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Hisashi Yokoyama

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Hisashi Yokoyama
Educational Unit for Studies of Hills,
Humans and Oceans
Kyoto University
Kyoto, Japan

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More than 60 years have passed since the official acknowledgment of the methylmercury poisoning incident in Minamata. Presently, most people who were directly involved in this incident have passed away. They are Drs. Masazumi Harada, Katsuro Irukayama, Syoji Kitamura, Tadao Takeuchi, Haruhiko Tokuomi, and Makio Uchida of Kumamoto University who had worked hard on medical researches as well as on the treatment of the patient; the director of Chisso Hospital, Dr. Hajime Hosokawa, who had faced this incident in sincerity and struggled with the fact that his mother company caused the disease; Mr. Jun Ui who had devoted himself to the elucidation of this incident and other pollution problems; an American photographer, Mr. William Eugene Smith, who had reported the tragedy in Minamata using excellent photographs taken with love to the patients and their families; and many patients who combated not only the disease but also irresponsible Chisso Co. and governments. I would like to express my deepest respect to them.

I want to thank my students who listened to my lectures with close attention and the Nippon Foundation for the financial support for the administration of the educational program as well as for the publication of this book. I received generous support from Ms. Mei Hann Lee of Springer Japan.

Contents

Abbreviations

BMDL	Benchmark dose level
EPA	Environmental Protection Agency, USA
FAO	Food and Agriculture Organization
FCM	Fishermen's Cooperative in Minamata City
FDA	Food and Drugs Administration, USA
FSA	Food Sanitation Act
FSC	Food Safety Committee, Japan
GEM	Gaseous elemental mercury
KP	Kumamoto prefectural government
KU	Kumamoto University Medical School
MAS	Mutual Aid Society of patients
MHLW	Ministry of Health, Labour and Welfare, Japan
MHW	Ministry of Health and Welfare, Japan
MITI	Ministry of International Trade and Industry, Japan
MPM	Methylmercury poisoning in Minamata
MSDAC	Minamata Strange Disease Action Committee
PTWI	Provisional tolerable weekly intake
UNEP	United Nations Environment Programme
RfD	Reference dose
SP	Shizuoka prefectural government
WHO	World Health Organization

Chapter 1
Introduction

Abstract This book overviews the poisoning which occurred in the 1950s and 1960s among the residents in Minamata, Japan, who ate seafood contaminated with methylmercury discharged from the chemical factory, Chisso Corporation. This chapter describes the purpose in writing this book and the reason why the author used MPM (methylmercury poisoning in Minamata) as a disease name instead of so-called Minamata disease.

Keywords Chemical factory · Central nerve disease · Chisso · Discrimination · Minamata disease · Motive for writing · Pollution-related disease

1.1 Why Did I Write This Book?

In July 2012, I was employed as a program-specific professor to implement the "Connectivity of Hills, Humans and Oceans Educational Program" which was opened to all graduate students of Kyoto University. In 2010 when I worked at the National Research Institute of Aquaculture, I visited the Minamata Disease Municipal Museum in south Kyushu. There, I learned details and personal accounts of a disease that is commonly called "Minamata disease." This disease is defined as methylmercury poisoning which occurred among people living along Minamata Bay and the Shiranui Sea (Yatsushiro Sea) in southwestern Kyushu (hereafter called "MPM" as an acronym), Japan, who ate local fish and shellfish contaminated with methylmercury discharged from a private company (Minamata Disease Study Group 1966). At that time, I was terribly shocked by the misery caused by the disease that made many residents suffer. I also knew that many doctors and researchers worked hard to care for the patients as well as to clarify the cause of this disease; however, some people involved with this incident hindered rather than helped to resolve this human and ecological tragedy. This experience moved me to add the lecture regarding this disease among seven lectures in my class "Environmental Conservation of Coastal Waters" in the educational program in Kyoto University from 2013. I considered that this incident was an inevitable consequence of Japan's rapid economic growth after World War II and that similar phenomena are a likely consequence of rapid economic development. This class was conducted in English

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in order to ensure ease of information and communication about this unfortunate incident for international students, mainly from developing countries. The class was concluded in January 2017 due to my retirement.

I met Dr. Hajime Nishimura who is an author of a book (Nishimura and Okamoto 2001) to which I had referred to in my lecture to explain the mechanism about how MPM occurred, at an academic meeting which was held on December 18, 2016. We agreed that it is important to ensure that young people all over the world need to have accurate information of this disease, considering that the disease occurred again in Niigata, Japan (Masano 2013), as well as in Ontario, Canada (Takaoka et al. 2014), and in China (Harada 1985). He strongly recommended to me to publish a book about MPM in English. There are many books and papers which describe this disease; however, most of such publications have been written in Japanese (e.g., Ui 1968; Harada 1972, 1985; Miyazawa 1996; Takamine 2016). Therefore, I wrote this book in English in the form of a lecture to notify young people throughout the world about the outline of the disease as well as the reasons why this disease occurred so that this tragedy is not repeated again.

1.2 Use of "Methylmercury Poisoning in Minamata (MPM)" Instead of "Minamata Disease"

At the beginning stage of the MPM outbreak, this disease had been locally called "Minamata strange disease," as the cause of the disease had not been found. A study group of this disease in Kumamoto University tentatively named "Minamata disease" in 1957, because the group considered that "strange" was not acceptable from the viewpoint of the medical term. Thus, the members named their own group as the "Minamata Disease Study Group." The name "Minamata disease" was used first in a paper (Takeuchi et al. 1957) which was published from *Kumamoto Igakkai Zasshi* (*The Journal of the Kumamoto Medical Society*). In 1958, most newspapers and mass media began to use this name.

In December 1969, the Examination Committee for Specification of Pollution-Related Illnesses of the Ministry of Health and Welfare (MHW) denominated this disease as "Minamata disease," and then the Committee reported to MHW in March 1970 as "It is appropriate to adopt 'Minamata disease' officially, because this name has been used widely in the society."

In general, diseases are denominated based on causative agents or on symptoms; however, "Minamata disease" was named based on the geographical or administrative name, resulting in groundless discrimination against residents in the Minamata area. Many people have often associated the name of "Minamata disease" with an endemic, infectious, or hereditary disease peculiar to the Minamata region. Such misunderstandings have led not only to damage to sales of local farm and marine products and to tourism in Minamata but also to discrimination against residents in the Minamata area at the time of marriage and employment. The discrimination

occasionally extended to elementary and junior high school students. For example, when they had a football game or a school trip, they received harsh words like "Don't touch me. Minamata disease will spread to me" from students living in other localities (Harada 1985; Iriguchi 2012).

In 1973, the Minamata city, the Minamata Chamber of Commerce, and the Tourism Association tried to change the name of Minamata disease. They collected signatures from 72% of electors in Minamata city which were sent to the Environment Agency (Minamata City 2007). Their efforts, however, were not acknowledged; therefore, "Minamata disease" is still in use widely in Japan. Considering that "Minamata disease" includes the harmful expression, Iriguchi (2012) recommended to use "methylmercury poisoning," while Ishihara (2014) recommended "methylmercury intoxication." On the other hand, Harada (1985) maintained the effectiveness of "Minamata disease," because he considered that the term included the geographical name which showed specificity that the methylmercury poisoning occurred through the bioaccumulation in the coastal ecosystem first in the world as well as the meaning of a vow to remember this incident.

In this book, "methylmercury poisoning" is used for a general term of the central nerve disease that is caused by the consumption of methylmercury irrespective of the consumption route, that is, direct consumption or consumption through food chains. When this disease occurred in the Minamata area (the area along the coast in Shiranui Sea), the abbreviation "MPM" that stands for "methylmercury poisoning in Minamata" is used. It is necessary to discuss an appropriate term of this disease. I expect a referendum at a local level to be conducted to determine the disease name.

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Chapter 2
Lecture on Methylmercury Poisoning in Minamata (MPM)

Abstract This chapter outlines the methylmercury poisoning in Minamata (MPM): about the history, symptom pathogenesis, research on the causal agent, and responses of the national and local governments and the responsible company, i.e., Chisso, to the outbreak of MPM. A book written by Nishimura and Okamoto (2001) played an important role to clarify the mechanism of the MPM outbreak. Based on this book and the published data on mercury concentrations of aquatic organisms and newborns' umbilical cords, how methylmercury generated in the plant, flew into the sea, transferred to aquatic organisms, and was consumed by residents are explained. Victims of MPM, compensation and environmental restructure, and court ruling against this incident are described. Based on lecture notes from a university course, students' suggestions for avoiding a repeat of the tragedy are also introduced.

Keywords Bioaccumulation · Fetus · Hunter-Russel syndrome · Intoxication · Methylmercury · Neurological syndrome · Poisoning

Thank you for joining my class. In this lecture, I would like to discuss the issues of the so-called Minamata disease, which is a typical pollution-related disease caused by effluents containing mercury from chemical factories. In this class, I will call this disease MPM (an abbreviation of methylmercury poisoning among people living in the Minamata area). The extent and severity of the health damage as well as the destruction of the natural environment caused by such environmental pollution was unprecedented in the human history. Before explaining MPM, I will mention the properties and toxicity of mercury briefly.

2.1 General Information on Mercury

Mercury is a ubiquitous environmental toxicant. It exists in three forms, that is, elemental (Hg^0), inorganic (Hg^{2+}), and organic forms. Hg^0 takes a liquid form at room temperature but readily evaporates into mercury vapor. Hg^{2+} occurs naturally in the environment in the form of divalent cationic salts of mercury, such as $HgCl_2$.

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Among the three forms, organic mercury, primarily methylmercury, is most hazardous. Methylmercury is bioavailable and can be bioaccumulated within food webs. Seafood consumption, especially the consumption of fish, is the main source of humans' exposure to methylmercury. MPM is the first incident in the world, although there were a few incidents where several persons had suffered from direct exposure of organic mercury in a laboratory or in a factory.

2.2 Outbreak of MPM

Let's look back on the time when MPM was first reported. In the 1950s, strange phenomena appeared in Minamata Bay. Shellfish began to die, fish floated on the surface of the water, seaweed failed to grow, and cats died in strange ways. On April 21, 1956, a young girl living in Tsukinoura District of Minamata City (Fig. 2.1b) was hospitalized at the Chisso Minamata factory hospital (Chisso Hospital) complaining of severe numbness of the limbs, inability to speak, and inability to eat. Following that, three patients were admitted to the hospital with similar symptoms. The director of the hospital, Hajime Hosokawa, notified a case of serious brain disorder to Minamata Health Center on May 1, 1956. This notification constituted the "official acknowledgement (recognition) of MPM." Just after this acknowledgment, a survey team which was composed of the Minamata Public Health Center, Minamata City, Minamata Medical Association, Chisso Hospital, and Minamata Municipal Hospital was formed, and the team confirmed the occurrence of other patients showing similar symptoms. By the end of 1956, 54 cases including 17 deaths since the outbreak in December 1953 were confirmed.

In November 1962, a child diagnosed with cerebral paralysis was certified as a congenital (fetal) MPM patient (the first official acknowledgment of a congenital MPM patient). As the investigation into the cause took a long time, the outbreak of MPM continued, and the geographical range of inhabitants affected by MPM expanded along the Shiranui Sea coast (Fig. 2.1a).

2.3 What Is MPM?

I will explain the symptoms of MPM. MPM is a neurological syndrome which was caused by eating fish and shellfish contaminated by methylmercury compounds discharged artificially. The first and second outbreaks of this kind of disease in Japan were caused by effluents discharged from a factory of Shin-Nippon Chisso Hiryo (hereafter, referred to as Chisso) in Minamata, Kumamoto Prefecture, and a factory of Showa Denko in Kanose Town, Niigata Prefecture, respectively (Fig. 2.1c).

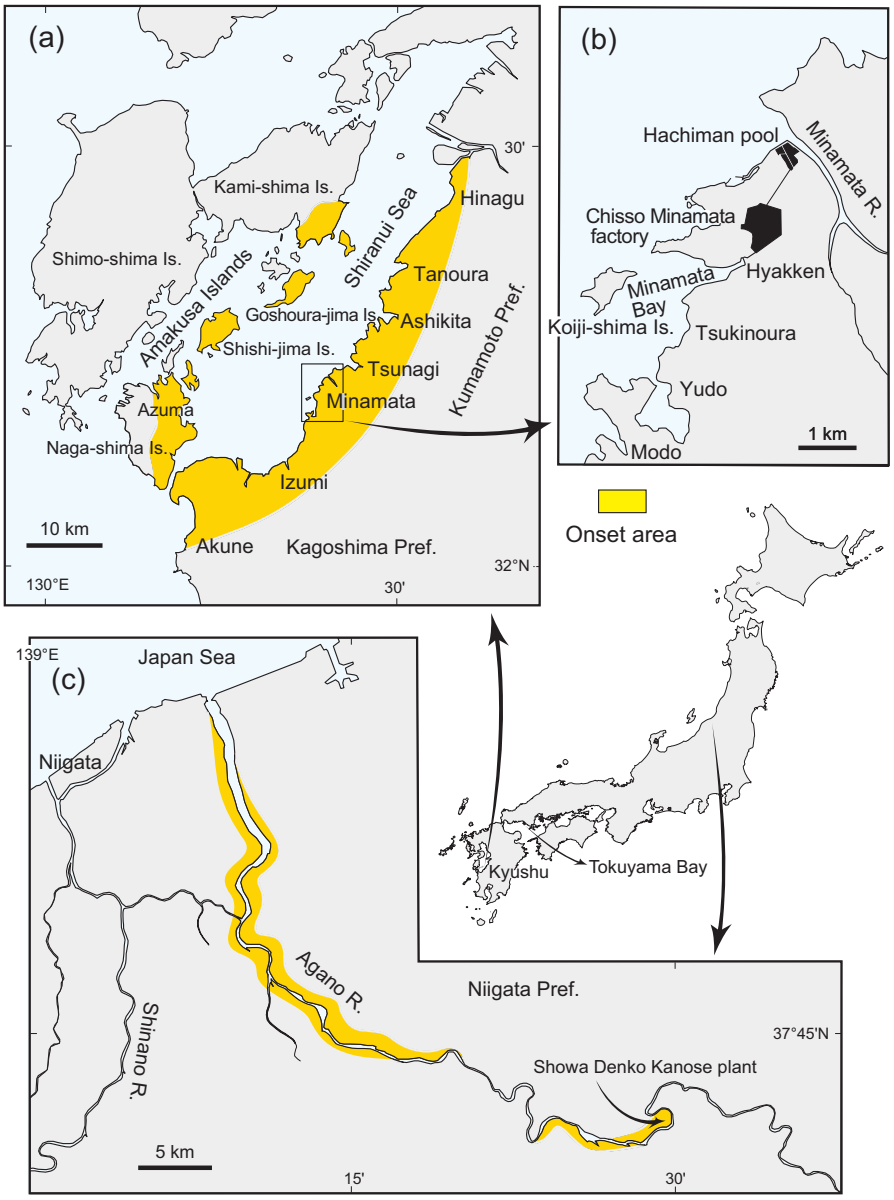

Fig. 2.1 Map showing areas where methylmercury poisoning through environmental contamination occurred. (**a**) The Shiranui Sea (Yatsushiro Sea). (**b**) Minamata area. (**c**) Agano River area. Residential areas of certified patients are shown by yellow (Data source: Harada 1972 and Masano 2013)

Methylmercury is a stable organic mercury compound and is the most toxic form of mercury in the environment not only to humans but also to wildlife (Wolfe et al. 1998, Henriques et al. 2015). Because methylmercury is lipid-soluble, it readily crosses the blood-brain barrier and accumulates in the brain. Methylmercury in the brain causes lysis of cells of the central nervous system, resulting in irreversible, permanent damages of the cells (Rabenstein 1978). Thus, MPM is widely recognized as a disorder in the brain, while Shiraki (1979) suggested that MPM produces lesions not only in the brain but also in the vascular and endocrine systems.

This methylmercury poisoning that occurred in Japan is classified into two types: typical and atypical. The medical condition of the former type was acute and fulminant due to the consumption of a large amount of methylmercury compounds during a short period. In severe cases, such patients fall into a state of madness, lose consciousness, and may even die. The acute type presented most of the following symptoms: (i) ataxia, that is, difficulty coordinating movement of hands and feet; (ii) dysarthria, that is, speech becomes slurred and unclear; (iii) concentric constriction of the visual field, that is, narrowing of the field of vision; (iv) paresthesia, that is, sensory disorders in the distal portion of the four extremities, e.g., loss of sensation in the hands and feet; (v) hearing impairment; (vi) disequilibrium, that is, impairment of faculties for maintaining balance; (vii) tremors, that is, trembling of the hands and feet; and (viii) disorder of the ocular movement, that is, eye movement becomes erratic.

The first organic mercury poisoning occurred at Saint Bartholomew's Hospital in England in 1865 when two laboratory technicians were poisoned with dimethylmercury during their experiments and ended in death (Iriguchi 2012). They complained of sore gums; salivation; numbness of the feet, hands, and tongue; deafness; and poor vision, which were similar to MPM patients excluding the first two symptoms that are characteristics of mercury vapor poisoning. This incident was first reported in "Saint Bartholomew's Hospital reports" (Edwards, 1865, 1866), which were the world's first case reports, and then it was described extensively in the journal *Chemical News* in 1866. Thereafter, the pathology of this affair was described by Hepp (1887) in detail as a disorder of the central nervous system due to methylmercury poisoning (Iriguchi 2014).

Hunter et al. (1940) reported the second methylmercury poisoning. That is, four patients occurred in 1937 in a factory in England where methylmercury compounds were used for seed dressing. The patients commonly had ataxia, dysarthria, and visual field constriction. After an interval of 15 years, Hunter and Russell (1954) dissected the brain of one of these patients and showed cerebellar cortical atrophy, selectively involving the granule cell layer of the neocerebellum and bilateral cortical atrophy around the calcarine sulcus (Fig. 2.2a), which were considered to cause the ataxia and visual field constriction, respectively. They also found small foci of atrophy in the cortex around the central sulcus, which controls physical function and perception. Based on these findings, Pentschew (1958) defined the Hunter-Russel syndrome as lesions of the brain tissue. Later, Takeuchi et al. (1960b) and Takeuchi (1966) found similar lesions in brains of MPM patients (Fig. 2.2a) as

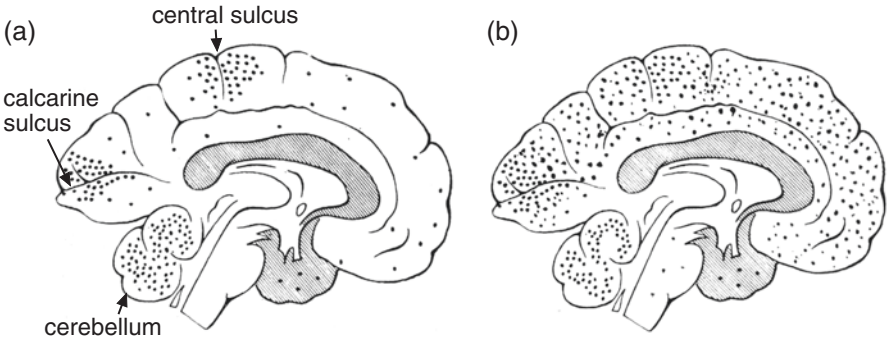

Fig. 2.2 Lesions in the brain of acquired adult (**a**) and congenital (**b**) "Minamata disease" patients. Lesion areas are indicated by spots (After Takeuchi 1966)

those found by Hunter and Russell (1954), which let to diagnose MPM as organic mercury poisoning.

Other than these two incidents that occurred at Saint Bartholomew's Hospital and the seed factory, poisoning by direct incorporation of methylmercury had occurred in Canada (Hill 1943, Ahlmark 1948) and Sweden (Lundgren and Swensson 1949, Höök et al. 1954) before the outbreak of MPM. Zangger (1930) also reported organic mercury poisoning among workers in the process of acetaldehyde production where inorganic mercury was used as a catalyst similar to the Chisso Minamata factory, suggesting that inorganic mercury had changed to organic mercury compounds in this production process.

In general, the symptoms of the typical MPM were similar to those of the preceding accidental cases of the methylmercury poisoning; however, there were some differences in the combination of symptoms and in the severity of the disease state between them, because the amount of and/or the exposure period to methylmercury were variable among the MPM patients. In relatively mild cases in MPM, the condition is barely distinguishable from other ailments such as headache, chronic fatigue, and a generalized inability to distinguish taste and smell.

Thus, besides the typical type, there was an atypical MPM which exhibited only one or a limited number of the symptoms. Such a type of case was liable to become chronic. For instance, neurological disorders such as a hypoesthesia at the distal parts of the extremities and around the lips, which were considered to be caused by a long-term dietary exposure to methylmercury compounds, were still detected among residents in a fishing village in Goshoura-jima island 10 years after the cessation of methylmercury dispersion from Minamata (Ninomiya et al. 1995). On the other hand, delayed MPM is defined as the latent development of methylmercury poisoning after multiple years of cessation from a long exposure through contaminated food (Miura 2014). Thus, there is a large variability in the type and the degree of symptoms, resulting in difficulties in diagnosis and certification of MPM.

There have been cases of congenital MPM, where fetuses were poisoned by methylmercury compounds via the placenta after their mothers ingested contaminated

foods during pregnancy and were born with a condition resembling cerebral palsy. The symptoms of patients were serious including both in mental and physical development due to extensive and intensive lesions of their brains (Takeuchi 1966: Fig. 2.2b). They showed significant impairments in chewing, swallowing, speech, gait, and other coordination and involuntary movement (Ekino et al. 2007). The most severe effects which were found following this high-dose poisoning included cerebral palsy, deafness, blindness, and dysarthria (National Research Council 2000). Shiraki (1979) proved the intrusion of methylmercuric chloride into fetuses after performing intravenous injections on mother rats by the autoradiography. Lipophilic methylmercury is readily transferred to the fetus across the placenta via neutral amino acid carriers and concentrated in the central nervous system of fetuses' brains (Kajiwara et al. 1996). The blood-brain barrier is not fully developed until after the first year of life, and methyl mercury can cross this incomplete barrier (Rodier 1995). Thus, the developing brain is extremely vulnerable to methylmercury.

What kind of medical treatment is effective for MPM? In the initial stages, causative treatments, involving patients taking medicines to force methylmercury compounds to be excreted from the body, are applied. However, a fundamental cure for MPM has not yet been found. The main treatments involve the temporary relief of symptoms (symptomatic therapies), as well as rehabilitation (physiotherapy and occupational therapy).

2.4 Investigations on the Cause of MPM

Investigations to clarify the cause of this disease started. On May 28, 1956, the Minamata Strange Disease Action Committee (MSDAC) which was established by Minamata Health Center, Minamata City, City Medical Association, Municipal Hospital, and Chisso Hospital was established. On August 14, 1956, MSDAC asked Kumamoto University Medical School (KU) to investigate the cause of the disease. Then, KU formed a Minamata Disease Study Group. On November 3, 1956, KU held an interim report meeting, where MSDAC members and Prefectural Public Health Department staff attended. At this meeting, KU reported that the disease was a kind of heavy metal poisoning and that the causative agent had entered the human body through consumption of fish and shellfish captured in this area. Although this report was "tentative," these findings show that in only 6 months since the official acknowledgment of MPM, researchers at KU strongly suspected that this disease was caused by seafood poisoning. At that time, this disease could have been avoided by banning all fisheries in Minamata Bay and prohibiting the consumption of local seafood (Tsuda 2014). However, such measures were not adopted. It was the start of a continuing tragedy.

It took 3 years to reveal the causative agent of MPM. At the initial stage of the research, manganese, selenium, and thallium were suspected as the causative agent. British neurologist Douglas McAlpine, who examined 15 patients admitted into the KU hospital in 1956, published a paper in collaboration with Shukuro Araki of KU,

suggesting that MPM symptoms resembled those of methylmercury poisoning which showed ataxia, dysarthria, and constriction of the visual fields (McAlpine and Araki 1958). They also suggested that this disease was caused by eating fish captured in Minamata Bay which were contaminated by "an inorganic chemical compound contained in the effluent which flowed into Minamata Bay from a nearby fertilizer factory." At that time, there was no fertilizer factory other than the Chisso Minamata factory. On September 26, 1958, Professor Tadao Takeuchi of KU also announced at the meeting of the study group "Pathological findings coincided completely with the Hunter-Russell syndrome." Investigations regarding the epidemiology, pathology, and etiology of MPM advanced further by KU, and the results were published mainly in domestic journals quickly and sequentially as follows.

2.4.1 Epidemiological Examinations

Kitamura et al. (1957a) confirmed 52 patients had MPM during the period from 1953 to 1956. They found that (1) the fatality rate in these patients was 33%; (2) the onset area was fishing and agrarian villages around Hyakken Port in Minamata City; (3) fishermen and their families comprised a high proportion of the total patients; and (4) cats inhabiting the same area also showed similar symptoms, and shortly after, the majority died. These findings suggested that exposure to an agent which was common to residents and cats caused this disease and that fish and shellfish inhabiting the Minamata Bay area were contaminated and these seafood contained the causative agent. This conclusion was supported by observations that migratory fish became poisonous during a short stay in Minamata Bay (Kitamura et al. 1957b). Further epidemiological observations showed that (1) in 1957, no new patients were diagnosed as seafood in this area was temporarily not consumed (Kitamura et al. 1957b); (2) in 1958, MPM patients occurred again as a result that residents restarted eating seafood (Kitamura et al. 1959); and (3) since 1959, the onset area expanded to northern and southern areas of Minamata City, associated with the shift of the wastewater outlet from Hyakken Port in Minamata Bay to the mouth of Minamata River (Kitamura et al. 1960a). Kitamura et al. (1960b) found high concentrations of mercury in organs, hair, and urine of MPM patients as well as in organs of cats that showed similar symptoms to MPM, suggesting mercury in wastewater from the factory as a potential causative agent.

2.4.2 Finding of the Congenital MPM

Kitamura et al. (1959) found nine infants having cerebral palsy around Minamata Bay, accounting for >10% of the total newborns in the MPM-prone area in 1956. They suspected that intoxicating substance moved to the infants through the placenta or mother's milk, even if their mothers showed no obvious symptoms of

MPM. Nagano et al. (1960) also reported similar 15 cases of infants who were born during the period of 1955–1958. The study group of KU, however, hesitated to conclude that such cases were caused by the congenital MPM, because similar cases had not been reported from the world. At the Kumamoto medical conference held on November 25, 1962, Dr. Tadao Takeuchi of the study group did a presentation about the anatomy of two congenital patients' brains (Takeuchi et al. 1964), while Dr. Masazumi Harada did a presentation about a clinical manifestation of a congenital patient whose brain was served for the dissection (Harada 1972). These presentations concluded that methylmercury consumed by mothers had impaired fetuses' brains (Fig. 2.2b). Thus, they revealed evidence of congenital MPM.

2.4.3 Feeding Experiments on Animals

Ito (1957) fed fish and shellfish collected from Minamata Bay to five cats, and he confirmed that symptoms of MPM appeared 7–47 days after, showing a lesion in the central nervous system. Thereafter, several animal experiments to feed cats, rats, or mice on fish and/or shellfish were conducted, indicating that coastal animals collected from the Minamata area contained the substance causing MPM (e.g., Takeuchi et al. 1957c, Shiraishi et al. 1959, Kojima 1960).

2.4.4 Pathological Examinations

Takeuchi et al. (1957a, b) dissected diseased cats and birds which were collected from the coastal area in Minamata City for pathological examinations and found that these animals were suffering from an intoxicated encephalopathy which was the same disease as residents. Takeuchi et al. (1959a, b) pointed out that the histopathological diagnoses on brains of acute and chronic MPM patients and the symptom of MPM such as ataxia, constriction of the visual field, and dysarthria closely resembled those of organic mercury poisoning known as the "Hunter-Russel syndrome." Tokuomi (1960) and Tokuomi et al. (1960) pointed out that (1) symptoms of MPM corresponded completely to those of organic mercury poisoning; (2) the concentration of mercury in the urine of patients was significantly high; (3) same symptoms and same lesions were found between MPM patients and experimental animals that were given methylmercury, and they concluded that MPM was food poisoning caused by the consumption of organic mercury. Takeuchi et al. (1960a) and Takeuchi and Morikawa (1960) also reached the same conclusion based on results on necropsies of patients, examinations of the clinical and pathological observations in stray cats and wild fish, and feeding experiments using cats and rats.

2.4.5 Field Surveys to Search for the Causative Agent

Kitamura et al. (1960b) found the accumulation of a large amount of mercury in the sediment of Minamata Bay as well as in aquatic organisms collected from Minamata Bay. They found an extremely high concentration (2010 ppm, wet sediment wt basis) of total mercury in the sediment of Hyakken Port close to the outlet of wastewater from the factory, and decreasing concentrations as the sampling location was shifted seaward (Fig. 2.3). They also found high concentrations of mercury (30–39 ppm dry wt basis) in the mussel, *Hormomya mutabilis* in Minamata Bay, and decreasing trend of the concentration (<20 ppm) as the habitat shifted outside of the bay (Fig. 2.3). Such trends suggest that mercury in the sediments and mussels originated from the Chisso Minamata factory.

As a result of these patient and steady researches, the study group of KU reached a conclusion. On July 22, 1959, KU made an announcement, saying that "MPM is a disease of the nervous system which is caused by eating fish and shellfish captured from Minamata Bay. Mercury has come to our attention as a likely cause of pollution of fish and shellfish." After this announcement, the study group of KU continued the research to reveal the causative agent of MPM. On September 29, 1960, Makio Uchida of KU announced that "We extracted an organic mercury compound from shellfish in Minamata Bay."

2.4.6 Feeding Experiments of Organic Mercury on Animals

Takeuchi and Morikawa (1960) and Takeuchi et al. (1962) fed methylmercury compounds on cats, and they confirmed the development of MPM. Other members of KU also showed that experimental animals orally dosed with certain amounts (~20 mg Hg kg^{-1} for cats, rabbits, and dogs, after Irukayama et al. (1964a)) of alkyl mercury compounds having CH_3, C_2H_5, and C_3H_7 induce symptoms consistent with MPM within 5 days to approximately 2 months (Tokuomi et al. 1960, Sebe et al. 1961, Takaba 1962, Irukayama et al. 1963, Takeshita and Uchida 1963). Morikawa (1961) confirmed that a kitten born from a mother cat which was dosed with bisethylmercuric sulfide had symptoms similar to congenital MPM.

2.4.7 Extraction of Organic Mercury from Aquatic Organisms

Uchida et al. (1961a, b), Hirakawa (1962), and Inoue (1962) extracted crystals from tissues of the mussel, *H. mutabilis*, collected from Minamata Bay and identified them as methyl methylmercuric sulfide (CH_3HgSCH_3) (Irukayama et al. (1964a) described that this organic mercury should be identified as $(CH_3Hg)_2S$). Irukayama et al.

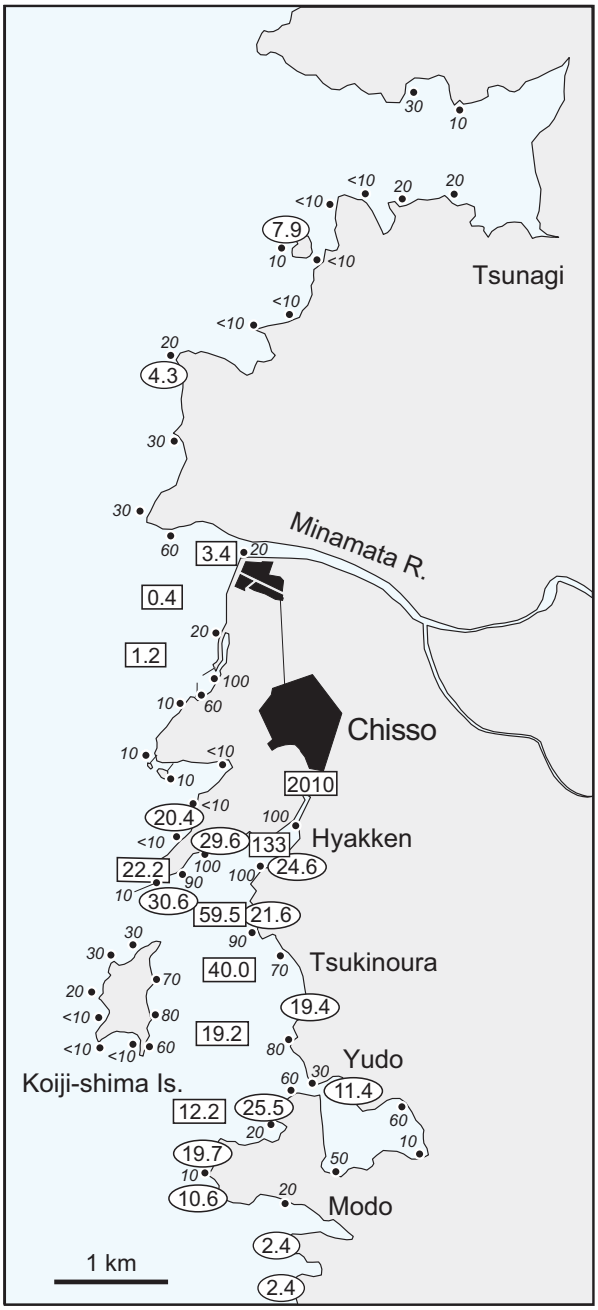

Fig. 2.3 Effects of mercury on the biota and sediment in the Minamata area. Numerals in italics: mortality (%) of oysters distributed along the shore of the Minamata area in summer, 1957, which was shown by the survey of Fisheries Experimental Station of Kumamoto Prefecture (Adapted from Fukai 1999). Numerals in squares: concentrations in mercury in the sediment in 1959 (ppm = μg g^{-1} wet sediment) (After Kitamura et al.1960b). Numerals in ellipses: concentrations of mercury in soft tissues of the mussel, *Hormomya mutabilis*, in 1959 (ppm = μg g^{-1} dry wt) (After Kitamura et al. 1960b)

(1962a) extracted organic mercury from the mussel, *H. mutabilis*, and the scarbreast tuskfin, *Choerodon azurio*, collected from Minamata Bay. This organic mercury contained in *H. mutabilis* as well as in the Japanese littleneck, *Ruditapes philippinarum*, was identified as methylmercuric chloride (CH_3HgCl) (Irukayama et al. 1964a).

2.4.8 Experiments on Bioaccumulation by Aquatic Organisms

Irukayama et al. (1962b) showed that *R. philippinarum* accumulated 40–129 ppm (dry weight basis) of Hg during 4–14 days of culture in seawater containing 0.2–0.3 ppm of alkyl mercury and that this clam accumulated 22.5 ppm within 5 days of culture in water containing mercury sludge discharged from Chisso Minamata factory.

2.4.9 Extraction of Organic Mercury from the Factory

CH_3HgCl was extracted from mercury sludge (mixture of inorganic mercury and activated charcoal which was used as the catalyst) in the acetaldehyde plant (Irukayama et al. 1962c) and from sediments in the drainage close to Hyakken Port (Irukayama et al. 1962d). Irukayama et al. (1964a) concluded that the causative agent of MPM was CH_3HgCl and that the functional group is methylmercury (CH_3Hg-).

Finally, the study group of KU concluded that (1) a variety of coastal animals contained large enough amount of methylmercury to cause MPM; (2) methylmercury occurred in wastewater and sludge in Chisso Minamata factory; and (3) methylmercury in coastal animals originated from Chisso Minamata factory. On February 20, 1963, KU made a formal announcement stating that "MPM is a disease of the central nervous system caused by eating fish and shellfish from Minamata Bay. The causative agent of poisoning is methylmercury compounds found in shellfish as well as in the sludge of the Chisso Minamata factory." Later, the study group summarized their results in a book (Minamata Disease Study Group 1966). Such a process shows that the researchers of KU accumulated scientific evidences sincerely and steadily. In those days, there was an atmosphere that researchers should avoid studies which might result in the conflict of becoming political issues. The researchers were at risk for suffering from the mercury poisoning themselves in the process of the extraction and synthesis of methylmercury during their experiments. They finally reached the truth; however, 7 years had passed after the official acknowledgment. During this period, the Chisso Minamata factory continued to drain wastewater containing organic mercury, and the number of MPM patients steadily increased.

2.5 Initial Responses of the National and Local Governments to the Outbreak of MPM

Let's look back to the national and local governments' responses. In November 1956, a research team of the Ministry of Health and Welfare (MHW) started an epidemiological survey. In March 1957, they suspected fishery products collected from Minamata Bay as a cause of the disease and recommended to investigate the relationship between wastewater discharged from the plant and fish in Minamata Bay. In addition to this, KU also suggested to the Kumamoto prefectural government (KP) to ban the fisheries in Minamata Bay on February 26, 1957. In March 1957, therefore, KP made enquiries to the Shizuoka prefectural government (SP) about the poisoning of Japanese littleneck *R. philippinarum* which had occurred in Hamana-ko lagoon, because SP used to stop the fishery and selling the clam and to prevent the occurrence of food poisoning by applying the Food Sanitation Act (FSA) (Fukai 1999). On August 16, 1957, KP made inquiries to MHW, on the possible implementation of FSA. On September 11, 1957, MHW replied, "Fish and shellfish collected from Minamata Bay may cause the disease, however, as there is no clear evidence that all fish and shellfish in Minamata Bay are contaminated, FSA should not be applied." KP followed this recommendation and did not implement the FSA. Nobuo Miyazawa who devoted his life to the clarification of the Minamata incident in favor of the patients after his assignment in Kumamoto as a broadcaster of NHK, however, revealed underlying facts by his thorough coverage (Miyazawa 1996). The vice-governor of KU, Chokichi Mizukami, who had been a government bureaucrat, requested MHW not to recommend the enforcement of FSA. Mayor of Minamata City, Hikoshichi Hashimoto, who designed the acetaldehyde plant of the Chisso Minamata factory and served as a director of the factory later, also opposed to be subject of FSA. The two persons might fear of paying the compensation money for fishery banning by Chisso.

On the other hand, the Fisheries Experimental Station of KP showed that the coastal waters were seriously affected based on a survey of the oyster (species belonging to Ostreidae) distributed along the shore in the Minamata area in summer, 1957 (Fig. 2.3). The mortality rate of the oyster distributed in Minamata Bay was very high, attaining to 60–100%. Even in Tsunagi which is located ~10 km north from Minamata, a mortality of 30% was found. The results were reported to the Fisheries Division of KP immediately; however, the findings were not reflected in an administrative measure.

In January 1959, the Minamata Food Poisoning Special Committee was set up under the Food Sanitation Investigation Council, MHW, to investigate the cause of MPM. On November 12, 1959, the committee submitted a report to the MHW minister, saying that, "the organic mercury compounds in fish and shellfish around

Minamata Bay are the main causative factor of MPM." Their conclusions, which were mainly based on the findings of the study group of KU, are as follows:

1. The main symptoms of this disease, which are ataxia, concentric constriction of the visual field, and paresthesia, as well as observations of the pathologic autopsy closely agreed with those of organic mercury poisoning.
2. Concentrations of mercury in the urine of patients were high in comparison with reference values.
3. Large amounts of mercury were found in the brain, liver, and kidney of patients in comparison with reference values.
4. Extremely large amounts of mercury were found in sediments in Minamata Bay in comparison with other regions.
5. Large amounts of mercury were found in mussels in Minamata Bay in comparison with other regions, and cats which ate these mussels developed similar symptoms and tissue abnormalities.
6. Large amounts of mercury were found in organs, especially in the brain, of cats which developed the disease experimentally or spontaneously.
7. Animals which were administered with organic mercury developed similar symptoms and tissue abnormalities.

Thus, the committee reached an exact conclusion that MPM was food poisoning caused by organic mercury. However, this report was not approved by the cabinet meeting due to an opposite opinion offered by the minister of the International Trade and Industry, Hayato Ikeda, who later became the prime minister in 1960 and promoted Japan's rapid economic growth in the 1960s (Masano 2013, Takamine 2016). This committee was dissolved on the following day, and MHW was unable to implement any appropriate measures.

As described in the next section, Chisso made a contract regarding the compensation with a patient group through the mediation of KP and Minamata City. At that time the local governments established a patient certification program for specifying persons who had suffered from MPM. This system continued after an establishment of the Act on Special Measures Concerning Relief for Health Damage by Pollution that was enforced in December 1969. For this purpose certification councils had been established; however, the certification criteria were too strict to cover all patients resulting in many lawsuits to claim for the compensation.

2.6 Initial Responses of Chisso to the Doubt that Its Own Wastewater Caused MPM

Now, I will focus on the responsible company that caused MPM, Chisso. This company first opened a chemical factory in Minamata in 1908. The factory initially produced fertilizer and then followed the nationwide expansion of Japan's chemical industry, branching out into the production of acetylene, acetaldehyde, acetic acid,

vinyl chloride, and octanol. The Chisso Minamata factory first started the production of acetaldehyde, a material used for production of plastics and other plasticizers, in 1932.

How did this company take countermeasures against the outbreak of MPM? In September 1958, Chisso changed the discharge system for plant effluents from the acetaldehyde manufacturing process. Before this change, effluents were discharged directly into the Hyakken Port in Minamata Bay (Fig. 2.1b). In this system, effluents were stored in the Hachiman Pool prior to discharge of the supernatant to the mouth of Minamata River. However, this new system resulted in the expansion of the onset area of MPM to the north of the river mouth in March 1959 and thereafter. In October 1959, the Ministry of International Trade and Industry (MITI) instructed the factory to remove the new drainage channel, and then in the next month discharging from the Hachiman Pool to the mouth of Minamata River stopped. Instead of this, the factory constructed a "wastewater purifying facility" in December 1959; thereafter wastewater was channeled into the Hyakken Port again after the treatment by this facility. This apparatus in this facility, however, has a function to neutralize acids and to remove suspended solids, but has no function to remove organic mercury compounds. Chisso publicized this as "complete purification of wastewater," and then many organizations including the research members of KU accepted this claim as true, resulting in the ending of investigations. Residents resumed eating fish again.

Later, the director of the Chisso Minamata factory, Eiichi Nishida, testified that the change of the discharge system aimed to dilute the wastewater by seawater in Shiranui Sea and that regarding this matter they continued to communicate with MITI (Miyazawa 1997). This evidence indicates that not only Chisso but also MITI recognized the toxicity of the wastewater discharged from the factory.

Kanji Irie, a managing director of Chisso, recorded a note regarding interviews with Hajime Hosokawa, a director of Chisso Hospital, which was confiscated by public prosecutors and later used for the criminal trial of the events leading to MPM (Miyazawa 2011). According to this, Dr. Hosokawa noticed that consumption of local fish by residents caused MPM by summer 1957. He suspected wastewater discharged from the plant as the cause of MPM; therefore, he proposed to the factory director to examine the relationship between the disease and wastewater. On July 21, 1959, Hosokawa started an experiment to give wastewater to two cats from his own will, and then he found that one of the cats (called as No. 400 cat) developed the symptoms on October 6. He reported this result to managers of Chisso Minamata factory and insisted to continue this experiment; however, they ordered to stop the experiment. Hosokawa resumed the experiment after August 1960 and then confirmed the development of the symptoms on cats again. On the other hand, in 1961, an engineer of the factory, Shun'ichi Ishihara, detected methylmercury from a drain in the plant and reported it to the managers; however, they did not reveal these results to the public.

In August 1959, Chisso asserted that as "The organic mercury theory of KU is speculation without definitive proof, and it is irrational in view of chemistry common sense" at a Special MPM Committee meeting of the Kumamoto prefectural assembly. In addition to this, Chisso introduced other hypotheses proposed by Takeji Oshima of the Japan Chemical Industry Association, Raisaku Kiyoura of

Tokyo Institute of Technology, and Kikuji Tokita of Toho University who insisted the consumption of fish polluted by abandoned explosive or decayed fish as the cause of the disease without significant data. As shown by these events, a hostility developed between KU and Chisso resulting in lack of trust and integrity. The non-cooperative attitude of the Chisso managers delayed the conclusion of the causative agent by the researchers of KU by 1962.

On November 25, 1959, the mutual aid society of patients (MAS) demanded compensation from Chisso. At the beginning, Chisso neglected the request, asserting as "There is no clear link between the mercury contamination and the factory wastewater." In December 1959, with mediation by the Kumamoto Prefecture governor and Minamata City mayor, MAS was persuaded to sign the "Mimai-kin (consolatory present of money)" agreements, in which Chisso paid lump sum compensation of ¥300,000 ($833 at that time) for each dead patient and an annual stipend for surviving patient (¥100,000 for an adult and ¥30,000 for a child). Even in contemporary terms, the sums awarded were extremely low. The agreements included the sentence "Even if it shall be revealed in the future that wastewater discharged from the factory causes MPM, no further demands for compensation will be made."

From these results, I must say that Chisso was trying to hide the truth and to reduce compensation to victims as much as possible and that they continued to produce acetaldehyde accompanied by wastewater containing methylmercury until 1968 when a new plant of the acetaldehyde production without using mercury started to produce at another factory of Chisso, even though they knew the fact that their own wastewater had caused MPM.

2.7 Counterclaims of Chisso

In 1959, when suspicion that MPM was caused by wastewater discharged from Chisso Minamata factory had strengthened by the research results conducted by KU, Chisso objected these results strongly, giving the following reasons:

1. Although we continue to use mercury as a catalyst in the plant for acetaldehyde production since 1932, why did an important number of MPM patients first occur in 1954?
2. There are many factories producing acetaldehyde not only in Japan but also all over the world; nevertheless, why did only Minamata factory cause MPM?
3. We are using inorganic mercury. There is no information that inorganic mercury changes to organic mercury compounds in plants as well as in natural conditions.

I will explain why these counterclaims by Chisso were wrong in the latter half of this lecture.

2.8 A Book Written by Nishimura and Okamoto (2001)

During the preparation for the lectures in Kyoto University, I came across a book written by Nishimura and Okamoto (2001). The first author, Hajime Nishimura, covers broad areas including not only his major, industrial chemistry and process engineering, but also gene technology, environmental sciences, and social sciences. The second author of that book, Tatsuaki Okamoto, was familiar with the circumstances of Chisso from 1957 to 1990 as an employee of Chisso. He described his opinion in the book, "I could not stand on the side of managers of Chisso who care nothing for anybody. I have chosen to voice my concerns as a member of the labor union of Chisso together with the patients of MPM."

That book attempted to answer the question why did MPM occur by examining the flow of the causative agent, methylmercury, quantitatively in the process from the acetaldehyde production in the factory through coastal environments including water, sediment, and marine organisms and finally to residents throughout the period of the disease outbreak. At that time, quantitative information on methylmercury in the production processes and in the coastal ecosystem was limited. Under such circumstances, the book showed several hypotheses. Some predictable expressions may be used, but it should be permitted in such a general book, whereas a few researchers have criticized this book severely by saying that this book includes some erroneous hypotheses (Suzuki 2007, Miyazawa 2010). However, I considered that this book played an important role in clarifying the underlying causes of MPM even if some hypotheses in light of new findings need revision; therefore, I decided to introduce this book in my lecture.

I will explain how methylmercury was produced in the acetaldehyde production plant of the factory and in coastal waters and how the local residents suffered from MPM mainly based on this book.

2.9 Chemical Reaction in Acetaldehyde Production Process

Acetaldehyde is produced by adding water to acetylene. This chemical reaction proceeds when acetylene is injected into a solution of sulfuric acid and mercury oxide. In this process, mercury ions are generated and work as a catalyst. Nishimura and Okamoto (2001) estimated the process of the methylmercury generation in the reaction of the acetaldehyde production theoretically (Fig. 2.4). In this reaction, acetylene can change to mercury acetate through intermediates 1 and 3 by adding mercury ion; then mercury acetate can change to methylmercury through decarboxylation. The generation of methylmercury was confirmed in the laboratory in the same production system of the Chisso factory (Irukayama et al. 1967a, Kitamura et al. 1967) as well as from the drainage in Chisso Minamata factory (Irukayama et al. 1967b).

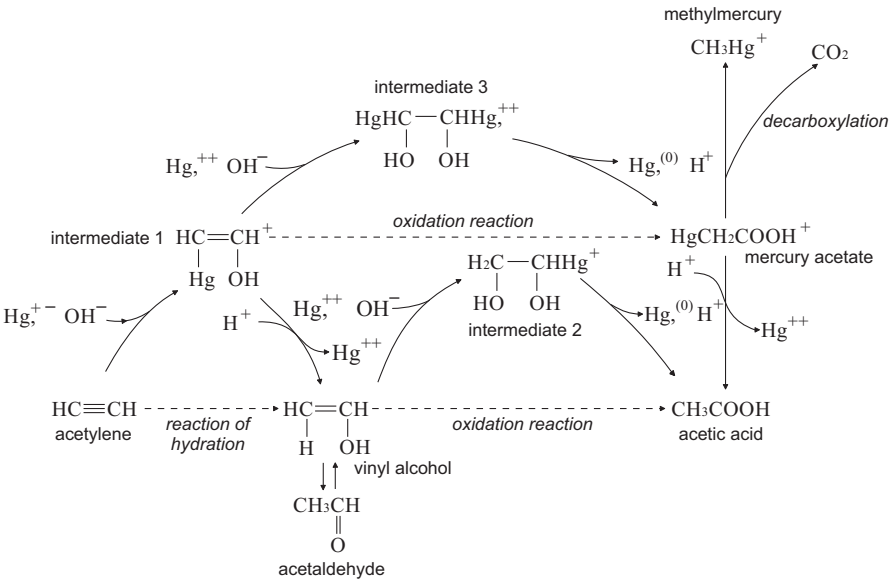

Fig. 2.4 Generation of methylmercury in the process of the acetaldehyde production (After Nishimura and Okamoto 2001)

2.10 Relationship Between the Methylmercury Emission and the MPM Outbreak

In this section, I will trace annual changes of several important components that were related to MPM based on Nishimura and Okamoto (2001) (Fig. 2.5).

After World War II, the demand for octanol had increased, because this was one of the basic materials used in the chemical industry. At that time, octanol produced by Chisso accounted for 85% of the market share in Japan. Acetaldehyde was a fundamental material for producing octanol. After the commencement of acetaldehyde production by Chisso Minamata factory in 1932, the production of acetaldehyde increased rapidly after the mid-1950s and attained the maximum production of 45,245 tons in 1960. In 1962, the production decreased to 26,500 tons due to labor troubles; however, in 1963, the production increased again to 38,500 tons. After 1964, the production decreased. In May 1968, the production was finished, because another factory of Chisso began to produce acetaldehyde using a different method.

Nishimura and Okamoto (2001) estimated the amounts of methylmercury emission and inflow into the coastal sea from the Chisso Minamata factory in each year using the techniques of chemical process engineering. There was a time lag in increasing and decreasing patterns between the acetaldehyde production and methylmercury emission (Fig. 2.5). In 1951, the methylmercury emission increased abruptly from 4.5 kg in the preceding year to 23.3 kg, all of which were considered to flow into the sea, in spite of the lack of a rapid increase in the acetaldehyde production. Nishimura and Okamoto (2001) pointed out three reasons for this rapid increase.

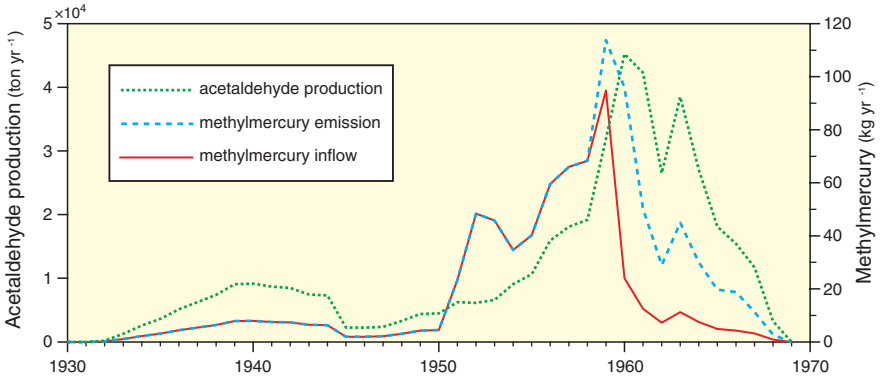

Fig. 2.5 Annual change in the amount of the acetaldehyde production by the Chisso Minamata factory, the methylmercury emission from the plant, and the methylmercury inflow into the coastal waters (Adapted from Nishimura and Okamoto 2001)

Firstly, the promoter, which is a substance that enhances the activity of the catalyst and increases the rate of the chemical reaction, was changed from manganese dioxide (MnO_2) to nitric acid (HNO_3) and iron sulfate ($Fe_2(SO_4)_3$) in 1951. This change was considered to result in the increase of the methylmercury emission, because HNO_3 and $Fe_2(SO_4)_3$ more readily induce the generation of methylmercury due to a weaker oxidation in comparison with MnO_2. Secondly, high concentrations of chloride ions in the reaction vessel promoted evaporation of methylmercury, resulting in an accumulation of methylmercury in a drain of the rectifying column. Irukayama et al. (1965) suggested that CH_3HgCl could be the causative agent of MPM due to the high stability in seawater and to the high bondability with proteins of aquatic organisms. They also showed that an intermediate, $(CH_3Hg)_2SO_4$, in the acetaldehyde production can readily transform to CH_3HgCl in the presence of chloride ions experimentally and that Chisso Minamata factory added seawater to industrial water since 1955 (Irukayama et al. 1967a) (Fig. 2.6). Actually, they measured >1000 ppm of chloride ion in wastewater discharged from the rectifying column of the acetaldehyde plant (Irukayama et al. 1967b). The practice of adding seawater into industrial water is far from common sense in chemical industrial processes. Finally, an increase of disposed and/or leaked reaction mother liquor contributed to the increase of the methylmercury emission. The latter two reasons indicate how Chisso managed the plant irresponsibly.

Irukayama et al. (1967a) introduced data of wastewater discharged from the acetaldehyde production plant as (1) the amount of wastewater, which contained 10–20 ppm of mercury, increased from 2 $m^3\ h^{-1}$ in 1952 to 6 $m^3\ h^{-1}$ in 1959 (Fig. 2.6); and (2) when the plant was cleaned four times a year, 30 $m^3\ h^{-1}$ of washing water was discharged. The data were provided by the Minamata plant in 1959, indicating that they had recognized the discharge of a large amount of mercury from their own factory.

The estimated annual methylmercury emission peaked in 1959, accounting for 114 kg (Fig. 2.5). In this year, the factory did not discharge wastewater for 2 months;

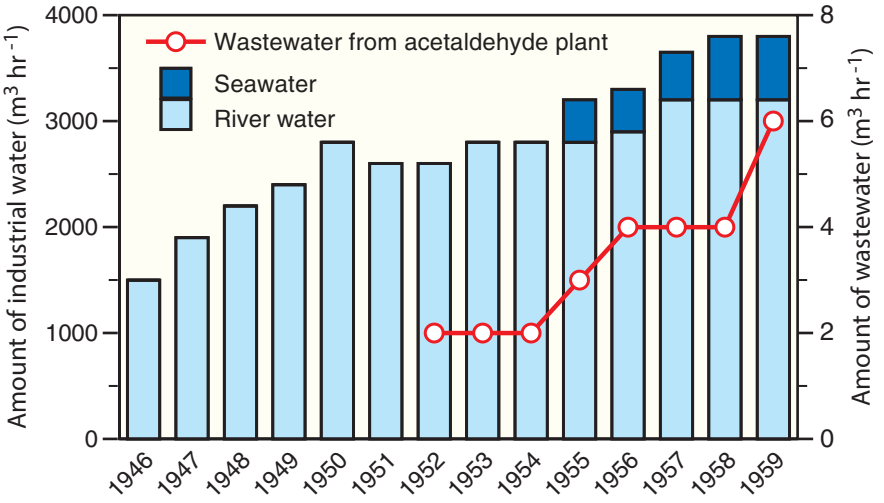

Fig. 2.6. Volume of industrial water and wastewater from the acetaldehyde plant in the Chisso Minamata factory. River water which was collected from Minamata River and seawater were used (Adapted from Irukayama et al. 1967a)

therefore, the outflow of methylmercury was estimated to be 95 kg. In 1960, the factory constructed a circulation system in the rectifying column drain to avoid discharging mercury to the sea. This construction was considered to reduce 75% of methylmercury outflow, contributing to the rapid decrease in the outflow, and then finally the outflow was finished in May 1968. The total amount of methylmercury that flowed into the sea from the factory was estimated to be approximately 640 kg. On the other hand, the total amount of mercury that flowed into the sea was estimated to be approximately 82 tons (Silver et al. 1994).

The exact number of MPM patients is unclear; however, we can trace the trend of this disease based on the number of the three kinds of patients in each year. One is the typical type of MPM patients which had been certified by the local governments by July 1970 as having most of the characteristic symptoms (i.e., paresthesia, visual field constriction, ataxia, impaired hearing and speech impairment, etc.). The second is the atypical MPM patients who had been recognized by the KU medical team, as having a limited number of the characteristic symptoms, at the time of mass examinations conducted in 1971 and 1972. The third is the congenital MPM patients who were certified by 2000. A patient of the typical MPM was recognized first in 1953.

The number of the typical type patients increased suddenly in 1954, 3 years after the rapid increase of methylmercury inflow into the sea (Fig. 2.7). Thereafter, a large number of the typical MPM patients were found during the late 1950s when the high levels of the methylmercury inflow were continuing. Especially in 1956, 46 patients that belonged to this type were found. After 1960, however, this type was not found, accompanied by the decreasing trend of methylmercury inflow. On the other hand, patient of the atypical type appeared first in 1941; then the number of

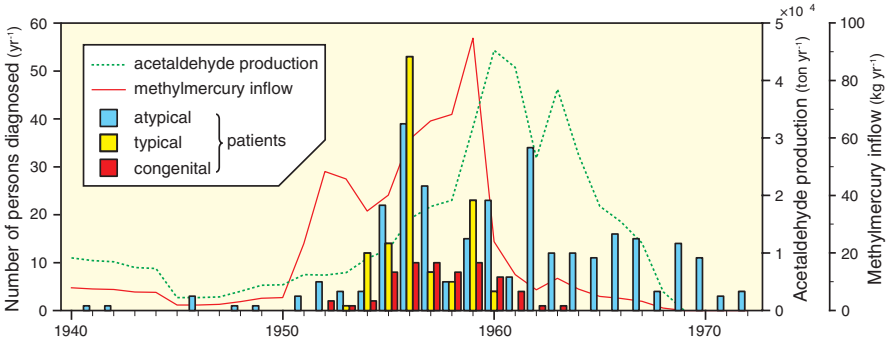

Fig. 2.7 Number of persons who were affected by typical, atypical, or congenital MPM in each year, with reference to annual changes of the acetaldehyde production and methylmercury inflow. See text for the three categories of the patients (Adapted from Nishimura and Okamoto 2001)

patients increased in the 1950s similarly to the typical type. However, even though the methylmercury emission decreased in the early 1960s, atypical MPM patients still appeared. Patients with congenital MPM were first found in 1952 and recognized every year through 1963. A large number of the congenital MPM patients (a total of 53 persons) were born in the late 1950s. Thus, the occurrence of the typical MPM and congenital MPM was roughly parallel to the trend of the methylmercury inflow rather than the trend of the acetaldehyde production.

2.11 Analysis of Umbilical Cords as an Indicator of Methylmercury Effects

Japanese people have a custom to preserve dried umbilical cords of newborns as a birth commemoration. Nishigaki and Harada (1975) and Harada et al. (1977, 1999) analyzed methylmercury concentrations in umbilical cords of babies who were born in the Minamata area (mainly Minamata City, Izumi City, and Tsunagi Town) during the period from 1935 to 1971 and found that (1) methylmercury concentrations in umbilical cords of babies born in the MPM-prone area were significantly higher than the value obtained from a reference cite (Tokyo, 0.11 ± 0.03 ppm); (2) methylmercury concentrations in umbilical cords of congenital MPM patients (1.6 ± 1.0 ppm) were significantly higher in comparison with those of acquired MPM patients (0.72 ± 0.65 ppm), mental retardation (0.74 ± 0.64 ppm), other diseases (0.22 ± 0.15 ppm), and no symptoms (0.28 ± 0.20 ppm); and (3) methylmercury concentrations attained the highest levels during the period from 1954 to 1964 when a large amount of acetaldehyde was produced. Akagi et al. (1998) estimated a daily mercury intake by mothers who gave birth to congenital MPM babies to be 225 μg which was 4–5 times higher than the current limit of mercury exposure.

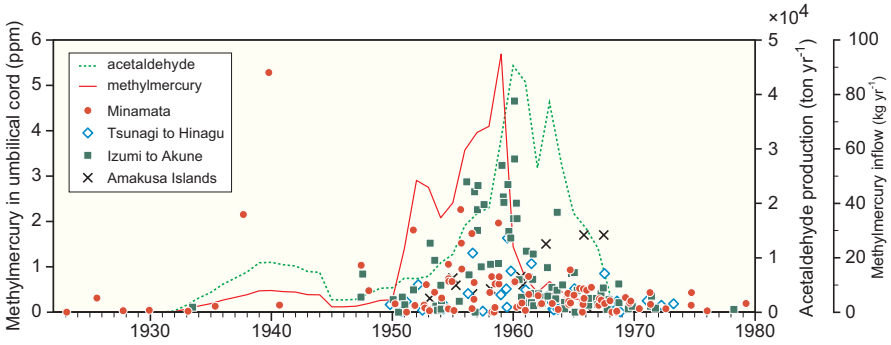

Fig. 2.8 Concentrations of methylmercury (ppm = μg g^{-1} dry wt) in umbilical cords of babies born in the MPM-prone areas (Minamata, Tsunagi to Hinagu, Izumi to Akune, and Amakusa Islands) during the period from 1923 to 1979, with showing annual changes of the acetaldehyde production and methylmercury inflow (Data source: Harada and Yorifuji 2009 and Nishimura and Okamoto 2001)

They also estimated methylmercury concentrations in cord blood and maternal hair of fully developed congenital or infantile MPM patients to be 20–699 μg L^{-1} (median, 216 μg L^{-1}) and 3.8–133 μg g^{-1} (median, 41 μg g^{-1}), respectively.

Subsequently, Yorifuji et al. (2009) added data obtained from residents living in the Minamata and Goshoura areas and pointed out that the temporal distribution corresponded to the acetaldehyde production. The raw data used in this study were published in Harada and Yorifuji (2009). Among them, I selected 232 measurements that contain information about newborns' dates of birth and birth places. The birthplace of the residents is categorized into four regions, i.e., Minamata, Izumi and Akune, Tsunagi to Hinagu, and Amakusa Islands (Nagashima and Goshoura-jima islands) (Fig. 2.1a). In 1937 and 1939, exceptionally high values, 2.15 and 5.28 ppm, were observed (Fig. 2.8). These values were obtained from two babies who were born in the same town located close to the Chisso Minamata factory. These babies have the same family name, suggesting that the two are sisters. Considering that such facts suggest that special circumstances, for example, the direct incorporation of mercury by a factory worker, I regarded these values as abnormal ones and excluded them further from the analysis. The results of the umbilical cord analysis are summarized as (1) four values of samples obtained before the start of the acetaldehyde production (0.10 ± 0.14 ppm) are regarded as a reference; (2) in 1947, values increased suddenly, showing a maximum of 1.03 ppm and a mean ± SD = 0.73 ± 0.36 ppm, suggesting the start of the noticeable consumption of methylmercury (Fig. 2.8); (3) the period from 1951 to 1967 when >1.0 ppm values were often found, the period from 1955 to 1963 when >2.0 ppm were found continuously (Fig. 2.8), and the period from 1955 to 1960 when >50% of samples attained >0.5 ppm of the methylmercury concentration (Fig. 2.9) are regarded as the most conspicuous period of the methylmercury contamination; and (4) high values of >1.0 ppm encountered in the area of Amakusa Island during the period from 1962

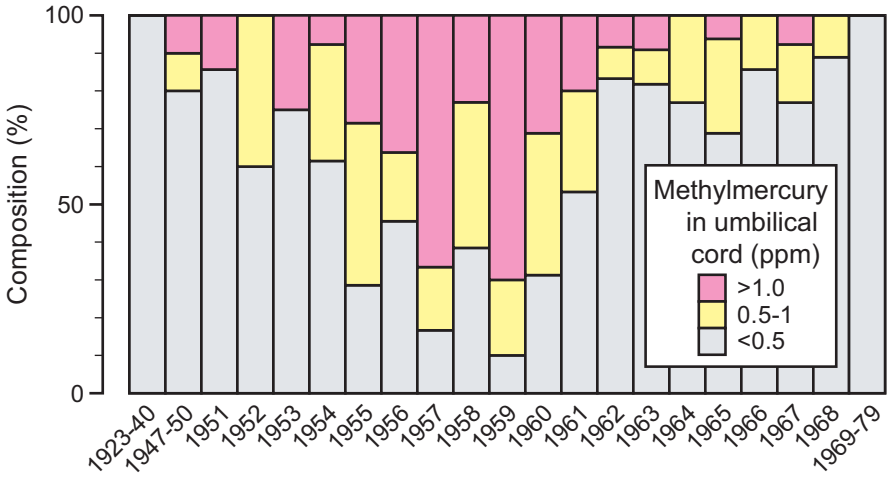

Fig. 2.9 Percent composition of three categories in the methylmercury concentration (< 0.5, 0.5–1, >1.0 ppm) in umbilical cords of babies born in the MPM-prone areas during the period from 1923 to 1979 (Data source: Harada and Yorifuji 2009)

to 1967 suggest that the influence of methylmercury contamination spread over to the opposite shore across the Shiranui Sea, although there were decreasing trends in the methylmercury inflow from the factory as well as in the methylmercury concentrations in umbilical cords of residents living in the Minamata area along the east coast of Kyushu (Fig. 2.8).

As the acetaldehyde production and methylmercury inflow into the sea increased, high levels of the methylmercury concentration in umbilical cords were frequently found. At the same time, low values were also observed, showing a large variation in methylmercury concentrations in umbilical cords, which are considered to have resulted from a large variation in the amount of seafood ingested among residents. Therefore, I considered that it is better to trace the maximum values rather than the mean values in each year for evaluating the influence of the acetaldehyde production and methylmercury inflow on the consumption of methylmercury by residents. There was a significant relationship between the acetaldehyde production rates and the maximum values of methylmercury ($r^2 = 0.343$, $n = 38$, $p < 0.001$) (Fig. 2.10a), while the methylmercury inflow rates showed a closer relationship with the umbilical cord values ($r^2 = 0.702$, $n = 38$, $p < 0.001$) (Fig. 2.10b). A significant positive relationship was also found between the methylmercury inflow rates and the number of congenital MPM patients ($r^2 = 0.364$, n = 12, $p < 0.05$) (Fig. 2.10c). These findings indicate that (1) methylmercury concentrations in umbilical cords can be a reliable indicator to monitor the methylmercury contamination in residents; (2) methylmercury which was generated from Chisso Minamata factory and flowed into the sea was consumed by the residents; (3) influences of methylmercury remained for several years after the decrease and stoppage of acetaldehyde production; and (4) the methylmercury inflow rate esti-

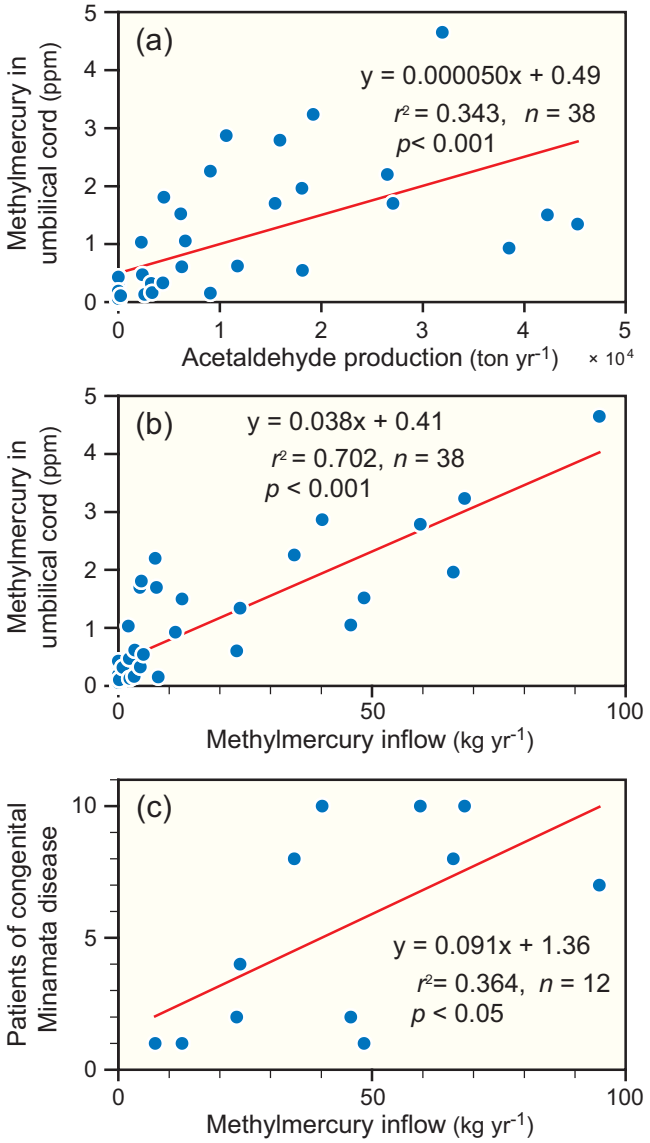

Fig. 2.10 Relationships between the acetaldehyde production by the Chisso Minamata factory and the maximum methylmercury concentration in umbilical cords of babies born in the MPM-prone area (**a**), between the methylmercury inflow rate from the Chisso Minamata factory to the coastal waters and the maximum methylmercury concentration in umbilical cords (**b**), and between the methylmercury inflow rate and the number of congenital MPM patients (**c**). Regarding the acetaldehyde production and methylmercury inflow rates (each, ton year^{-1} and kg year^{-1}, respectively), values obtained in the year preceding the birth were adopted. The number of congenital MPM patients is shown in Fig. 2.7 (Data source: Harada and Yorifuji 2009 and Nishimura and Okamoto 2001)

mated by Nishimura and Okamoto (2001) explains the consumption of methylmercury by residents and the outbreak of MPM in this area clearly.

2.12 Concentrations of Mercury in Aquatic Organisms

I estimated the relationship between the production and inflow of methylmercury and the outbreak of MPM in the Minamata area. These two components can be explained thoroughly by revealing the bioaccumulation of methylmercury in aquatic organisms.

Since 1958, intensive surveys had been carried out to determine mercury concentrations in marine organisms collected from Minamata Bay and the Shiranui Sea (Fishery Research Institute 1960, Kitamura et al. 1960b, Chisso Co. 1961, Kumamoto University 1961, Seikai Regional Fisheries Research Laboratory 1964, Irukayama et al. 1967b, 1972). When evaluating the effects of mercury on the environments, we should analyze methylmercury compounds as target toxic substances. In the 1950s and early 1960s, however, the method to analyze methylmercury had not been established yet. At the early stage of the investigation, the arc light emission line spectrum analysis was used for the detection of total mercury. In this method, concentrations were estimated by the strength of the emission line. Thereafter, the colorimetric method using dithizone was used for the quantification of organic and total mercury. Presently, gas chromatography (GC) with detection by electron capture detector (ECD) is the most widely used technique for the determination of organic mercury species.

Jernelöv and Lann (1973) showed approximate proportions of methylmercury to total mercury of components of freshwater and estuarine ecosystems as <1% for water, 1–10% for sediments, and 90–99% for biota. Kannan et al. (1998) found <0.003–52% for water, 0.77% for sediments, and 83% for fish muscle in estuarine waters in the Florida peninsula. It has been also reported that methylmercury accounts for the majority of total mercury in fish, regardless of the level of contamination found within the environment (Silver et al. 1994, Mason et al. 2000, Bowles et al. 2001, Ikingura and Akagi 2003, Maršálek et al. 2006, Amlund et al. 2007, Magalhães et al. 2007), implying that we can evaluate the toxicity of marine animals using values of total mercury. Inorganic divalent mercury and organic mercury compounds are absorbed through gills, intestine, or skin, distributed through bloodstreams and accumulated in the liver; thereafter, the former is excreted through the kidney, and organs like muscles and brain are only affected to a small extent, whereas the latter is not rapidly excreted and subsequently it accumulates in muscle and brain (Jernelöv and Lann 1971). The lipophilic nature, affinity for the sulfhydryl groups of certain proteins, and long biological half-life (e.g., 2 years in fish) of methylmercury lead to a rapid accumulation in organisms (Jernelöv and Lann 1971, Magalhães et al. 2007).

Concentrations of total mercury in coastal animals in Minamata Bay and the Shiranui Sea had been analyzed frequently since 1958 by several organizations

including KU and the Chisso Minamata factory. The mercury concentrations at reference sites to the Minamata area were approximately <1.0 ppm (all values are shown on the basis of dry wt; 2.5 (fish) or 5.0 (invertebrates) was used for the conversion) (Kitamura et al. 1960b). Regarding coastal animals collected from Minamata Bay and the Shiranui Sea during the period from 1958 to 1966, 62 species/species groups showed ≥1.0 ppm of the mercury concentration, and 33 species/species groups showed ≥10.0 ppm (Fig. 2.11), indicating that a variety of phyla and species and both pelagic and benthic/sedentary species were contaminated by mercury.

Regarding benthic/sedentary species that live in/on seabed or in bottom layers, extremely high levels of mercury were found in benthic/sedentary three species, *Acanthopagrus schlegelii* (Japanese name, Kurodai; maximum value, 117.5 ppm; sampling site, off Hachiman, data source, Irukayama et al. 1972), *Hormomya mutabilis* (Hibarigaimodoki, 111 ppm, unpublished data of Chisso Co., after Nishimura and Okamoto 2001), and *Ruditapes philippinarum* (Asari, 100 ppm, the mouth of Minamata River, Kitamura et al. 1960b). The former species, the black seabream, is a sedentary carnivorous fish. Relatively high levels of mercury were found also in other sedentary carnivorous fish, *Terapon jarbua* (Kotohiki, 64.3 ppm, Minamata Bay; Chisso Co. 1961), *Pennahia argentata* (Shiroguchi, 59.2 ppm, the Shiranui Sea, Kitamura et al. 1960b), *Apogon* sp. (Tenjikudai, 47.5 ppm, mouth of Minamata River, Kitamura et al. 1960b), and *Lateolabrax japonicus* (Suzuki, 41.5 ppm, mouth of Minamata River, Kitamura et al. 1960b). Such high levels of mercury are estimated to have resulted from the bioaccumulation through food chains.

Among the three species showing extremely high concentrations of mercury, *H. mutabilis* and *R. philippinarum* are suspension feeding bivalves, which consume phytoplankton, indicating intense bioaccumulation occurred even in animals belonging to the trophic level 2 (primary consumers, see Fig. 2.11). These findings mean that intense bioaccumulation occurred between water and phytoplankton or that mercury was directly incorporated into bivalve tissues. The mercury concentration in plankton at that time is unclear, excepting for two case studies. Kitamura et al. (1960b) noted 5–6 ppm (wet weight basis) in the inner part of Minamata Bay. The other case was conducted by Fisheries Research Institute (1960), indicating that 289 ppm of mercury was accumulated in the green alga *Dunaliella* sp. during 12 days of culture in water containing 0.1 ppm mercury. These results suggest that phytoplankton has a large ability to accumulate mercury into cells or to adsorb mercury onto the surface of cells even if mercury concentrations are extremely low.

Regarding the mercury concentrations of pelagic animals that live in the middle and/or surface layers, piscivorous fish, *Sphyraena* sp. (Kamasu), showed a high value, 58.3 ppm (Kumamoto University 1961: Fig. 2.11). Such piscivorous fish, which belong to the trophic level 4 (tertiary consumers), feed on other fish belonging to the trophic level 2 or 3, probably resulting in high levels of the mercury concentration through the food chain. Planktivorous suspension feeder, *Engraulis japonicus* (Katakuchi-iwashi), which constitutes one of key fish species in the food web in Japanese coastal waters, is also distributed densely in the Minamata area. Most cats living in fishing villages along the coasts of Shiranui Sea

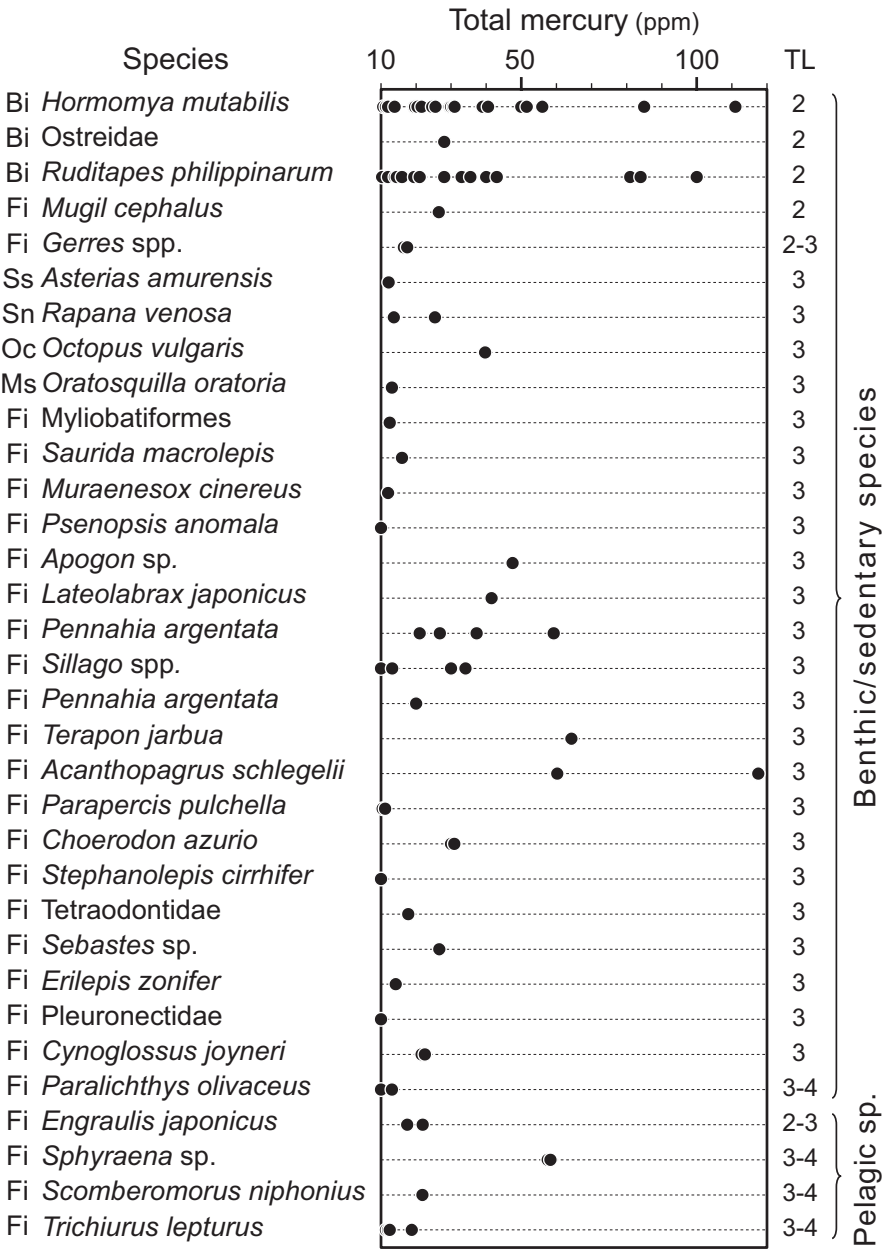

Fig. 2.11 Aquatic organisms showing high concentrations of total mercury (>10 ppm = μg g^{-1} dry wt) collected from Minamata Bay and the Shiranui Sea during the period from 1958 to 1966. Values which were shown in terms of wet weight in original papers were converted by multiplying 2.5 for fish or 5.0 for other animals. Abbreviations of animal groups are Sn = snail, Bi = bivalve, Oc = octopus, Ms = mantis shrimp, Ss = sea star, and Fi = fish. TL means the trophic level (suspension feeders and herbivores belong to TL 2, omnivores belong to TL 2–3, carnivores digesting invertebrates and small-sized fish belong to TL 3, and piscivores belong to TL 4) (Data source: Fishery Research Institute 1960; Kitamura et al. 1960b; Chisso Co. 1961; Kumamoto University 1961; Seikai Regional Fisheries Research Laboratory 1964; Irukayama et al. 1967b, 1972; and unpublished data of Chisso Co. after Nishimura and Okamoto 2001)

became MPM probably due to eating this species extensively. A maximum concentration of mercury for this species was 21.9 ppm (Chisso Co. 1961), which was similar to the values obtained for *Scomberomorus niphonius* (Sawara, 21.8 ppm, the mouth of the Minamata River, Kitamura et al. 1960b) and *Trichiurus lepturus* (Tachiuwo, 18.8 ppm, Tsunagi, Kitamura et al. 1960b). Considering that these species have a pelagic life and large moving ability, these fish contaminated by mercury potentially played a large role in the dispersal of the mercury pollution.

2.13 Bioindicators of Mercury Pollution

Mussels usually attach to hard substrata using byssus threads and feed on suspended particles mainly composed of phytoplankton (Bayne 1976). *H. mutabilis* was used for evaluating the second step of the bioaccumulation of methylmercury. Nishimura and Okamoto (2001) summarized the literature values for total mercury in *H. mutabilis* collected from Minamata Bay (Kitamura et al. 1960b, Kojima 1960, Kumamoto University 1961, Chisso Co. 1961, Irukayama et al. 1972, Chisso Co. unpublished data) (Fig. 2.12). In 1958, the highest value of 111 ppm was measured (Chisso Co., unpublished data, after Nishimura and Okamoto 2001). As time went on, the mercury concentration decreased to ~10 ppm in 1962 and succeeding years, accompanied by a variation (the light blue zone in Fig. 2.12). In 1959, however, the value decreased abruptly from 80–100 ppm to an average value of 30 ppm during the period of May to July, accompanied by the change of the wastewater outlet from Hyakken Port in Minamata Bay to the mouth of the Minamata River in September 1958. Wastewater flowed again into Minamata Bay in November 1959; then the level of mercury increased again in January 1960 showing 40–80 ppm. These results suggest that the mercury concentration changed corresponding to the levels in water and phytoplankton within a few months.

In the MPM-prone area, residents ate a certain amount of seafood including fish, shrimp, octopus, and sea cucumber which inhabited mainly the bottom layer in coastal waters. Therefore, it is important to examine the mechanism how methylmercury reached to and contaminated sedentary fish. Nishimura and Okamoto (2001) summarized the literature values of total mercury in the sand borer/whiting (*Sillago* spp., Kisu), yellow-barred red rockfish (*Sebastiscus albofasciatus*, Ayamekasago), and skilfish (*Erilepis zonifer*, Aburabouzu) which feed mainly on benthic animals (Chisso Co. 1961, Kumamoto University 1961, Seikai Regional Fisheries Research Laboratory 1964, Irukayama et al. 1972) (Fig. 2.13). In 1960 and 1961, there was a large variability in the mercury concentration of up to ~100-fold difference between the minimum and maximum values, whereas after 1968 when the acetaldehyde production by the factory was finished, the variability was relatively small showing only ~5-fold difference. The mercury concentrations shown in Fig. 2.13, therefore, could be classified into two zones, zone I (<1.5 ppm) and zone II (>1.5 ppm). The concentrations belonging to zone I can be explained by the contamination by methylmercury which was transformed from inorganic mercury in

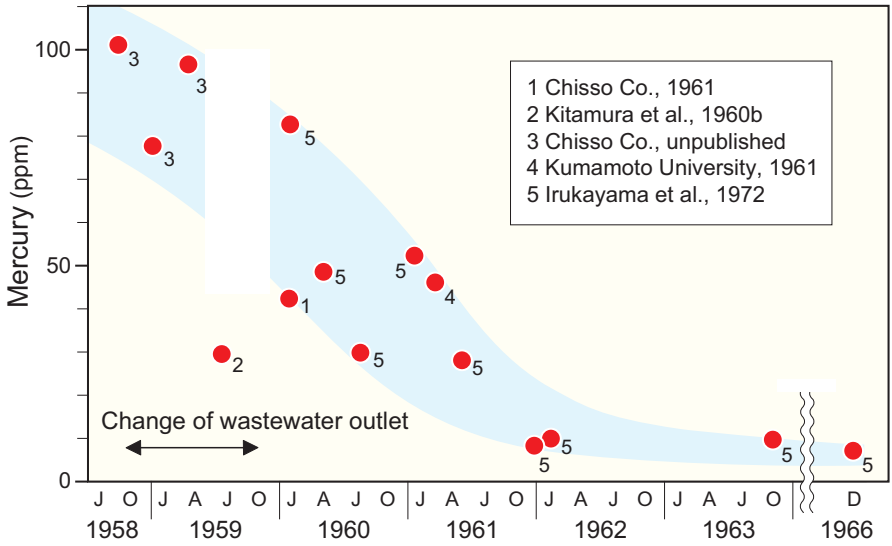

Fig. 2.12 Concentrations of total mercury (ppm = μg g^{-1} dry wt) in soft tissues of the mussel, *Hormomya mutabilis*, collected from Minamata Bay during the period from 1958 to 1966. The values were cited from five sources (1–5) (Adapted from Nishimura and Okamoto 2001)

the sediment, while the concentrations belonging to zone II should be considered to have resulted from consumption of methylmercury discharged into seawater.

To confirm this hypothesis, Nishimura and Okamoto (2001) examined the relationship between the mercury concentrations in sediments and in the sedentary fish *Pennahia argentata* (croaker, Shiroguchi). The fish were collected from both sides of the Shiranui Sea (mainland side and Amakusa islands side) as well as from Tokuyama Bay, Yamaguchi Prefecture (Fig. 2.1), where inorganic but not organic mercury flowed into the sea from a caustic soda factory. Values obtained from stations close to the mainland in the Minamata area and from Tokuyama Bay showed similar levels in the relationship between the two components (shadowed area, Fig. 2.14), indicating that as the mercury concentration in the sediment increased, levels of mercury contamination in the fish increased. These findings suggest that part of inorganic mercury transformed to methylmercury in the sediment by bacteria, methylmercury moved to interstitial and bottom water, and then methylmercury was incorporated into sedentary fish. Fujiki and Tajima (1974) confirmed that inorganic mercury in the sediment in Minamata Bay can be transformed to methylmercury under the aerobic conditions in the laboratory. On the other hand, it has been widely known that methylation of mercury occurs in aquatic environments. Sulfate-reducing bacteria are primary methylators (Compeau and Bartha 1985, Gilmour and Henry 1991, Choi and Bartha 1993, King et al. 2000, Jeremiason et al. 2006). Mason (2012) showed Fe reducers in the genus *Geobacter* also have the function of methylation. Considering that the growth rate of sulfate-reducing bacteria is high in reduced conditions, organically enriched sediments of Minamata Bay are consid-

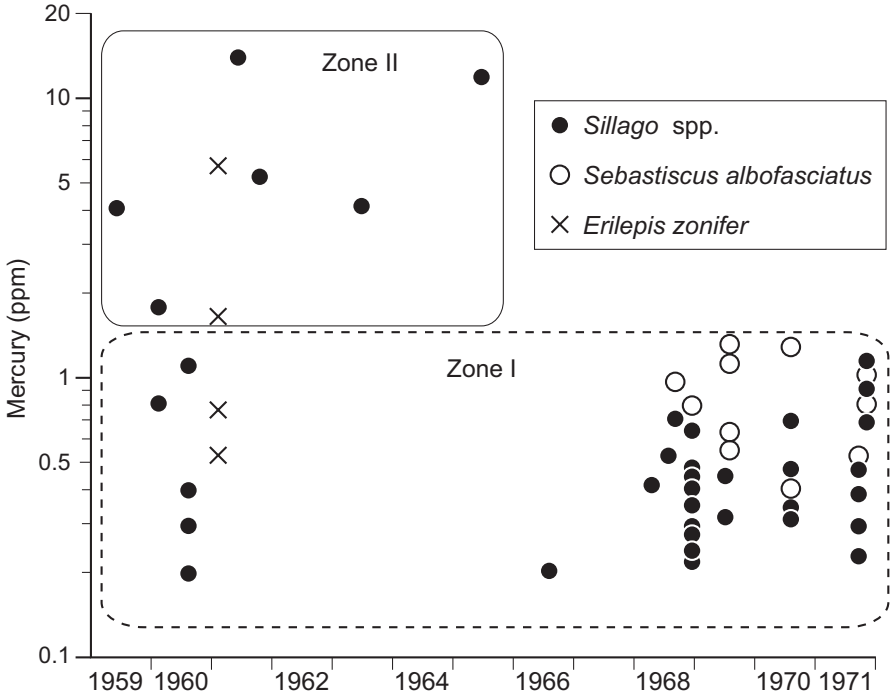

Fig. 2.13 Concentrations of total mercury (ppm = μg g^{-1} wet wt) in sedentary fish collected from Minamata Bay during the period from 1959 to 1971. See text for zones I and II (Adapted from Nishimura and Okamoto 2001)

ered to promote transformation to methylmercury. Based on the stable mercury isotope data, Balogh et al. (2015) suggested that methylmercury was produced in bottom sediments of Minamata Bay and entered the food web, possibly from sediment porewaters or near the sediment-water interface.

Irukayama et al. (1964b) surveyed the horizontal and vertical distributions of total mercury in the sediment in Minamata Bay in October 1963 and compared the results obtained by Kitamura et al. (1960b) in 1959 (Fig. 2.15). They described that (1) we could not find an extremely high value such as 2010 ppm which was found in 1959 (see Fig. 2.15a); (2) the mercury concentration in the surface sediments in Hyakken Port still remained high, showing values of >100 ppm at stations 4 and 9 (Fig. 2.15b); (3) in Hyakken port, a large amount of mercury was found to a depth of 4 m from the sediment surface, and peak concentrations were often found below the surface (stations 4–7, 10, Fig. 2.15c); and (4) in the southern part of Minamata Bay (stations 12–16), mercury was found to be confined to the surface layer (0–10 cm), and the concentration was below 20 ppm. Although Irukayama et al. (1964b) did not detect organic mercury in the sediment, it can be estimated that such a large amount of inorganic mercury and enriched sediments enabled the transformation to organic mercury. However, considering the confined distribution of the

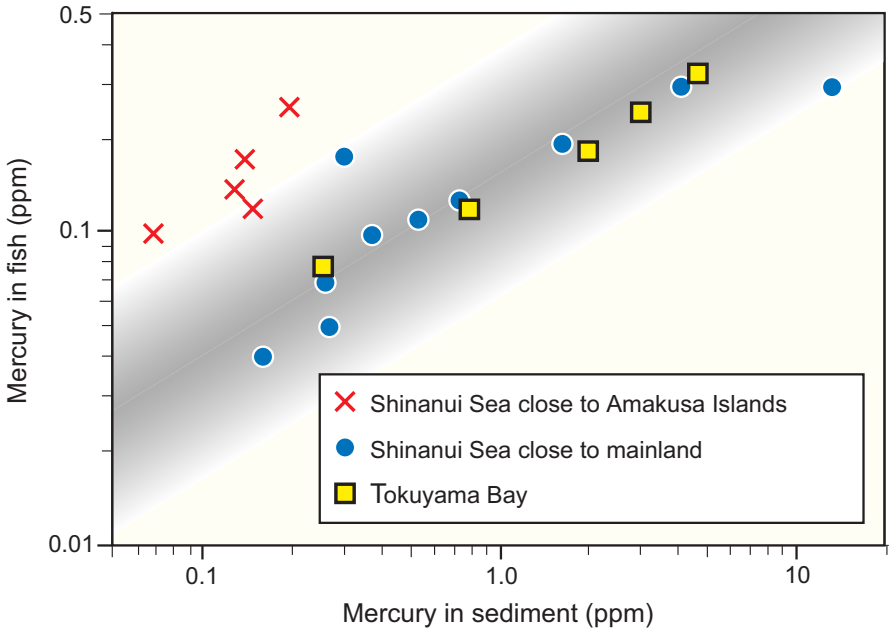

Fig. 2.14 Relationship between the concentration of total mercury in bottom sediments and the concentration of total mercury in the white croaker *Pennahia argentata* on both sides of the Shiranui Sea and in Tokuyama Bay (Data source: mercury survey conducted by Environment Agency, Japan, in 1973; adapted from Nishimura and Okamoto 2001)

high concentrations of mercury to the northern area in Minamata Bay (Fig. 2.15a, b), the degree and extent of organic mercury transformed from inorganic mercury were considered not to be as much as methylmercury generated from the acetaldehyde plant of Chisso.

On the other hand, *P. argentata* collected from the area close to Amakusa Islands (Fig. 2.1) accumulated higher concentrations of mercury (Fig. 2.14) irrespective of the low levels of mercury in the sediment and of being distant from the pollution source, that is, Chisso Minamata factory, suggesting that the fish incorporated methylmercury from seawater directly or from food items, i.e., plankton that had accumulated and/or adsorbed methylmercury from seawater (Nishimura and Okamoto 2001).

2.14 Accumulation Pathways of Methylmercury in Aquatic Organisms

There are arguments about the pathways by which methylmercury is accumulated in aquatic organisms, that is, whether the animals incorporate methylmercury directly from water through the gills or from components of the food chain. Higher

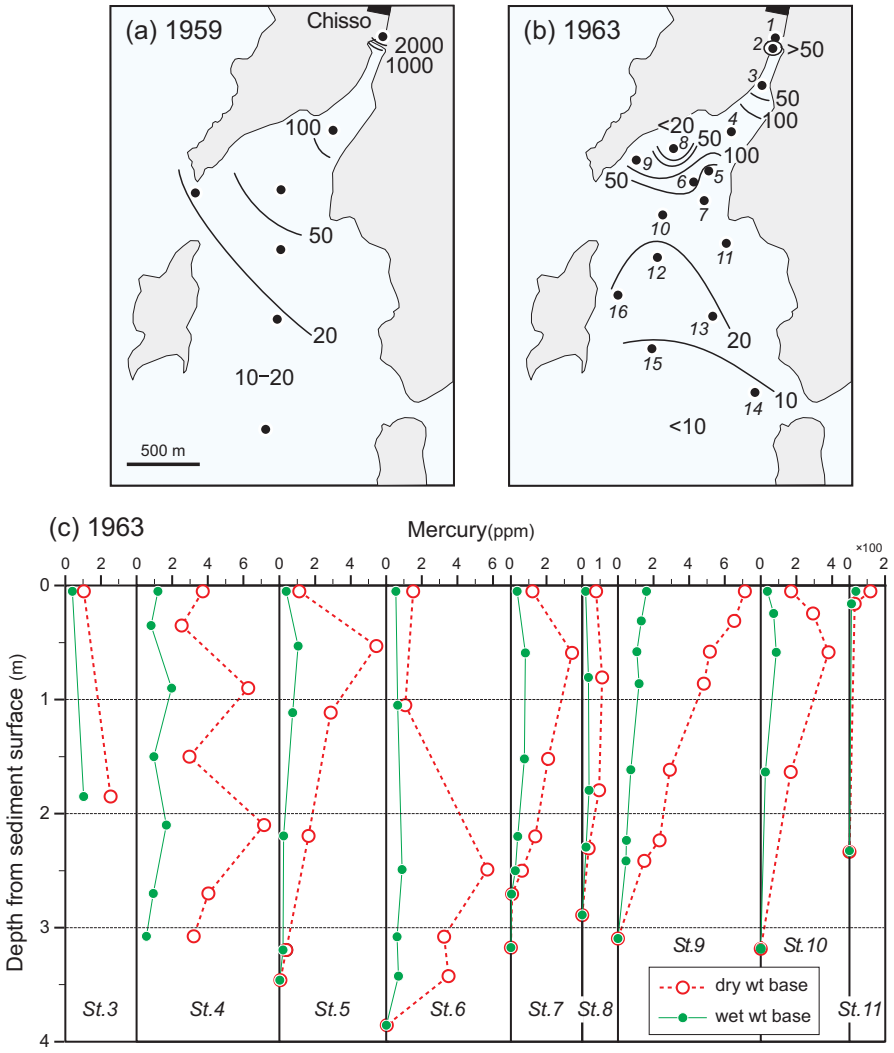

Fig. 2.15 Concentrations of total mercury in sediments. Horizontal distributions of mercury in the surface sediments in 1959 (**a**) after Kitamura et al. (1960b) and in 1963 (**b**) after Irukayama et al. (1964b) and vertical distributions (**c**) after Irukayama et al. (1964b). Roman numerals in the upper figures: mercury concentrations (ppm) in terms of wet sediment. Numerals in italics in the upper right figure: station numbers

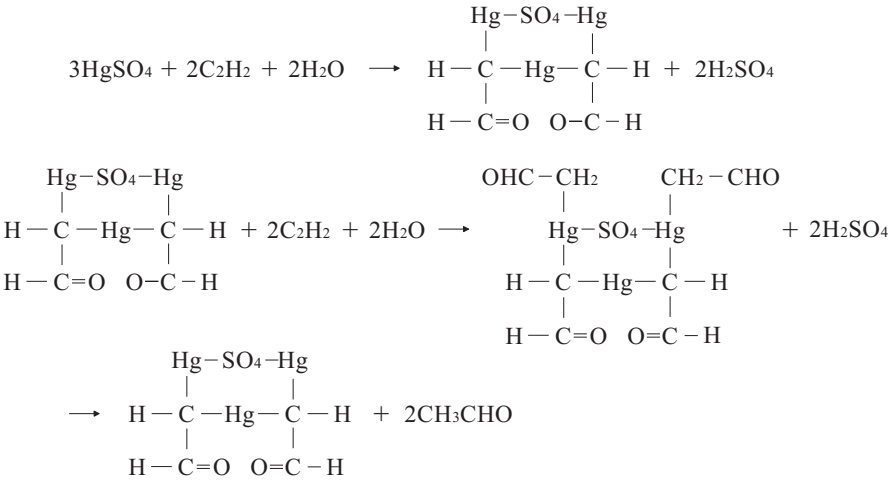

Fig. 2.16 Empirical chemical formulae in the acetaldehyde production shown by Vogt and Nieuwland (1921). Vogt and Nieuwland (1921) indicated that the catalytic mercury compounds being organic were readily hydrolyzed, resulting in the production of acetaldehyde

concentrations of mercury with increasing trophic level have often been found, suggesting that the bioaccumulation of methylmercury occurs through food chains (Mason et al. 2000, Bowles et al. 2001, Ikingura and Akagi 2003, Magalhães et al. 2007). Several dietary exposure studies also have shown that fish readily accumulate methylmercury, mainly in the muscle (Amlund et al. 2007). Hall et al. (1997) indicated that the freshwater fish (*Phoxinus neogaeus*) concentrated methylmercury mainly through the diet, while water contributed, at most, 15% of the mercury to fish at natural levels of methylmercury. Lawson and Mason (1998) confirmed the transfer of methylmercury from seawater to an experimental food chain which constituted of phytoplankton (*Thalassiosira weissflogii*), copepod (*Eurytemora affinis*), and sheepshead minnow (*Cyprinodon variegatus*). They also showed that a benthic amphipod *Hyalella azteca* was able to incorporate methylmercury from decayed phytoplankton. Bowles et al. (2001) showed that the greatest bioaccumulation of methylmercury occurred between seston (plankton) and the water column (bioaccumulation = $10^{5.36}$) in a tropical lake; then methylmercury was biomagnified through a plankton-based food chain comprising of four trophic levels (phytoplankton, zooplankton, planktivore, piscivore). Bioenergetic models for methylmercury accumulation in walleye and yellow perch also suggested that food is the overwhelming (99%) uptake pathway at a water methylmercury concentration of 0.05 μg m^{-3}; however, as the water methylmercury concentration increased to 0.3 μg m^{-3}, the food pathway decreased to 90% (Harris and Snodgrass 1993). Wang and Wong (2003) showed that 56–95% of methylmercury in ingested prey was retained in a marine predatory fish 1 day after digesting. These studies indicated that methylmercury is assimilated and retained by fish from dietary sources.

On the other hand, there are several studies which suggested the importance of direct uptake from water through the gills. Jernelöv and Lann (1971) suggested that for bottom-feeding freshwater fish, >75% of methylmercury, and even in predatory fish (pike), 60% of methylmercury was taken up directly through the gills. Rodgers and Beamish (1981) found that the methylmercury uptake rate of rainbow trout was positively correlated with both oxygen consumption and methylmercury concentration and that the percent utilization of methylmercury from water was ~8%, assuming an oxygen percent utilization of 33%. A similar value (10%) was found also by Phillips and Buhler (1978). At the same time, they showed 68% of methylmercury ingested was assimilated by rainbow trout as well, suggesting that food and water both are important pathways of methylmercury accumulation.

Laboratory rearing experiments of Japanese littleneck, *Ruditapes philippinarum*, showed that the clams accumulated organic mercury from water containing alkyl mercury (0.2–0.3 ppm) into their bodies (40–129 ppm dry wt basis) during 4–14 days (Irukayama et al. 1962b), suggesting that the clams incorporated organic mercury directly from water. Chloride ions may enhance uptake of methylmercury from water by forming membrane permeable methylmercury complexes (Boudou et al. 1983).

Nishimura and Okamoto (2001) suggested that Japanese anchovy (Katakuchi-iwashi) is able to uptake methylmercury directly from water through its gills, rather than through feeding on plankton. In this case, the biological concentration ratio after 1 month of exposure to contaminated seawater (~9.1 ppm of methylmercury in fish muscle vs. 10 ng of methylmercury in seawater) is close to a million times, if the following equation can be adopted:

Uptake rate of methylmercury by fish = 1260 mg O_2 kg^{-1} h^{-1} × (10 ng L^{-1}/10 mg L^{-1}), where 1260 mg O_2 kg^{-1} h^{-1} is the oxygen uptake rate by fish, 10 ng L^{-1} is the concentration of methylmercury in seawater, and 10 mg L^{-1} is the concentration of oxygen in seawater.

Values obtained from stations close to Amakusa Islands in the Shiranui Sea showed relatively high mercury concentrations, suggesting the expansion of methylmercury over a large area. It is considered that methylmercury was incorporated into anchovy, which were preyed on by carnivorous fish through the predator-prey relationship, and then methylmercury settled onto the seabed after the death of fish. Considering the results in the previous studies and the temporal and spatial pattern of the methylmercury concentrations in fish found in the MPM-prone area, direct uptake by fish in this area was possible. There are no practical observations which show the direct incorporation of methylmercury from water by Japanese anchovies under the condition of the methylmercury uptake rate that is the same as or similar to the oxygen uptake rate. Due to the lack of evidence, the hypothesis of the direct methylmercury incorporation presented by Nishimura and Okamoto (2001) has

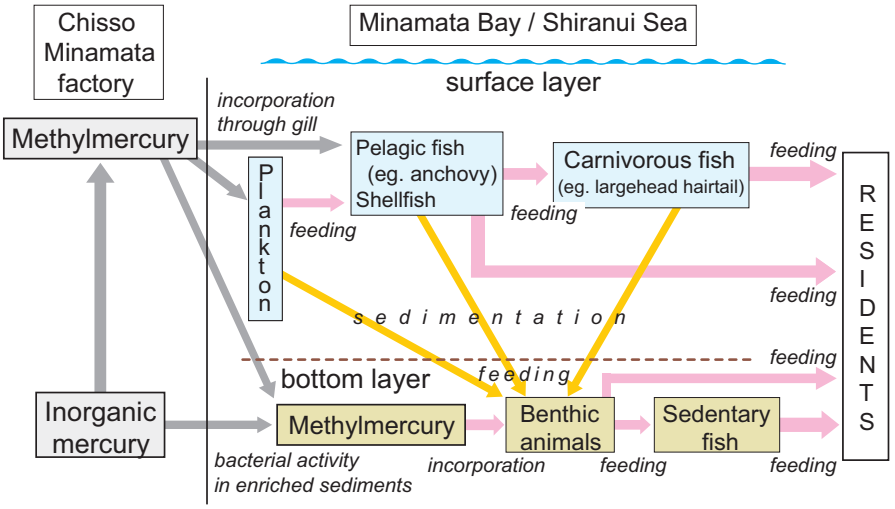

Fig. 2.17 Schematic drawing of the estimated flow of methylmercury from the Chisso Minamata factory, through Minamata Bay and the Shiranui Sea, and finally to residents mainly based on Nishimura and Okamoto (2001)

been criticized severely by a few researchers (Suzuki 2007; Miyazawa 2010). Further studies should be conducted to prove this hypothesis.

I summarize the flow of mercury from the Chisso Minamata factory to the coastal waters and then finally to residents mainly based on findings obtained so far (Fig. 2.17). Methylmercury compounds produced as by-products in the acetaldehyde production plant were discharged into coastal waters. Part of methylmercury might be incorporated into pelagic fish through the gills. Such fish were fed on by carnivorous fish. Part of methylmercury was incorporated into phytoplankton and might have been bioaccumulated through food chains. After the death of plankton and aquatic organisms, they settled onto the bottom, and then they were incorporated into benthic animals. Part of methylmercury might have been deposited directly to the seabed. Inorganic mercury flowing into coastal areas was accumulated in sediments and was transformed to methylmercury due to bacterial activities, a process which might be accelerated under organic pollution. Methylmercury was incorporated into benthic animals and then moved to demersal fish. By eating these polluted fishery products, people became MPM.

2.15 Disapproval of Chisso's Counterclaims

As described earlier, Chisso had repeated claims that they were not responsible based on three viewpoints.

First, against the Chisso's counterclaim, that is, why did a significant number of MPM patients first occur in 1954, there are reasons to disapprove these as below:

1. Chisso changed the promoter from manganese dioxide to iron sulfate and nitric acid in 1951. As a result, the production of methylmercury had increased rapidly.
2. Chisso added seawater to industrial water since 1955, resulting in high concentrations of chloride ions in the reaction vessel, which promoted evaporation and accumulation of methylmercury in a drain of the rectifying column.
3. Chisso used pyrite cinders as an alternative to iron sulfate to reduce costs since 1951, which disturbed the continuous running of the system, resulting in the discharge of a large amount of mother liquor, which contained methylmercury.
4. Chisso discharged a large amount of effluents into the sea.
5. MPM first occurred in 1941.

Second, the Chisso's counterclaim, why is Chisso Minamata factory the only one which caused methylmercury poisoning, is disapproved by the following reasons:

1. Showa Denko also caused methylmercury poisoning in Niigata Prefecture.
2. Methylmercury poisoning occurred in other localities in the world (e.g., China in the 1970s, the Amazon basin in the 1990s, Ontario in Canada, Mindanao in the Philippines).
3. Industrial water in Chisso Minamata factory included a lot of chloride ions due to poor management of wastewater.

Finally, the Chisso's counterclaim, we have used inorganic mercury, but not poisonous organic mercury, is disapproved by the following reasons:

1. It was widely known that methylmercury was generated in acetaldehyde production plants using acetylene and inorganic mercury as the material and catalyst, respectively. According to Iriguchi (2012, 2014) and Ishihara (2014), the generation of organic mercury in this process had been suggested by Hofmann and Sand (1900), Nieuwland and Maguire (1906), Whitmore (1921), and Vogt and Nieuwland (1921) repeatedly. For example, Vogt and Nieuwland (1921) showed chemical formulae in the acetaldehyde production which had been employed commercially (Fig. 2.16). Nishimura and Okamoto (2001) pointed out that these formulae contained wrong intermediates; however, it is notable that Vogt and Nieuwland (1921) had suggested the generation of methylmercury before the start of acetaldehyde production in Minamata. The abstracts of Nieuwland and Maguire (1906) and Vogt and Nieuwland (1921) were introduced in the journals *Tokyo Kagaku Kaishi* (later, *Nippon Kagaku Kaishi*) in 1906 and *The Journal of the Society of Chemical Industry, Japan*, in 1922, respectively, in Japanese. Ochi and Onozawa (1920) also reported the same chemical reaction in 1920. A chemical company in Germany, Wacker Chemie/Consortium, started the production of acetaldehyde using acetylene as raw material and mercury as a catalyst in 1916 for the first time in the world. Within the same year, workers who came into contact with the sludge discharged from the plant developed central nervous system disorders. According to the suggestion of Professor Heinrich Zangger of the University of Zürich, the factory disposed the sludge and wastewater under-

ground avoiding underground aquifers, thereby limiting exposures to mercury and development of nervous system disorders. Later, Zangger (1930) concluded that this disorder was caused by organic mercury poisoning in a result of reference to Edwards (1865, 1866), Hepp (1887), Hofmann and Sand (1900), Nieuwland and Maguire (1906), and Whitmore (1921) (after Iriguchi, 2014). In addition to this, by 1932 when Chisso started to produce acetaldehyde, it was in the public domain that methylmercury was able to cause the serious poisoning to the central nervous system of human beings as shown by the accident which occurred in 1865 at Saint Bartholomew's Hospital. This information had been introduced to Japan through a paper written by Hepp (1887) and the journal *Chemical News* at least by 1927.

2. It had been proved that methylmercury could be generated from inorganic mercury in natural environments.
3. Chisso obtained the information that methylmercury had been detected from a drain in the plant in 1961.

2.16 Government's Consensus Opinion

While effective measures by the national and local governments were not taken, methylmercury spread to another locality. On May 31, 1965, Niigata University reported to the Niigata Prefectural Public Health Department that "There have been sporadic cases of mercury poisoning from an unknown source in the lower Agano river." In June 1967, patients in Niigata Prefecture sued Showa Denko as the pollution source of Niigata MPM and sought a compensation claim in the Niigata District Court.

On September 26, 1968, the MHW and the Science and Technology Agency announced the consensus opinion of the government that "Minamata disease" in Kumamoto Prefecture was caused by a methylmercury compound generated by the acetaldehyde and acetic acid manufacturing facilities at the Chisso Minamata factory (Ministry of the Environment, Japan 2013). Niigata methylmercury poisoning was recognized at the same time. Twelve years had passed since the official acknowledgment in 1956. How should we interpret these environmental perturbations?

2.17 Victims

The number of the patients who had been recognized officially before January 1970 was 121, among which 98 patients comprised of adults and children who had eaten fish and shellfish polluted by methylmercury, while 23 were congenital MPM patients (Harada 1972). However, these patients were included in the typical type of MPM, and this was only the tip of the iceberg in the total number of MPM patients.

The exact total number of the dead caused by methylmercury poisoning is not clear. On August 29, 1956, Dr. Hosokawa of Chisso Hospital reported to the Ministry of Health and Welfare that 11 persons had died among 30 patients within a month

(Harada 1972). It was also reported that this disease caused death of 17 of 54 patients during the period of the initial stage of the outbreak (December 1953 to December 1956) (Minamata City 2007). These results indicate that the mortality rate was high, attaining ~30%. Harada and Tajiri (2009) reported that 17 of 188 newborns in the disease-prone area in Minamata City during the period from 1955 to 1958 were diagnosed as having congenital MPM.

The number of certified patients recognized by the "Law Concerning Compensation and Prevention of Pollution-Related Health Damage" by January/February 2016 was 3017 including 1787 in Kumamoto Prefecture, 493 in Kagoshima Prefecture, and 704 in Niigata Prefecture (Takamine 2016). Figure 2.1 shows residential areas of the certified patients, extending over a 60 km-long and 25 km-wide area surrounding Shiranui Sea in Kumamoto and Kagoshima Prefectures and over a 50 km-long area along the Agano River in Niigata Prefecture. Among the certified patients, ~70 persons were born having congenital MPM (Harada and Yorifuji 2009) in Kumamoto and Kagoshima prefectures. In Niigata Prefecture, only one person was born as having congenital methylmercury poisoning. At that time, most of pregnant women aborted, or birth control was recommended by the local government to women of childbearing age who lived in the polluted area and who had hair mercury concentrations of 50 ppm or higher.

In the 1950s, fisheries were one of the major industries in coastal areas around the Shiranui Bay. However, due to the outbreak of MPM, fishermen had been compelled to stop fisheries. The Fishermen's Cooperative in Minamata City (FCM) placed self-imposed restrictions on harvests in Minamata Bay since August 1957. In July 1959, the Minamata City Fresh Seafood Retailers Union determined not to buy any fish and shellfish captured from the coastal area around Minamata.

It was recognized that the outbreak of MPM drew to a close after 1960 owing to FCM's self-imposed restrictions on fishing and to the construction of a sedimentary pool and effluent-treatment device. In April 1962, FCM lifted the voluntary restrictions on fishing partially, and in May 1964, FCM completely abolished all restrictions. In May 1973, however, they enforced restrictions again according to the announcement by KU, "The fish and shellfish of Minamata Bay and surrounding areas are still unsafe." The FCM did not carry out harvesting operations in the bay from 1975 to 1992.

2.18 Compensation and Environmental Restructure

The damage caused by methylmercury discharged from the responsible companies includes (i) health damage to individual persons, (ii) environmental pollution including the toxification of fish/shellfish, and (iii) psychological distress in the local community due to discrimination of the victims and conflicts among local residents (Ministry of the Environment, Japan 2013).

In the late 1950s, residents who suffered from methylmercury poisoning established the mutual aid society of patients (MAS), and then MAS started to negotiate for compensation with Chisso. In April 1969, MAS split into two groups, those who would lodge the pledge and request mediation by the government in settling the

matter (the mediation faction) and those who would negotiate directly with Chisso but later took their claims to court (later referred to as the litigation faction).

Based on the newly established law, the "Law Concerning Special Measures for the Relief of Pollution-Related Health Damage," the certification system started in December 1969. In this system, applicants who wanted to be certified as a methylmercury poisoning patient were subject to medical examination by the prefecture, followed by medical review by the certification council; then the prefectural governor determined whether or not a person suffers from methylmercury poisoning. Among the applicants, however, only a limited number of persons have been certified. Persons who were not certified as methylmercury poisoning patients or belonged to the litigation faction sued responsible companies and national and local governments successively mainly between the late 1960s and the 1990s. These suits had been reported widely by the mass media, making it a subject of social concern. The national government decided to settle the problems politically in 1995, and 11,152 persons accepted compensation, while in 2009 the "Act on Special Measures Concerning Relief for Victims of Minamata disease and Solution to the Problem of Minamata disease" was enacted; then based on this law, 32,244 persons accepted compensation. It is said that more than 100,000 people, approximately half of the population in the Minamata area, had health issues due to methylmercury discharged from Chisso; however, these persons have not been granted compensation yet.

In 1959, fishermen in Minamata City and in the coastal area of the Shiranui Sea who had not been able to continue fisheries demanded to Chisso for (i) compensation to the fishing industry, (ii) complete removal of sedimentary sludge, and (iii) installation of an effluent-processing device. After the first and second fishermen's disputes (large-scale demonstrations associated with violence), fishermen won the compensation from Chisso. Chisso also paid compensation money to the fishermen's cooperative association, because the fishermen were compelled to stop fisheries by 1997.

Even though the discharge of the methylmercury compound was stopped in May 1968 by the Chisso Minamata factory and in May 1965 for the Kanose factory of Showa Denko, it was necessary to remove the polluted sediments close to the discharge point. From 1977 to 1990, Kumamoto prefectural government (KP) reclaimed 58 ha of the inner part of Minamata Bay where the seabed was heavily contaminated by mercury using sediments (1.5×10^6 m^3) dredged from the outside of this area (151 ha) where the mercury concentrations were above the provisional reference value for removal (25 ppm). The cost was paid by Chisso, the national government, and KP. Nowadays the reclaimed land is maintained as a park. In Niigata Prefecture, in 1976, Showa Denko paid the costs of dredging mercury-containing sediments from locations near the factory wastewater drain outlet.

In 1974, KP installed dividing nets to contain polluted fish inside Minamata Bay. In 1997, the governor of KP declared that fishery products collected from Minamata Bay were safe based on the fact that the mercury levels for seven species of fish were below the provisional control values (mercury <0.4 ppm, methylmercury <0.3 ppm) for three consecutive years, and then the dividing nets were removed.

2.19 Court Ruling

The methylmercury poisoning incidents have been laid before a number of courts. In June 1969, patients filed a suit against Chisso in the Kumamoto District Court for compensation for damages. On March 20, 1973, the district court found Chisso responsible, severely admonishing the company's actions. The presiding judge, Jiro Saito, read out the judgment (extract):

1. When chemical factories drain wastewater, they have to carry out detailed surveys in order to evaluate whether wastewater contains substances that are possible to endanger lives and health of humans and animals or not. Regarding discharge of effluents, the factories must use highest levels of information, technology, literature surveys, environmental monitoring, and safety verification.
2. If wastewater is revealed to contain harmful substances or if there is any suspicion about it, chemical factories have to prevent pollution beforehand as possible as they can, using measures such as halting the operation of the plant immediately. Especially, chemical factories have a duty to protect from harm the life and health of local residents beforehand.
3. If Chisso discharged their duty, they could predict the risk of wastewater to humans successfully and never triggered MPM or expanded this disease over wide areas. Chisso, however, did not perform appropriate countermeasures in all aspects including environmental monitoring, fishery compensation, investigation on the cause of MPM, and treatment of wastewater.
4. The "Mimai-kin agreements" should be avoided. The agreements took advantage of the victims' ignorance and poverty to deprive them of a legitimate right to claim further damages in exchange for a low amount of compensation. The agreements should be deemed invalid, because these are offensive to public order and morals.

The judgment also pointed out relationships between responsible companies and residents in pollution disasters and residents as:

1. Pollution disasters are usually caused by companies irrespective of residents' will.
2. Residents scarcely escape from pollution disasters, and in most cases, no blame is imputable to them.
3. Pollution disasters often have an influence on an unspecified large number of residents inhabiting over a large area, resulting in having serious adverse impacts on the society.
4. Residents living in the same environment suffer similar damage although to varying degrees. Within a family, it is not rare that all or most of the members are affected, resulting in ruin on the entire family.
5. Companies aim to make profit by manufacturing activities which may produce pollution, whereas such activities never bring benefits to residents directly.

On February 29, 1988, the Supreme Court sentenced the former president of Chisso, Kiichi Yoshioka, and the former director of Minamata factory, Eiichi Nishida, of being guilty, that is, 2 years of imprisonment but with probation of 3 years for their crimes as causing death or injury through negligence in the pursuit of social activities. These were the criminal penalty to Chisso. It can be said that Chisso succeeded in lessening charges which they deserved.

On October 15, 2004, the Supreme Court handed down its ruling on the lawsuit which had been brought by patients who had moved from the Minamata area to the Kansai district. The ruling found the national government and KP jointly liable for the payment of the compensation in view of their failure to prevent the outbreak and spread of MPM. However, nobody was accused of any criminal charges.

2.20 Assignment to Students

I asked students in my class to submit a report on the subject, that is, reasons why MPM expanded over the vast area in the Shiranui Sea and also other localities and why did many people suffer from this disease? I summarized the reasons that were described in the students' reports into five groups:

1. Lack of information/experience
   - Incorrect information
   - Unknown cause of the disease at the initial stage of the outbreak
2. Physical and biological aspects
   - Migration of contaminated marine organisms and movement of polluted water by current
   - Polluted water and bioaccumulation in aquatic products
3. Lacking responsibility of the causative company, Chisso
   - Facts being hidden by Chisso
   - Chisso's dishonest initial reaction and long period (12 years) to admit responsibility
   - Ethical misconduct by Chisso
   - Change of the promoter, rapid increase of the acetaldehyde production, change of the discharge point, and insufficient purification apparatus constructed by Chisso
4. Neglecting obligations by the governments
   - Slow response to the pollution, neglect in preventing the disease, and the failure to institute a compulsory ban on fishing

5. Social background
   - Pursuit of economic interests by the enterprises, government, and individuals
   - Ordinary citizens' reaction: consideration for the economically "contributing" company, Chisso, and treating the patients like nuisances

In addition to these reasons, there was no organization to research MPM except Kumamoto University Medical School (KU). They were not always familiar with industrial chemistry, marine ecology, and environmental sciences. Chisso not only diffused to inform the production process as well as to provide materials for clarifying the disease cause to KU but also disrupt their research works. Researchers in other faculties like the engineering in KU were not included in the members of the study group of KU. Thus, they were ridden with limited information and resources.

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Chapter 3
Past, Present, and Future of Mercury Pollution Issues

Abstract In this chapter, countermeasures and solutions to methylmercury poisoning (MPM) and current and outstanding issues on the mercury pollution are discussed. Correct information and data, public access to information, establishment of company ethics, rapid response by governments, societal responsibility, and penalties on responsible organizations are necessary for preventing the similar kind of pollution and human hazard. Recent studies which show the relationship between the anthropogenic emissions of mercury and the risk to human health, especially to fetuses and infants, are summarized. Finally, outstanding issues on MPM that are in connection with the global mercury cycle are discussed.

Keywords Anthropogenic mercury emission · Global mercury cycle · Low-dose exposure · Mental retardation · Neurodevelopmental deficits · Root causes

3.1 Lessons from MPM

If we can clarify the root causes of poisoning events such as MPM, then we can make effective countermeasures. From this viewpoint, summarization of students' opinions regarding the causes of MPM (the Sect. 2.20) may lead to antipollution measures as shown below:

1. Correct information and data and public access to information
2. Establishment of company ethics
3. Rapid response and approaches to give priority to human rights of citizens rather than to protecting profits of companies by governments
4. Societal responsibility where all people recognize the importance of public welfare and environments
5. Strict and justifiable penalties on organizations (e.g., companies, governments) that have caused/permitted environmental pollution

Over 60 years have passed after the initial acknowledgment of MPM. Many people are still suffering from this disease. In modern Japan, we have experienced many environmental pollution issues from the Ashio Copper Mine mineral pollution incident in the 1880s–1980s to the Fukushima nuclear power plant accident in 2011. Especially during the rapid economic growth period from the late 1950s through the

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1970s, four major pollution diseases including MPM, methylmercury poisoning which occurred in Niigata (Niigata "Minamata disease"), Yokkaichi asthma, and ouch-ouch disease had occurred sequentially. It seems that these environmental pollution-related diseases share key characteristics. It is necessary to investigate this root cause for prevention of recurrence.

A few students' reports stated that the unclear etiology at the initial MPM stage outbreak had resulted in the disease expansion. Even without exact information on the causative agent, if banning of fisheries and selling marine products was enforced by the late 1956 or 1957, the expansion of MPM must have been avoided. At that time, the national and local governments knew already that the disease had occurred through ingesting local seafood based on epidemiological surveys conducted by KU. Kumamoto Prefecture (KP), however, never applied the Food Sanitation Act, even though KP had sufficient authority to apply this Act independently and to ban fisheries and selling by themselves. The national and local governments maintained the stance that they would not act until the identification of the causative agent. The inexcusable fault to allow the expansion of MPM lies with the national and local governments.

On the other hand, Chisso noticed that their own factory was producing toxic material by 1958 at the latest, when the discharge system for plant effluents was changed; nevertheless they continued the acetaldehyde production, resulting in harming the life and health of residents. The behavior of Chisso should be charged with a crime not a fault. Such criminal companies which prioritize own profits rather than public welfare can exist in all times and countries. Governments might support such companies rather than the public. In these cases, prosecution should function to protect social justice and public health. In the MPM incident, however, the police and prosecutor never took action; instead they charged patients who had made a violent protest to Chisso with assault immediately and severely. I can't help thinking that MPM occurred in the economy-first policy of Japan society in the years following the World War II and such atmosphere continues today. In order to avoid pollution disasters such as MPM, it is necessary to inspect why MPM occurred and to assess where and who take responsibility.

I have to refer to the approach of the pollution research. Members of KU have played a central role in the research to determine the cause of MPM. They reached a conclusion of the truth in 1959 by the continuous, sincere efforts. Meanwhile, a few researchers made objections to this conclusion based on unfounded inferences in support of Chisso's opinion. Professor Tetsuzo Kitagawa of Yokohama National University also disturbed the resolution of methylmercury poisoning incident occurred in Niigata by showing erroneous data. Such patronized scholars avoided the truth and occasionally twisted data in favor of the criminal companies to receive benefits. Their attitude resulted in the lowering of professional integrity among scientists and in eternal dishonor upon themselves.

In Japan, studies on environmental pollution tend not to be favored by researchers, or even if researchers in universities or research institutes of governments want to carry on researches, superiors occasionally disrupt such subjects in fear of large impacts on the society and pressures from companies or governments. Such trends, however, are decreasing in recent days, accompanied by the increased awareness of the environment. Researchers of universities and research institutes should take on environmental pollution problems for the welfare of humanity.

Environmental pollution affairs often cause controversies among residents, patients, company managers, factory laborers, government officers, and researchers. Even among researchers, severe debates have sometimes arisen at minor things. At that time, it is important to open all data and materials which would serve as their claims and then to discuss with each other scientifically and objectively.

We have to recognize the serious pollution like the MPM incident destroys nature, humans, and societies and how long time it takes to recover. Controversies were generated not only between patients and responsible companies but also between patients and residents. A part of residents living in the MPM-prone area who had depended on Chisso are economically alienated patients and referred to mildly symptomatic patients who had requested compensations disparagingly as "fake patients." There were also severe controversies among patients over the method of negotiation with Chisso and the governments. In 1994, the mayor of Minamata City, Masazumi Yoshii, apologized publicly for the patients about the administrative actions during the period of the MPM outbreak that had intended to maintain the operation of the plant, and then he pursued a policy "Moyai-naoshi" in Japanese, which means "reconnection" between individuals as well as between humans and environments. In recent years, the effects seem to be realized gradually, and I am encouraged by the changing attitudes toward the environment not only in Japan but also in the world.

3.2 Global Mercury Cycle and Low-Dose Exposure

3.2.1 Global Mercury Cycle

In recent years, greater attention has been given on the global mercury cycle (Downs et al. 1998). UNEP (2013) which estimated that total anthropogenic emissions of mercury to the atmosphere in 2010 were 1960 t (30% of total mercury), while another 10% came from natural geological sources, and the rest (60%) were from "reemissions" of previously released mercury that had built up over decades and centuries in surface soils and oceans. Artisanal and small-scale gold mining (727 t in 2010, 37% of total anthropogenic emissions) and coal burning (474 t, 24%) were

the largest components of anthropogenic emissions in 2010, followed by cement production (173 t), large-scale gold production (97 t), and consumer product waste (96 t). Gworek et al. (2016) also showed the similar levels of mercury emission (total emission = 5000–6600 t year^{-1}; anthropogenic emission = ~2200 t year^{-1}) by citing many papers. Asia contributes almost half of global anthropogenic emissions, accounting 40% of the total emission by East and Southeast Asia, in which China accounts three-quarters (UNEP 2013). Fu et al. (2015) estimated that the annual emission of anthropogenic gaseous elemental mercury (GEM) over the past decade in China was 632–1138 t and that anthropogenic GEM increased by 2.4–2.5% year^{-1}. Emissions of anthropogenic mercury to the air have peaked in the 1970s, have declined over the following two decades, and then have been stable between 1990 and 2005; however, since then, there were indications of increases in emissions from fossil fuel combustion and metal and cement production (UNEP 2013). It is widely recognized that increases in industrial mercury emissions in recent years result in elevated levels of mercury concentrations in the atmosphere.

The anthropogenic mercury emissions were considered to contribute significantly to the burden of mercury in precipitation from the findings that the increases of mercury in precipitation are global (Downs et al. 1998). Mercury in the atmosphere is transported into the aquatic environments through wet and dry depositions and then constitutes a main source of mercury to aquatic biota in the absence of point source discharges. On the other hand, UNEP (2013) listed mercury sources which are released directly into the aquatic environments, that is, point sources from industrial sites (185 t year^{-1} including 93 t year^{-1} of nonferrous metal production, 89 t year^{-1} of consumer product waste), sources from contaminated sites (8–33 t year^{-1}), artisanal and small-scale gold mining (800 t year^{-1}), and soil erosion following deforestation (800 t year^{-1}). These estimates remain uncertain; however, the total releases were calculated to be more than 1000 t year^{-1}, which exceeded estimated natural releases, 150–960 t year^{-1}. Amos et al. (2013) showed that atmosphere and surface ocean (0–54 m) are enriched by 2.6- and 2.3-fold, respectively, in comparison with the preindustrial (1840) reservoir mass using a simulation model.

UNEP (2013) also showed the pathways and fate of mercury in the oceans. Pathways by which mercury reaches the oceans include direct deposition from the atmosphere (3700 t in 2008), supply from hydrothermal vents (<600 t) or from groundwater, and remobilization from sediment (100–800 t) and inflow from rivers (380 t except for 2420 t which is trapped in estuaries). Anthropogenic emissions and releases over time have increased mercury loads in the oceans, resulting in the doubled amount of mercury in the top 100 m of the world's oceans in the last 100 years. Accumulated inorganic mercury can be converted into methylmercury by bacterial activities as described in Sect. 2.13. In freshwater and coastal environments, methylation occurs primarily in sediments, while in the open ocean, this takes place largely

at intermediate depths, between 200 m and 1000 m in the water column. Approximately 300 t of methylmercury is produced in the oceans in a year, 80 t is transported from other sources to the oceans, 240 t is removed by photochemical reaction or by microbial activity, and then 40 t per year is taken up into marine food webs.

3.2.2 Bioaccumulation of Mercury and Effects on Public Health

Among mercury species, methylmercury is accumulated selectively by phytoplankton, accounting $10^{5.5}$-fold bioaccumulation rate between water and phytoplankton, subsequently bioaccumulating methylmercury approximately by fourfold, and then followed by subsequent bioaccumulation to planktivorous fish at similar rate (Mason et al. 1995). Thus, the pathway of methylmercury to fish is dominated by the food chain, resulting in highest levels of methylmercury in top predators and in posing risks to humans through consumption of contaminated seafood.

Due to the increased anthropogenic emissions of mercury, mercury concentrations in Arctic marine animals have increased by 12 times since the preindustrial period (UNEP 2013). Downs et al. (1998) also described that established background levels for fish (0.2–1.0 μg g^{-1}) exceeded the preindustrial level of 0.15 μg g^{-1}, suggesting anthropogenic origin. Gworek et al. (2016) showed ranges of the mercury concentration in various sea fish collected from ten areas in the world. Maximum values obtained from six areas exceeded 0.5 μg g^{-1} dry wt, while the values from four areas exceeded 1.0 μg g^{-1}. These results suggest that the effects of anthropogenic mercury expanded over the whole world.

As described in the previous sections (2.3, 2.4 and 2.11), methylmercury is a neurotoxicant, and its severe toxicity to residents was first recognized in Minamata. They are considered to consume seafood containing high concentrations of methylmercury exceeding 10 ppm (μg g^{-1} dry wt) usually or 100 ppm occasionally, which are considered to be accumulated through the process of food chains. Since the late twentieth century, it has been recognized that elevated levels of mercury in normal environments pose increasing concerns on human health hazards by low-dose mercury exposure. Zahir et al. (2005) summarized the effects of low-dose mercury toxicity in Table 3.1. The effects extend over not only in the nervous system but also in motor, renal, cardiovascular, immune, and reproductive systems of all age groups. Among the effects listed, special concerns have been focused on mental retardation of fetuses and infants. Populations who routinely consume fish or particular fish species have high exposure to methylmercury. Mothers consuming diet containing methylmercury pass the toxicant to fetuses through the blood-brain barrier and to

Table 3.1 Effect of low-dose mercury toxicity on various organ systems (Zahir et al. 2005)

1. Nervous system	
Adults	Memory loss including Alzheimer-like dementia, deficit in attention, hypoesthesia, ataxia, dysarthria, subclinical finger tremor, impairment of hearing and vision, sensory disturbances, and increased fatigue
Children/infants	Deficit in language (late talking) and memory deficit in attention, and autism
2. Motor system	
Adults	Disruption of fine motor function, decreased muscular strength, and increased tiredness
Children/infants	Late walking
3. Renal system	Increases plasma creatinine level
4. Cardiovascular system	Alters normal cardiovascular homoeostasis
5. Immune system	Decreases overall immunity of the body, exacerbates lupus-like autoimmunity, multiple sclerosis, autoimmune thyroiditis, and atopic eczema
6. Reproductive system	Decreases rate of fertility in both males and females, and birth of abnormal offspring

infants through breast milk. Exposure of methylmercury to children under age 14 is two to three times high because of higher food intake per unit weight. The developing brain is susceptive and vulnerable to methylmercury; therefore, even low-dose exposure may damage the brain of fetuses and infants.

Biomarkers of methylmercury exposure, such as total mercury levels in hair or blood, are regarded as more accurate measures of human exposure than dietary assessment because methylmercury concentrations vary both between and within fish species and because recall of specific species may be imprecise (Groth 2010). Karagas et al. (2012) defined "low-dose mercury exposures" as mean measured mercury levels of <4 μg g^{-1} in maternal hair, 20 μg L^{-1} in cord blood, or <12 μg L^{-1} in adult blood.

Gribble et al. (2016) summarized major cohort studies examining early-life mercury exposure and neurodevelopment in children. Four of nine populations showed the positive association. First, in the Faroe Islands where residents consumed pilot whale meat, neurodevelopmental deficits (i.e., language, attention, memory, and visuospatial and motor functions) were found at birth and early school years. An upper limit for "safe" exposure in terms of the maternal hair mercury concentration was considered to be 10 ppm (Grandjean et al. 1997, 2014). Second, in Massachusetts, USA, higher mercury levels of maternal hair (the range of maternal hair mercury = 0.02–2.38 ppm) were associated with lower infant cognition at 6 months of age (Oken et al. 2005). Third, in Seychelles, an Indian Ocean archipelago, neurodevelopmental performance at 30 months infants decreased with increased methylmercury exposure (mean maternal hair methylmercury = 5.9 ppm), although in the initial studies (Davidson et al. 1998; Myers et al. 2003), no effects were observed

(Davidson et al. 2008). Lastly, in Italy, mercury in hair of 7-year-old children was fairly correlated with mercury in maternal hair at delivery and was strongly correlated with child's seafood consumption. Children born from mothers with hair mercury levels ≥2.0 ppm had lower intelligence quotient (IQ) than children born from women with lower mercury levels. (Deroma et al. 2013).

3.2.3 Tolerable Methylmercury Intake and Recommendations for Public Health

Since the 1980s when concerns about low-dose exposure were raised, a lot of efforts have been paid to identify the tolerable methylmercury intake for protecting human health. The US Environmental Protection Agency (EPA) requested the National Academy of Sciences to prepare recommendations on the appropriate reference dose for mercury exposure. Then, the National Research Council (2000) assessed preceding studies which examined children who experienced methylmercury exposures in utero at concentrations relevant to current and concluded that (1) neurodevelopmental deficits are the well-documented effects, (2) mercury concentrations in cord blood would be expected to correlate most closely with fetal brain mercury concentrations during late gestation, (3) the preferred estimate of a benchmark dose level (BMDL) is 58 ppb (μg L^{-1}) of mercury in cord blood (corresponding to 12 ppm Hg in hair) based primarily on the Faroe Islands study and secondary on the New Zealand and Seychelles studies, and (4) the value of EPA's current methylmercury exposure reference dose (RfD), 0.1 μg kg^{-1} d^{-1} (0.7 μg kg^{-1} $week^{-1}$), is a scientifically justifiable level for the protection of public health. RfD was calculated by

$$\mathrm{RfD} = \left(C \times b \times V\right) / \left(A \times f \times bw \times \mathrm{UF}\right),$$

where:

C = concentration in blood (44 μg L^{-1})
b = elimination constant (0.014 $days^{-1}$)
V = volume of blood in the body (5 L)
A = absorption factor (expressed as a unitless decimal fraction of 0.95)
f = fraction of daily intake taken up by blood (unitless, 0.05)
bw = body-weight default value of 60 kg for an adult female
UF = uncertainty factor: mathematical adjustments for reasons of safety when knowledge is incomplete (10)

On the other hand, the Joint Expert Committee on Food Additives and Contaminants (JECFA) which was organized by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) provided recommendations on methylmercury in 2003 as follows: (1) 14 μg kg^{-1} maternal hair mer-

cury was recommended as BMDL based on the Faroe Islands and Seychelles studies, and (2) a provisional tolerable weekly intake (PTWI) of 1.6 μg kg^{-1} $week^{-1}$ methylmercury was considered sufficient to protect developing fetuses (WHO 2004).

The Ministry of Health, Labour and Welfare, Japan (MHLW), requested a risk assessment of methylmercury in seafood to the Food Safety Committee (FSC) in the Cabinet Office. FSC (2005) calculated PTWI using the following equation:

$$\begin{aligned}\mathrm{PTWI} = \mathrm{RfD} \times 7 &= \left\{ \left(C \times b \times V \right) / \left(A \times f \times bw \times UF \right) \right\} \times 7 \\ &= \left\{ \left(44 \times 0.14 \times 5.4 \right) / \left(0.95 \times 0.05 \times 60 \times 4 \right) \right\} \times 7 \\ &= 2.0 \ \mu\mathrm{g\ kg^{-1}\ week^{-1}}\end{aligned}$$

The difference in PTWI among three organizations (EPA, 0.7 μg kg^{-1} $week^{-1}$; FAO/WHO, 1.6 μg kg^{-1} $week^{-1}$; MHLW, 2.0 μg kg^{-1} $week^{-1}$) resulted mainly from the values of the uncertainty factor adopted (10.0, 6.4, and 4.0, respectively). This means that the difference in the PTWI value reflects the difference of view to food safety among organizations, that is, EPA imposed a high standard for avoiding low-dose methylmercury hazards, whereas MHLW set a laxest standard.

MHLW (2005a) summarized data on the concentrations of total mercury in 529 food materials including 495 raw aquatic fish/animals and 34 processed sea-/freshwater food. As I explained in Sect. 2, we can evaluate the toxicity of aquatic organisms using values of total mercury, because methylmercury usually accounts for the majority of total mercury in aquatic organisms. Among these materials, 31 fish/animals show >1.0 ppm (μg g^{-1} wet wt) in the maximum value. Except two materials of which identification is unclear, data of 29 fish/animals are shown in Fig. 3.1. These materials consisted of 23 fish species/species groups, 5 whale species that belong to *Odontoceti*, and 1 crustacean species. All species are carnivores. Excluding American lobster, all species are large sized and piscivorous, indicating that they are the highest on the food chain and are ready to accumulate methylmercury. In Fig. 3.1, the highest value, 37.0 ppm (μg g^{-1} wet wt), was found in a specimen of the bottlenose dolphin (no. 1, *Tursiops truncatus*). This species also ranked at the top of the mean value (20.8 ppm). High maximum and mean values are also found in other whale species such as the short-finned pilot whale (no. 3, maximum = 8.9 ppm; mean = 7.1 ppm), the sperm whale (no. 5, 4.6 ppm, 2.1 ppm), the Baird's beaked whale (no. 9, 2.6 ppm, 1.2 ppm), and the Dall's porpoise (no. 25, 1.2 ppm, 1.0 ppm). Several marlin (nos. 2, 7, 11, 13) and tuna (nos. 2, 4, 6, 10, 17, 22) species almost always showed high mercury concentrations (marlin, range of maximum values = 1.7–9.3 ppm, range of mean values = 0.6–1.2 ppm; tuna, 1.3–6.1 ppm, 0.2–0.7 ppm). Similar to these fish, two species belonging to the genus *Scomberomorus* (nos. 14, 15) which actively swim in the pelagic zone showed high mercury concentrations (max = 1.6–1.7 ppm, mean = 0.3–0.7 ppm). On the other hand, there are a variety of demersal/sedentary fish which have high mercury concentrations, such as tilefish (no. 6, max = 3.7 ppm, mean = 1.2 ppm), the splendid alfonsino (no. 12, max = 2.2 ppm, mean = 0.7 ppm), three species of grouper (nos. 23, 24, 29, max = 1.0–1.3 ppm, mean = 0.5–1.1 ppm), and two species of halibut (nos. 16, 27,

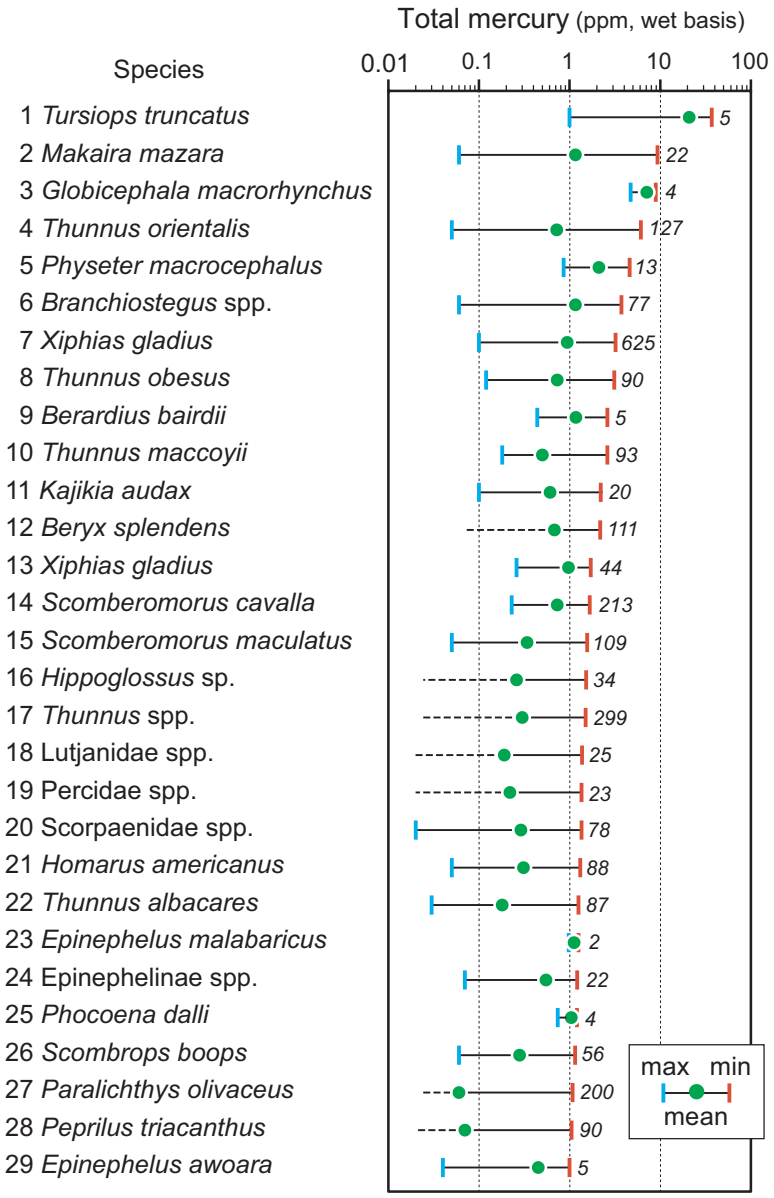

Fig. 3.1 Aquatic organisms collected from waters around Japan and other localities, showing high levels in the maximum value (>1.0 ppm = μg g^{-1} wet wt). Minimum, maximum, and mean values and the sample size (italics in the figure) are indicated. Solid lines show the range of values, while broken lines are used when minimum values are unknown. Among the numbers that precede, the scientific names in the figure, nos. 1–5, 8–10, 12, 13, 22, 23, 25–27, and 29 animals, were collected from waters around Japan, while nos. 6, 7, 11, 14–21, 24, and 28 animals were collected from other oceans. English names are as follows: 1, bottlenose dolphin; 2, Indo-Pacific blue marlin; 3, short-finned pilot shale; 4, bluefin tuna; 5, sperm whale; 6, tilefish; 7, swordfish; 8, bigeye tuna; 9, Baird's beaked whale; 10, southern bluefin tuna; 11, marlin; 12, alfonsino; 13, swordfish; 14, king mackerel; 15, Spanish mackerel; 16, halibut; 17, tuna; 18, snapper; 19, perch (freshwater); 20, scorpionfish; 21, American lobster; 22, yellowfin tuna; 23, Malabar grouper; 24, grouper; 25, Dall's porpoise; 26, gnomefish; 27, bastard halibut; 28, butterfish; and 29, banded grouper (Data source: MHLW 2005a)

Table 3.2 Three kinds of aquatic products categorized by FDA and EPA, USA, for avoiding low-dose methylmercury hazards (EPA 2007)

A. Best choices
Anchovy, Atlantic croaker, Atlantic mackerel, black sea bass, butterfish, catfish, clam, cod, crab, crawfish founder, haddock, hake, herring, lobster (American and spiny), mullet, oyster, Pacific chub mackerel, perch (freshwater and ocean), pickerel, plaice, pollock, salmon, sardine, scallop, shad, shrimp, skate, smelt, sole, squid, tilapia, trout (freshwater), tuna (canned light, including skipjack), whitefish, whiting
B. Good choices
Bluefish, buffalo fish, carp, Chilean sea bass/Patagonian toothfish, grouper, halibut, mahi mahi/dolphinfish, monkfish, rockfish, sablefish, sheepshead, snapper, Spanish mackerel, striped bass (ocean), tilefish (Atlantic Ocean), albacore tuna/white tuna (canned and fresh/frozen), yellowfin tuna, weakfish/sea trout, white croaker/Pacific croaker
C. Choices to avoid
King mackerel, marlin, orange roughy, shark, swordfish, tilefish (Gulf of Mexico), bigeye tuna

max = 1.1–1.5 ppm). Among these species, the splendid alfonsino is known as a deepwater fish (depth, > 200 m), while perch (no. 19, max = 1.4 ppm) is a freshwater fish. These data show that carnivorous aquatic animals can accumulate methylmercury irrespective of their habitat and the taxonomic group to which they belong.

Based on the results on mercury concentrations in aquatic products, the Food and Drug Administration (FDA) and EPA in the USA issued advice regarding amounts of seafood ingested (EPA 2007). This advice was geared toward helping women who are pregnant or may become pregnant as well as breastfeeding mothers and parents of young children. FDA/EPA categorized aquatic products into three groups (Table 3.2) and recommended that (1) people can eat 227 g to 340 g a week of fish in the "best choices" category, (2) people can eat 113 g a week of fish in the "good choices" category, and (3) people should not eat fish in the "choices to avoid" category or feed them to young children.

The Japanese government published a document about the mercury risk of consuming seafood (MHLW 2005b). The summary is as follows: (1) fish and shellfish are an important diet; (2) mercury contaminations in fish and shellfish are very small, but some species contain higher levels in the mercury concentration; (3) reported mercury effects on fetuses are minor ("no more than degree" in original), for example, auditory response is delayed by less than one-thousandth second, and its intake through normal meals will not affect the baby's future life; (4) this advice is intended not to ask pregnant women to avoid fish and shellfish that contain high levels of mercury; and (5) women who are or may be pregnant should follow the recommendations in order to reduce the health risk to the minimum. MHLW (2005b) also categorized aquatic products having risks into four groups (A–D, Table 3.3) mainly based on mean values shown in Fig. 3.1 as well as on 2.0 μg kg^{-1} $week^{-1}$ of PTWI which was established by themselves (FSC 2005). The objects of the recommendations are women who are or may be pregnant, while lactating women, infants, children, and adults are removed from consideration, because MHLW (2005b) considered that they are not affected by normal consumption of any aquatic food. The

Table 3.3 Recommendations for pregnant women on consumption of aquatic products concerning mercury contamination by MHLW (2005b)

Target species	Recommendations
A. Bottlenose dolphin (1)	
Pregnant women should restrict the consumption of meat within 80 g (average amount per one meal) per 2 months	
B. Short-finned pilot whale (2)	
Pregnant women should restrict the consumption of meat within 80 g per 2 weeks.	
C. Alfonsino (12), swordfish (7), bluefin tuna (4), bigeye tuna (8), finely-striate *Buccinum* (30), Baird' beaked whale (9), sperm whale (5)	
Pregnant women should restrict the consumption of meat within 80 g per 1 week.	
D. Yellowback seabream (31), marlin (11), Hilgendorf saucord (32), southern bluefin tuna (10), blue shark (33), Dall's porpoise (25), Japanese bluefish (34)	
Pregnant women should restrict the consumption of meat within 160 g per 1 week.	

See Fig. 3.1 for scientific names of species that are assigned numbers from 1 to 25 in parentheses. Scientific names of species that are assigned numbers 30–34 are as follows: 30, *Buccinum striatissimum*; 31, *Dentex tumifrons*; 32, *Helicolenus hilgendorfii*; 33, *Prionace glauca*; and 34, *Scombrops gilberti*

observed maximum concentrations of whales, marlins, and tunas, however, were at the same level as those found in Minamata around 1960, suggesting that if these food was consumed by humans freely, even adults would become the acute type of MPM. The document includes the sentence "you can eat other tune species (yellowfin tuna, Albacore and juvenile bluefin tuna) than listed ones and canned tuna without any particular restriction." Reasoning of this recommendation is supposed to be relatively low mean values of the mercury concentration in these species; however, we can find a high maximum value, 1.25 ppm, in yellowfin tuna. The observed mean and maximum values are usually affected by the sample size and locality collected; we should be careful when listing risky species. Thus, the recommendation of MHLW seems to emphasize the advantage of consuming aquatic food and to dispel concerns about consuming aquatic food by underrepresenting the risk of mercury. Should we think to follow international standards not the laxest standard (2.0 μg kg^{-1} $week^{-1}$) that MHLW established by themselves, to list risky aquatic organisms not at a species level but at a trophic level, and to recommend avoiding the consumption of highly risky organisms during the gestational period?

Consumption of seafood provides risks and benefits for humans. Seafood is the primary source of protein for many populations. It has many nutrients including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which give benefit by reducing heart diseases. Therefore, balanced assessments of the risks and benefits of seafood are required. In general, as trophic level increases, methylmercury

concentrations in marine animals increase, whereas there is no relationship between trophic level and nutrient concentrations, suggesting that consuming lower trophic level seafood can minimize the risk of mercury exposure without reducing the benefits of nutrient intake.

As noted in Sect. 3.2.2, there is competent evidence for the fetal neurotoxicity of methylmercury at low-dose exposure (Gribble et al. 2016). That is, the positive association of mercury with neurodevelopment was found in four of nine populations, while five populations did not show any evidence (Kjellström et al. 1989; Davidson et al. 1998; Myers et al. 2003; Valent et al. 2013; Tatsuta et al. 2014; Strain et al. 2015). Further studies are necessary to clarify the relationship between low-dose mercury exposure and health hazards and to make appropriate suggestions regarding the acceptable dose level.

3.3 Outstanding Issues

Dr. Masazumi Harada, who contributed to the study on MPM as well as to MPM patient care, published a book entitled *Minamata Disease Not Settled Yet* in 1985. In those days, many patients were not acknowledged officially and sought redress from the court. As of 2017, legal battles over MPM still persist. This is mainly due to a strict criterion for diagnosing MPM which was established by the national government in 1977. In this criterion, multiple symptoms among (i) sensory disturbance, (ii) ataxia, (iii) equilibrium disturbance, (iv) visual field constriction, (v) central visual disturbance, (vi) central auditory disturbance, and (ii) others are needed for the diagnosis of MPM, resulting in discarding many patients. Such a conflict seems to be caused from a lack of understanding the whole context of victims through detailed surveys by the government. Urgent and thorough surveys are necessary, although long overdue. Besides, pathology of MPM should be elucidated further. If methylmercury damages the vascular system and/or acts as an endocrine-disrupting agent as suggested by Shiraki (1979), lesions will extend over the whole body resulting in a variety of symptoms, and even tiny amounts of methylmercury may affect the whole human body. Such studies may provide a useful clue as to resolving low-dose mercury issues in the global mercury cycle.

Gworek et al. (2016) described that the average residence time of mercury in oceanic waters, 20–30 years, is much longer than that in the atmosphere (0.8–2 years), resulting in that the mercury discharged into the ocean is removed from there much more slowly than the mercury emitted into the atmosphere and that an increase in the mercury concentration level in oceanic waters will be very slow and may take hundreds of years. This fact means that the mercury concentration will continue to increase gradually, even if anthropogenic emissions of mercury to the atmosphere stop right now. Methylmercury concentrations in some aquatic animals have reached the threshold level to cause neurodevelopmental deficits in fetuses and infants already; therefore, we have to minimize the mercury emissions as soon as possible.

In this context, it is gratifying that the "Minamata Convention on Mercury" entered in force on August 16, 2017. Its major highlights include a ban on new mercury mines, the phasing out of existing ones, the phasing out and phasing down of mercury use in a number of products and processes, control measures on emissions to air and on releases to land and water, and the regulation of the informal sector of artisanal and small-scale gold mining.

An American photographer, William Eugene Smith, took excellent pictures of MPM patients. Among these, a picture titled "Tomoko Uemura in Her Bath," which depicted a mother cradling her severely deformed, naked daughter in a traditional Japanese bathroom, is impressive. The mother called Tomoko as "Takara-ko" in Japanese which means "treasure daughter" for the reason that the mother was able to keep her health because Tomoko had drawn all mercury and accumulated it into Tomoko's own body and that her six children grew up healthy and helped each other as a result of learning the importance of mercy from assisting their elder sister (Harada 1985). Tomoko passed away on December 12, 1977, at the age of 20. We can provide a description of the assailant who took the life of Tomoko. On the other hand, presently, we may be living in the world full of toxicants including mercury. In this world, we have a high probability of becoming a victim, and at the same time, we can be an assailant. Let's consider what we can do under such circumstances.

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