |
|---|------------------|
| Exposure assessment of methylmercury and other heavy metals in pregnant women and fetuses | Mineshi Sakamoto |

| | |
|--|------------------|
| Protective effect of selenium against methylmercury toxicity and co-existence of mercury and selenium in human and sea-mammals | Mineshi Sakamoto |
| Study on information transmission and risk perception on health risk of low level exposure to methylmercury | Noriyuki Hachiya |
| Feasibility study of Methylmercury Exposure and Adverse Cardiovascular effects in experimental animals | Masanori Sasaki |
| Effect of mercury on immune function (feasibility study) | Rie Yanagisawa |

(4) [Social and epidemiological approaches to Minamata disease]

| Research subject | Chief researcher |
|---|------------------|
| Study on risk management in Minamata disease history | Noriyuki Hachiya |
| Change of the ADL of fetal and puerility Minamata disease patient entering | Liu Xiao Jie |
| Life and healthy present conditions survey by Minamata disease patient | Liu Xiao Jie |
| Research on regeneration in Minamata disease area | Tazusa Arakaki |
| Research on the Cooperation of Job Creation and Social Welfare at Minamata City that experienced Pollution Damage | Rie Harada |

(5) [Regional and global environment research group]

| Research subject | Chief researcher |
|--|------------------|
| Marine ecosystem and mercury behavior in Yatsushiro Sea. –Quantitative survey of marine benthic community in Yatsushiro Sea and mercury concentration of several fishes through food web– | Keisuke Mori |
| Research on its influences and behaviors of mercury in an aquatic environment of Minamata Bay | Akito Matsuyama |
| Research on chemical reactions, transport and deposition of atmospheric mercury | Koji Marumoto |
| Study on natural emission sources of atmospheric mercury | Koji Marumoto |

3. Other activities

(1) [Clinical research group]

| Activities subject | The chief person in charge |
|--|----------------------------|
| Practice of rehabilitation for patients with Minamata disease and transmission of information on care and rehabilitation | Fusako Usuki |
| Community development project for home care support including health care practice | Masaaki Nakamura |
| Health seminars | Koji Murao |

(2) [Working group on risk recognition and information service]

| Activities subject | The chief person in charge |
|---|----------------------------|
| Organization of documents and materials on Minamata disease, and information providing in Minamata Disease Archives | Noriyuki Hachiya |
| Hair mercury examination of areas concerning for mercury pollution around the world | Masatake Fujimura |
| Digitization of histopathological slides of Minamata disease patients for permanent preservation | Masumi Marumoto |

(3) [Regional and global environment research group]

| Activities subject | The chief person in charge |
|---|----------------------------|
| Information service using hair mercury analysis | Noriyuki Hachiya |
| Cooperation of research in the international organization | Mineshi Sakamoto |
| NIMD Forum and International Workshop | Mineshi Sakamoto |

(4) [Others]

| Activities subject | The chief person in charge |
|---|----------------------------|
| Global mercury research promotion project | Masanori Sasaki |