ITAI-ITAI DISEASE: THE ROLE OF MINING IN THE DEGRADATION OF JAPANESE SOCIETY AND PUBLIC HEALTH

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Dang-Huy Daniel Nguyen

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Approved by

Motomu Ibaraki, Advisor
School of Earth Sciences

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ABSTRACT

This study investigates the transport and pathways of cadmium exposure in humans due to mining pollution, the development of itai-itai disease and the public health impacts, as well as legal action and victim compensation. The aim of this study is to determine how mining contributed to long-lasting consequences for people in the Jinzu River Basin.

As a result of inadequate facilities and handling of mining waste, the waste discharged into the Jinzu River, resulted in cadmium transport downstream and contamination of the river water and paddy fields. Residents were exposed primarily via ingestion of drinking water and rice grains. Characteristics of cadmium and rice allowed for high cadmium bioaccumulation in the environment. This includes the immobile nature of cadmium during flooded paddy field conditions, the high mobility in soil during drained field conditions, and the high absorption of cadmium by rice crops. Dietary Cd intake of residents exceeded 300 µg/day in various polluted areas of the Jinzu River Basin, with 600 µg/day being the highest intake in the endemic area. Nutritional deficiencies, including iron, zinc, and calcium, may promote the absorption of cadmium in the body. Evaluation of the residents' diets did not indicate nutritional deficiencies expect for calcium.

With chronic exposure, people began developing itai-itai disease, which is characterized by kidney disorders, osteomalacia, and osteoporosis. Patients experienced bone deformation, severe pain related to bone effects, and shortened lifespan. Women, particularly postmenopausal women, were at a much greater risk than men for developing the disease due to risk factors like kidney sensitivity, pregnancy, genetics, enzyme differences, and lower iron stores. Of the 200 officially recognized patients, 195 patients were women (97.5%).

Social impacts of cadmium pollution hurt the livelihoods of farmers and fishermen because cadmium damaged agriculture and fisheries. Patient experienced disability and incurred high medical costs. Lawsuits against Mitsui Mining Co., Ltd resulted in a total of ¥46 billion in compensation: ¥7.8 billion in medical compensation, ¥26.8 billion in compensation for agricultural damage and soil damage, and ¥12.0 billion in pollution prevention investments. However, people suffered from cadmium pollution for decades before proper compensation was awarded.

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INTRODUCTION

Itai-itai disease is one of the four major “Kougai-byou” (pollution diseases) in Japan, which was caused by environmental pollution from industrial sources. The outbreak of itai-itai disease began around 1912 and occurred in Fuchu Town and the surrounding Jinzu River Basin in Toyama Prefecture, Japan. The Kamioka Mine is located upstream of the endemic area of the disease. The mine primarily processed zinc ore, which resulted in cadmium byproducts that were discharged into the Jinzu River. Cadmium was able to accumulate in the river water, soil, and crops in the paddy fields. After chronic exposure to cadmium, nearby residents began developing itai-itai disease. The disease is characterized by kidney disorder and bone diseases, and it occurred mainly in postmenopausal women.

The first case appeared around 1912, but it would be several decades before medical research began. Victims suffered various health and social consequences without proper compensation or support. Once medical research began, evidence pointed to mining pollution as a potential cause. However, the prefectural government and Mitsui Mining Co., the owner of the Kamioka Mine, rejected these claims to protect their business interests. Victims and residents banded together to fight Mitsui in court. Eventually, the victims won long-deserved compensation for the suffering they endured. Mitsui also agreed to put measures in place to prevent environmental pollution from happening again.

This study offers insight to the history and the social and public health consequences that resulted from mining pollution. Also, this study attempts to address knowledge gaps. The prevalence of itai-itai disease in postmenopausal women is not well understood, so the available literature on the subject is compiled. Nutritional deficiencies are thought to be an aggravating

risk factor of itai-itai disease, but some studies have found conflicting results. The evidence for both sides is presented.

STUDY DESIGN AND PHYSICAL SETTING

To investigate the implications of itai-itai disease upon society, this study utilized methods involving compilation and synthesis of peer reviewed literature and research. Electronic databases including The Ohio State University Library Catalogs, PubMed, and Web of Science were used to search for relevant literature. PubMed and Web of Science databases was accessed through the university library website. After preliminary research, appropriate keywords were determined. Keywords were used in combination with the Boolean "AND" operator and wildcard characters as appropriate.

This study involves the history of mining activity at the Kamioka Mine and the effects of environmental cadmium pollution in the Jinzu River Basin, Toyama Prefecture, Japan. The evolution of the disease is established with discussion of its initial appearance and development in affected people and the medical discoveries about the disease. With an understanding of the historical context, the mechanisms of cadmium transport and exposure are explained. Finally, the consequences on society and public health are investigated, which includes disproportionate effects on women and the elderly, loss of livelihood, shortened lifespan, etc.

Location and Topography

The study location is known as the endemic area of itai-itai disease, which covers an area of 1,500.6 hectares along the Jinzu River Basin in Toyama Prefecture, Japan (Figure 1) (Figure 2). The study area contains rice paddy fields in the Toyama Plains near Fuchu Town (ICETT, 2010). The source of the pollution, the Kamioka Mine, is located along the Takahara-Jinzu River in Gifu Prefecture, approximately 30 km upstream (south) of the rice fields. The study area, more generally, is located on the northwest coast of Central Japan. Figure 2 shows the location of the endemic area and Kamioka Mine.

Toyama Prefecture contains five major rivers. The Jinzu River runs through the endemic area, spanning 120 km and flowing northward into Toyama Bay of the Japan Sea (Aoshima, 2016). The basin area is approximately 2,720 km^2, and the elevation varies from 200 to 2,000 m (Admojo et al., 2017). The Jinzu River originates at the boundary of the Gifu and Toyama Prefectures, where it is fed by two source streams: the Miya and Takahara Rivers (Figure 2) (Aoshima, 2016). The Miya River originates in Mount Kaoredake, which has an approximate elevation of 1,600 m (ICETT, 2010). The Takahara River originates in the Northern Japan Alps, which has an approximate elevation of 3000 m (Aoshima, 2016). The Jinzu River passes through terraced hills, and near Oosawano Town, the land begins to fan out into the Jinzu River Basin (Figure 2) (Aoshima, 2016).

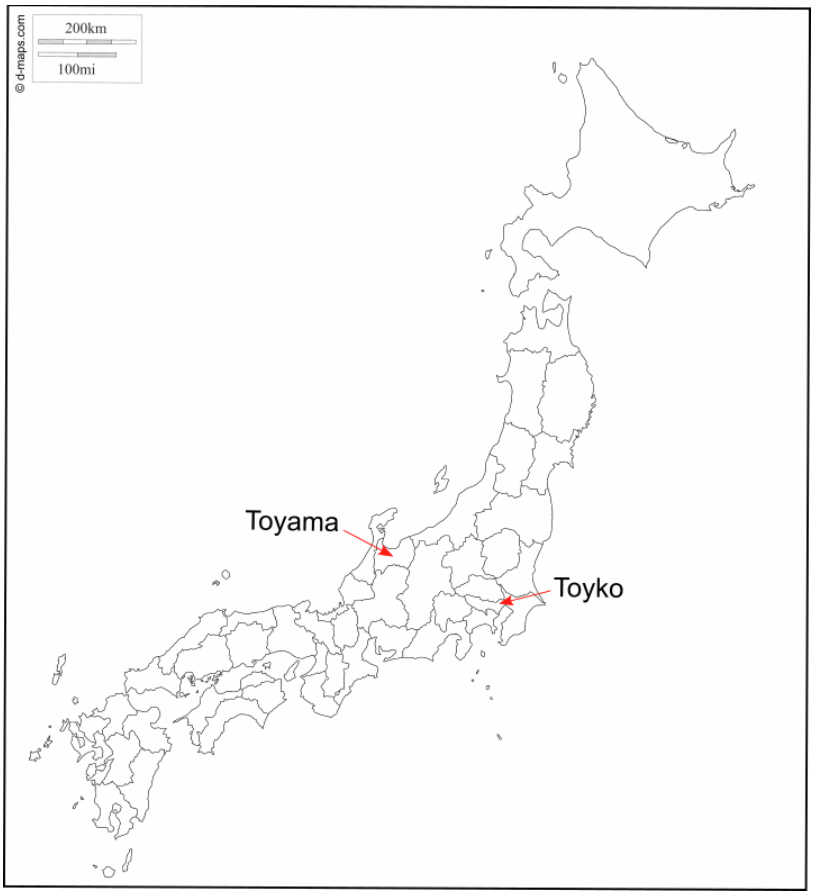

Figure 1 Location of Toyama Prefecture in Japan. Map was modified from https://d-maps.com/carte.php?num_car=24833&lang=en

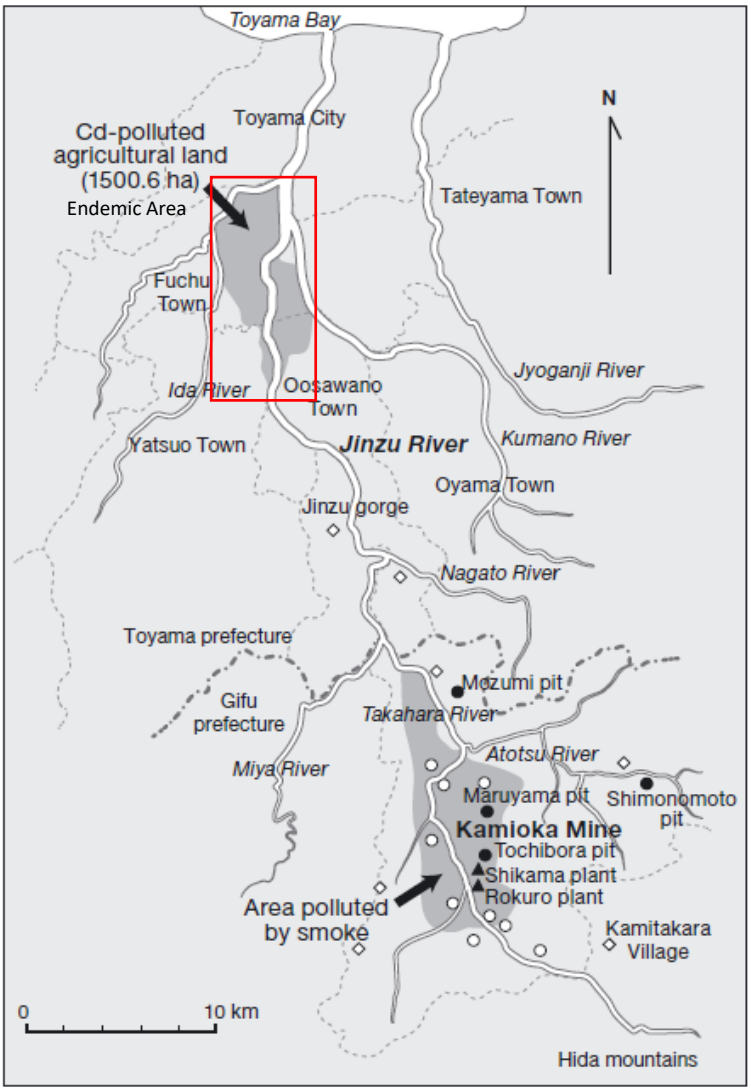

Figure 2 Map of study area. The red rectangle shows the endemic area of itai-itai disease near Fuchu Town (Kaji, 2012)

As the Takahara River flows down from the mountains, it passes through the Kamioka mining region (Figure 2): the region extends approximately 10 km east-west and 20 km north-south (ICETT, 2010). The rice fields located in the endemic area are supplied by irrigation canals from the Jinzu River (Figure 3).

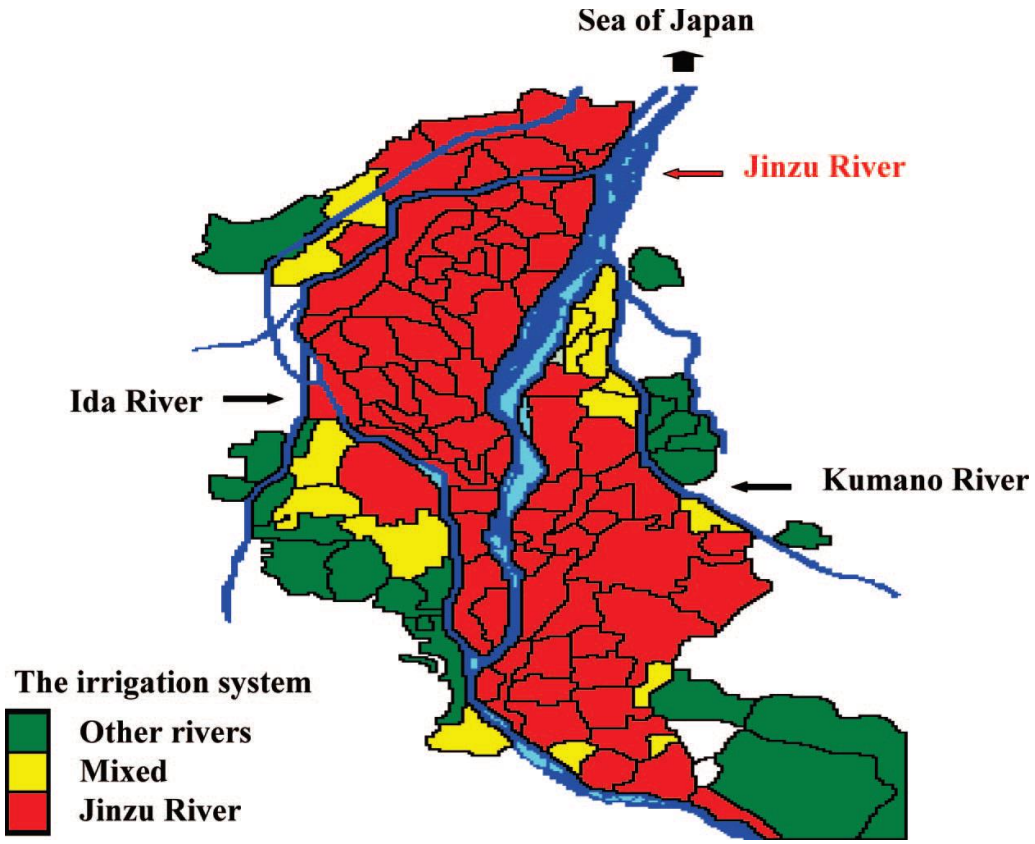

Figure 3 Irrigation sources for farmland in the endemic area (Uetani et al., 2007)

Lithology

The Toyama Plains is a sedimentary basin that resulted from continental rifting forming back arc basins in the Early Miocene (Nakajima et al., 1998) . Arc-arc collisions rapidly uplifted the Japan Alps to the South of the basin, especially during the Quaternary (Ishiyama et al., 2017) This uplift resulted in high rates of sedimentation as new and old fans formed from rivers flowing down the mountains (Kamishima & Takeuchi, 2016; Nakajima et al., 1998). The uppermost sedimentary layer in the basin consists of alluvial fan deposits of gravel, sand, and mud (Figure 4). This layer lies atop 5^{+} km thick sediments from the Neogene Period (Ishiyama et al., 2017).

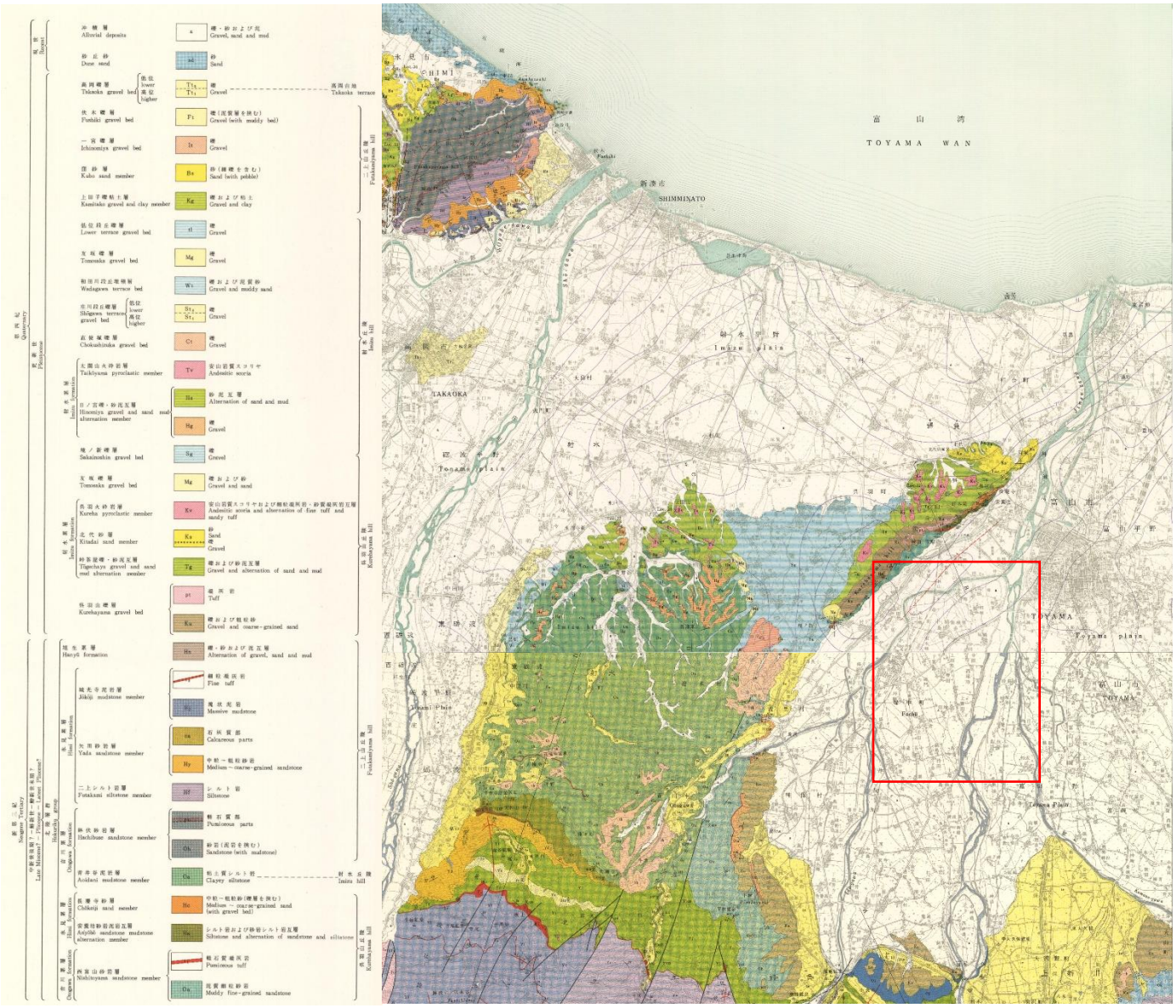

Figure 4 Geologic Map of Toyama Prefecture. The study area is found within the red rectangle. Maps taken from https://www.gsj.jp/

Soils

The Jinzu River Basin primarily consists of Gray Lowland soil, which forms on alluvial plains from Holocene parent material (Amano, 1985) . It is minimally developed with gray to gray-brown subsurface horizons and moderate permeability (Makino et al., 2006). Based off soil samples from Toyama, the texture is classified as a sandy loam (15.3% clay, 17.6% silt, and 67.1% sand) (Makino et al., 2006).The soils remain submerged in water for at least three

consecutive months during the warm season, which is conducive for rice paddy cultivation (Datta, 1981). Japanese lowland soils are generally acidic with an average pH of 5.5 in the plow layer (Datta, 1981).

Climate

The climate of north-central Japan is temperate with high rainfall. The average air temperature in Toyama Prefecture from 1950 to 1970 was approximately 13.5 °C with an average annual precipitation of approximately 2404 mm (Table 1). Precipitation is generally consistent throughout the year and it is especially high during the summer rainy season (June to July). The months of April to September correspond to the rice growing season due to high precipitation and sunny conditions. Also, the average temperatures are highest from June to September.

Table 1 Normal temperature and precipitation monthly values from 1950 to 1970. Data obtained from the Japan Meteorological Agency (JMA)

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Avg
Temperature (°C)	2.0	2.4	5.5	11.4	16.6	20.2	24.6	25.9	21.6	15.6	10.3	5.4	13.5
Precipitation (mm)	294.4	184.9	159.8	137.5	129.8	196.9	254.3	190.8	232.2	163.7	182.3	277.4	2404.0

Mining History

The Kamioka Mine first began major mining operations in 1589, when silver was discovered (ICETT, 2010). The Tokugawa shogunate gained control of the mines in 1692, and they continued to mine for silver, copper, and zinc until their demise (ICETT, 2010).

After the Meiji Restoration in 1868, the new government put the Mitsui Clan, one of the largest private capital groups, in charge of the Kamioka Mining region in order to restore production (ICETT, 2010; Kaji, 2012). With westernization occurring in Japan, Mitsui began in 1887 to implement western technology and management practices to produce lead and zinc (ICETT, 2010; Kaji, 2012). In 1890, the residents of Kamioka Town filed complaint for the pollution caused by the recent installation of rotary furnaces (Yoshida et al., 1999). In response, Mitsui installed a detoxification chamber to remove heavy metal particles from the dust exhaust (ICETT, 2010; Kaji, 2012).

Since 1905, the mining operations have focused primarily on zinc ore, which had been previously been discarded as an impurity (ICETT, 2010; Yoshida et al., 1999). To improve yield from the poor-quality ore, Mitsui refined its ore-dressing and separation process in 1901 with the installation of Potter's preferential floatation system (Yoshida et al., 1999). In 1909, froth floatation was introduced, which uses surfactants and wetting agents. (Yoshida et al., 1999). This process resulted in finer particles in the tailing slurry, which was dumped into the Jinzu River. Around 1912, the first occurrences of itai-itai disease began to appear (ICETT, 2010).

In 1931, local farmers, peasants, and fishermen were represented by an organization to request that Mitsui establish proper facilities to prevent pollution; Mitsui complied by building a tailing dam in the Shikamadani Valley (Yoshida et al., 1999). However, production of zinc and zinc waste increased fourfold during 1935-1945 to meet the demands of World War II (ICETT, 2010). Also, the mine began producing zinc and sulfuric acid in 1943, and cadmium in 1944.

After World War II, the metal division of the company was separated from the main organization, Mitsui Mining Co., Ltd, and became the Mitsui Mining and Smelting Co., Ltd. (ICETT, 2010). Japan experienced high economic growth from 1950 to 1975, and productivity of

the mine increased over tenfold (ICETT, 2010). This period of growth also included innovative changes. In 1966, the company rehauled the ore dressing process from the direct bulk differential flotation process to integrated bulk differential process. This process could treat a greater amount of ore, which both increased the amount of tailing waste and decreased particle size of the waste (Yoshida et al., 1999). As the global oil crisis occurred in the 1980s, mines began to close, and the Kamioka Mining Co., Ltd. became an independent company in 1986 (ICETT, 2010). Today, the company and the Kamioka Mine remains internationally competitive (ICETT, 2010).

Disease History

Around 1912, the first cases of an unknown disease started to appear in the downstream basin of the Jinzu River (ICETT, 2010). Locals began calling it itai-itai disease to describe the extreme pain that victims experienced (in Japanese, "itai" is used to express pain). Many cases began to appear around 1935, but since the disease was endemic in nature, research did not begin until after World War II (Aoshima, 2016; ICETT, 2010). In 1946, the first medical evaluations began as the local agricultural association requested an investigation from Kanazawa University (Aoshima, 2016). The following year, researchers published a paper describing the condition as a rheumatoid disease (Aoshima, 2016). They found that many cases appeared in the Jinzu River basin, but there were no cases in the neighboring Ida River Basin (Aoshima, 2016). They initially suspected the cause was lead poisoning from the Kamioka Mine, and blood tests were conducted on patients to see if they had lead-induced anemia (Aoshima, 2016).

Concurrently in 1946, Dr. Noburu Hagino, a physician, returned from military service and reopened his private clinic in Fuchu Town, Toyama Prefecture (Aoshima, 2016; Yoshida et al., 1999). He saw many patients with this unknown disease who complained of bone pain (later characterized as osteomalacia), especially in the pelvic girdle and legs while moving or walking

(Aoshima, 2016; Yoshida et al., 1999). The disease seemed to be occurring the most in women over the age of 40 years (Aoshima, 2016).

However, itai-itai disease was not reported to the public and recorded in social and medical history until 1955. The next 35 years of itai-itai research and studies consist of three periods as described by Aoshima (2016), "(1) an early phase of epidemiology, symptom characterization and attempts at treatment (1955−1961); (2) a middle period during which diagnostic criteria were formalized and research focused on the influence of heavy metal contamination, particularly Cd; and (3) a third period (around 1970−1990) in which the role of Cd accumulation in disease etiology was firmly established" (Aoshima, 2016).

The first period began in 1955: Dr. Hagino and others revealed itai-itai disease to the public and presented their research at a medical research meeting (Aoshima, 2016). Despite many early reports identifying malnutrition, hard farming labor, and multiparity or menopause as the cause of the osteomalacia, Dr. Hagino and Dr. Kin-ichi Yoshioka, an agronomic scientist, investigated other possibilities as the cause of the disease (Aoshima, 2016; Yoshida et al., 1999). In 1961, after Dr. Jun Kobayashi published a study on the cadmium content in contaminated rice, Dr. Hagino and Dr. Yoshioka published a study to investigate cadmium as a possible cause, and they reported that the disease occurred and was restricted to areas of farmland fed by the Jinzu River Basin (Aoshima, 2016; Yoshida et al., 1999). These areas had higher Cd levels in crops grown in the Jinzu River Basin compared to the neighboring Ida Basin and other basins.

The second period began in 1961 when the Ministry of Health and Welfare, the Ministry of Education, and Kanazawa University launched an investigation on Cd as a potential cause (Aoshima, 2016; Yoshida et al., 1999). Kanazawa University confirmed findings from the first period, which includes: itai-itai disease was restricted to the Jinzu River Basin, proximal renal

tubular dysfunction (the earliest stage of Cd poisoning) occurred in many local residents, and Kamioka Mine was the source of Cd pollution (Aoshima, 2016). However, the 1966 report also downplayed Cd as the primary cause, claiming that other factors (i.e. nutritional deficiencies) were also responsible. This angered victims, and the same year, the victims established the Task Force on Itai-Itai Disease to emphasize cadmium as the issue (Yoshida et al., 1999). In 1967, the Task Force began negotiations with Mitsui, but nothing materialized (Yoshida et al., 1999). As a last resort, they pressed a lawsuit against Mitsui with the support of residents and local government. In 1968, the Ministry of Health and Welfare declared and accepted chronic cadmium poisoning causes itai-itai disease in people with states of pregnancy, lactation, imbalance of internal secretion, aging, lack of calcium, etc. (Aoshima, 2016).

The lawsuit against Mitsui caused complications during the third period (Aoshima, 2016). During the lawsuit, Juguro Takeuchi, a professor at the School of Medicine at Kanazawa University, testified for Mitsui (Kaji, 2012) . Before the lawsuit, Takeuchi had researched and accepted cadmium as the cause for itai-itai disease (Kaji, 2012) However, in his testimony, he denied cadmium as the cause and claimed vitamin D deficiency was responsible for causing itai-itai disease (Kaji, 2012). His motivations for denying his previous research are not known (Kaji, 2012). Research firmly established the relationship between the disease and cadmium (Aoshima, 2016). Further research was conducted to better understand the relationship between Cd exposure and health effects. Epidemiological studies measured levels of proteinuria (abnormal levels of protein in urine) of residents in Cd-polluted areas throughout Japan (Aoshima, 2016). Results showed that many residents in the Cd-polluted areas had renal tubular dysfunction. Also, the relationship between amount of Cd or exposure length and severity of renal tubular dysfunction was clarified (Aoshima, 2016).

MECHANISMS OF CADMIUM TRANSPORT & EXPOSURE

Cadmium is a highly toxic heavy metal, which naturally occurs in soils at concentrations of 0.1-1 mg Cd kg^{-1} and is commonly associated with zinc, lead, and copper ore (Faroon et al., 2012; Smolders & Mertens, 2012). In natural surface water and groundwater, concentrations are usually <1 µg/L (Faroon et al., 2012). In the general environment, it only occurs as the divalent form (Cd^{2+}) and it does not readily oxidize or reduce (Faroon et al., 2012). In freshwater, cadmium can exist as an ion or it can form ionic compounds with inorganic or organic substances (Faroon et al., 2012). In comparison to other heavy metals, cadmium and cadmium compounds are relatively water soluble, making it easy for them to migrate in water (Faroon et al., 2012; Smolders & Mertens, 2012). For insoluble compounds of cadmium, they will settle and adsorb to sediments (Faroon et al., 2012). Soils in the contaminated rice paddies had a concentration of 1–10 mg Cd kg^{-1} (Smolders & Mertens, 2012). Upon release into the environment, cadmium remains for several decades and its bioavailability does not decrease appreciably in the long term (Smolders & Mertens, 2012; WHO, 2003). These characteristics allowed anthropogenic sources of cadmium to accumulate and persist in the Jinzu River Basin, which wreaked havoc on the environment and residents.

Pathways and Transport

The primary pathway was river transport from the source at Kamioka Mine via the Jinzu River. At the mine, Mitsui Mining Co., Ltd sorted and processed zinc ore by grinding the rocks and separated zinc using differential floatation and froth floatation. This produced fine waste particles known as ‘tailings’ with a relatively high Cd content. The tailing slurry was discarded into a sedimentation basin, however, the pond capacity was insufficient to prevent discharge into the Jinzu River, especially during heavy rains (Figure 5) (Aoshima, 2016; Kubota, 2020). In

1972, approximately 35 kg/month of cadmium was discharged into the river (Yoshida et al., 1999). Once in an aquatic system, cadmium can be transported as an ion in solution, but the majority are transported as suspensions that easily attach to soil particles through chelation and electrostatic and chemical adsorption (Aoshima, 2016). Farmers irrigated the rice paddies using the polluted water from the Jinzu River, which contaminated the soils (Figure 5). The immobilization of cadmium allowed it to accumulate in the paddy soil for approximately 60 years (Aoshima, 2016). When paddy fields were drained of water, cadmium mobilized towards crop roots, which led to bioaccumulation in crops (Figure 5).

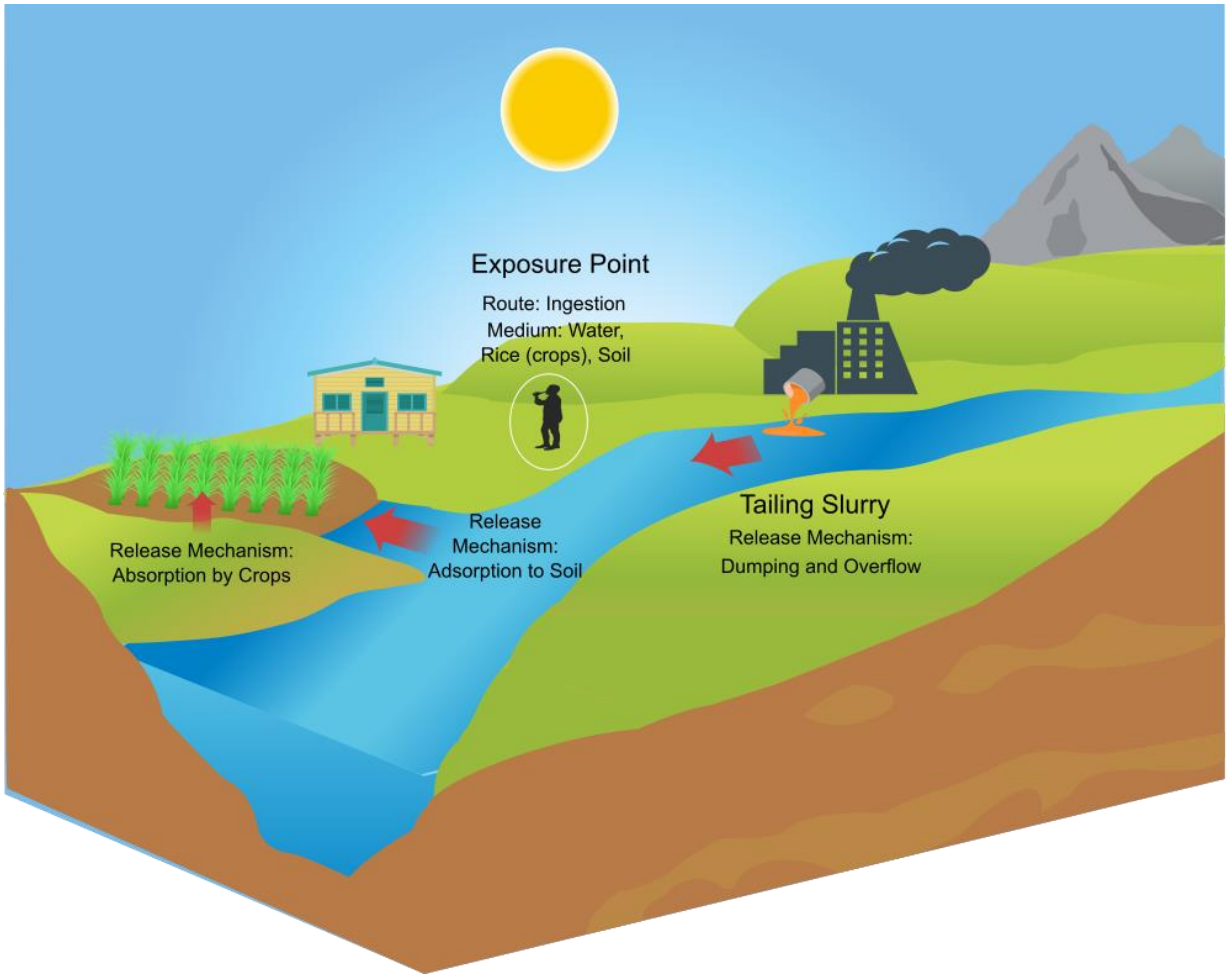

Figure 5 Pathways of cadmium transport and routes of intake. Vector images from vecteezy.com

Another pathway was industrial emission of cadmium-polluted dust. The smelting process involved roasting zinc concentrate in rotary furnaces, which released dust containing cadmium into the air (Figure 5). In response to complaints of air pollution, Mitsui installed a detoxification chamber to remove dust in 1893, which addressed the major concerns of air pollution (ICETT, 2010). Figure 2 shows that smoke pollution from the mine is confined to the surrounding area and the endemic area is approximately 30 km downstream of the mine.

Routes of Intake

The main route of cadmium intake is through ingestion. All other routes have insignificant contributions (WHO, 2003). Residents in the Jinzu River Basin consumed locally grown rice and used river water, which were polluted with cadmium (Figure 5). Intake through atmospheric exposure is minimal for the general population in Japan (Ikeda et al., 2004). This exposure route is not usually a concern except for people near industrial emitters.

Chemical Behavior in Paddy Soils

The biogeochemical behavior of cadmium (Cd) in soil depends on several factors, in particular, redox potential (Eh) and pH, which describe the availability of electrons and protons (Zhao & Wang, 2020). These geochemical properties change in a complicated manner during the rice growing season. Typically, fields are flooded for at least three months and end up being drained at two stages throughout the rice-growing season, namely, the late tillering stage (production of side shoots) to control tillering, and the mid-late grain filling stage to harvest the rice grains (Datta, 1981; Zhao & Wang, 2020) . The pattern of flooding dramatically changes the redox potential, pH, and ultimately the solubility of Cd (Zhao & Wang, 2020). When the fields are flooded, Eh in the soil decreases rapidly due to depletion of O_2 due to microbial processes, which promotes reduction reactions (Zhao & Wang, 2020). Coupled reactions occur as the

reduction reactions give rise to microbe-driven oxidation of organic substances in soil (Zhao & Wang, 2020). Reduction of sulfate to sulfide occurs, which precipitates cadmium sulfide (CdS), a relatively insoluble compound (Zhao & Wang, 2020). As a result, flooding of paddy soils decreases solubility of Cd due to CdS formation (Zhao & Wang, 2020). Also, reduction reactions consume protons/increase pH of the lowland soils in the area, which promotes sorption of Cd to the soil (Datta, 1981; Zhao & Wang, 2020).

Soil pH has a major influence on Cd solubility: with a one unit decrease in pH, Cd solubility in soil increases approximately fourfold (Zhao & Wang, 2020). In a large-scale paired soil-rice grain survey, the inverse relationship is clearly shown (Zhao & Wang, 2020). A change in pH from 7.0 to 5.0 caused the median Cd transfer ratio (i.e. rice grain to soil Cd concentration ratio) to increase 10-fold (from 0.08 to 0.85) (Figure 6). When fields are drained during the grain

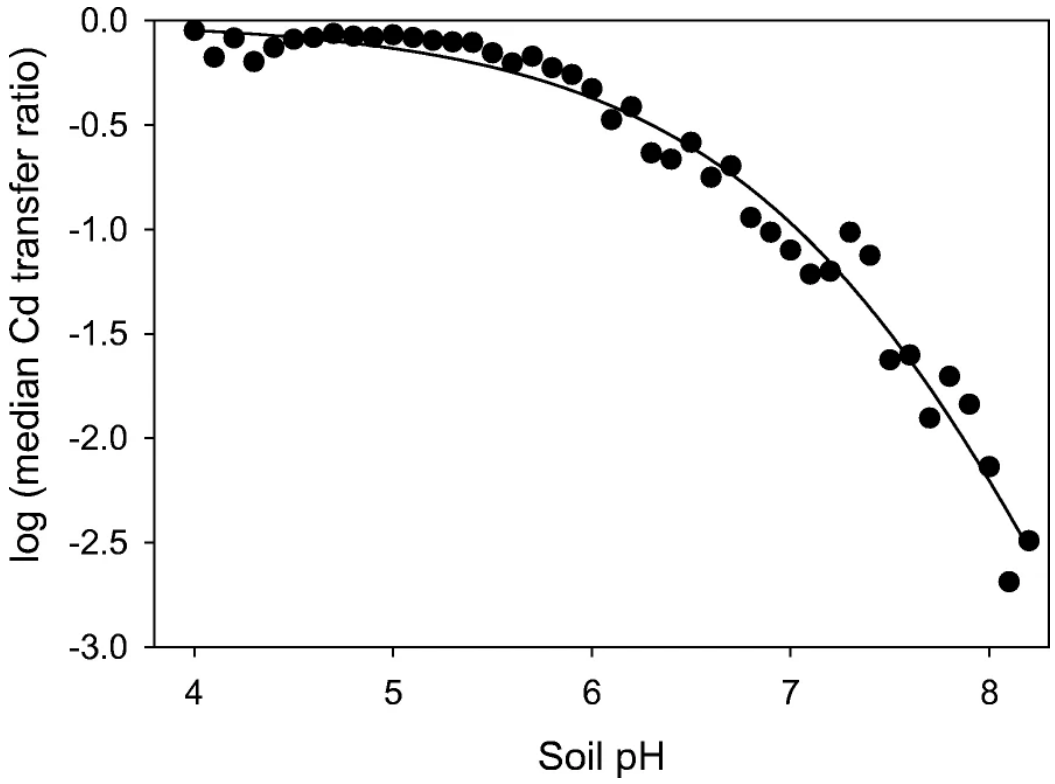

Figure 6 Median Cd transfer ratio (rice grain Cd / soil Cd concentration) (Zhao & Wang, 2020)

filling stage, about 80% of Cd accumulation in rice grain occurs due to soil pH reverting to its initial acidic value (Zhao & Wang, 2020). As the solubility of Cd increases, mobility towards the root surface increases and Cd is transported across the plasma membrane into the root cells (Zhao & Wang, 2020).

Along with the high mobility of Cd in soil, rice crops are particularly prone to Cd bioaccumulation due to element and plant factors including physiological regulation, solubility, translocation, and phytotoxicity (Zhao & Wang, 2020). Because Cd is a non-essential metal, plants do not regulate Cd uptake based on physiological limits. Experimental studies show an increase of cadmium in the soil (as a Cd^{2+} salt) will cause a linear increase in plant uptake assuming all soil properties remain constant (Smolders & Mertens, 2012). As discussed above, Cd has a relatively high solubility for a heavy metal, so it is mobile in mediums like soil, and can readily bioaccumulate (WHO, 2003). Not all elements move through the plant root, some elements may be sorbed to the root. However, others will transfer from the root to edible components like the shoot (Zhao & Wang, 2020). The gene expression of transporters in rice crops allows for efficient translocation of Cd to the stem, leaves, and grains (Zhao & Wang, 2020).

Typically, Cd levels are not high enough in paddy soils to cause phytotoxicity in rice crops (Zhao & Wang, 2020) . This is problematic as Cd can accumulate in rice grains with no apparent effect on crop yield, while in humans, it will cause toxicity (Zhao & Wang, 2020). Damages to crops began to appear in the 1890s coinciding with mine development. Farmers began seeing “milky” and “cloudy” river water due to increased cadmium discharge from the mine. The appearance of crop damage indicates that Cd levels were extremely high, however, the polluted irrigation water would continue to be used for the next several decades.

Levels of Cd Intake

The outbreak of itai-itai disease was caused by the consumption of Cd-polluted rice and drinking water from the Jinzu River Basin. Doses tended to be high because rice is a staple food in the Japanese diet. In non-polluted areas of Japan, rice accounted for 30-40% of daily Cd intake, while in polluted areas, rice accounted up to 70% of intake (Nogawa et al., 2018). The contaminated rice grains contained about 0.75 μg g^{-1} of Cd (Smolders & Mertens, 2012). Because Cd has a half-life of 15-20 years in humans, it can accumulate with regular consumption of contaminated rice (Smolders & Mertens, 2012). This makes chronic exposure at moderate levels much more dangerous than rare exposure at high levels (Smolders & Mertens, 2012). Because of this steady accumulation of Cd over an individual's lifetime, effects tend to manifest more in the elderly. Table 2 compares cadmium exposure at background concentrations to polluted concentrations in the endemic area of Fuchu Town. Surveys conducted in the 1960's revealed that Cd-D intake (dietary Cd intake) exceeded 300 μg/day (the point of severe poisoning) in various polluted areas of the Jinzu River Basin, with 600 μg/day being the highest intake for residents in the endemic area (Table 2) (Ikeda et al., 2004; Smolders & Mertens, 2012).

River water was another major source of exposure. Residents used river water from irrigation canals for drinking, cooking, washing, and bathing until around 1960 (Aoshima, 2016). With the inclusion of river water in the calculation of Cd intake, intake levels could be as high as 1,600 to 2,000 μg/day (Ikeda et al., 2004). For the general population in Japan, the dietary intake of Cd is about 8-20 μg/day (Table 2). According to the Joint FAO/WHO Expert Committee on Food Additives, the tolerable weekly Cd intake in 1972 was 400-500 μg per individual (WHO, 1984). Residents in the endemic area were exceeding the tolerable weekly intake in a single day.

Table 2 The human exposure to soil Cd at ambient conditions (away for point sources) and in the region where the Cd related itai-itai disease was first observed in the 1960s (Smolders & Mertens, 2012)

Exposure conditions	Soil Cd (mg Cd kg^{-1})	Grain Cd (mg kg^{-1}, fresh weight basis)	Dietary intake for adult (μg Cd day^{-1})	Cumulative lifetime intake (g Cd)
Non-contaminated (ambient)	0.1–1	0.01–0.10 wheat 0.02–0.20 rice	8–20	0.1–0.4
Contaminated (Fuchu, Japan)	1–10	0.20–2.0 rice	160–600	2–10
Limits	0.8–39	0.10–0.40	70 (WHO 1992–2009[a])	
	Various legislations	Cereal grain, wheat and rice FAO/WHO (CODEX, 2010)	25 (EFSA opinion, 2009[b]) 58 (WHO 2010[c])	

The lifetime Cd intake that is associated with severe Cd disease onset for 50% of the itai-itai patients is 3.8 g Cd and is 5.4 g Cd at death [32] Environmental exposure to soil Cd mainly occurs via the intake of contaminated food; grains or potatoes are the major contributors to the human Cd diet. Numbers have been compiled by the author based on [22] and [19]

[a]Provisional tolerable weekly intake of 7 μg Cd kg^{-1} body weight and converted here for an adult of 70 kg

[b]Opinion of the European Food Safety Authority defined as 2.5 μg Cd $week^{-1}$ kg^{-1} body weight and converted here for an adult of 70 kg

[c]Adopted in the 73th meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) June, 2010 and defined as a provisional tolerable monthly intake (PTMI) of 25 μg kg^{-1} body weight and converted here for an adult of 70 kg [34]

Effect of Nutritional Deficiencies on Cadmium Absorption

Early on, researchers suspected malnutrition as the potential cause of itai-itai disease. However, by 1968, Cd pollution became the accepted explanation. While malnutrition was not the primary cause of the disease, nutritional deficiencies can influence Cd absorption. The typical Japanese diet is low in iron due to low meat consumption and Fe absorption inhibitors, such as soybeans and green tea, which are traditional Japanese foods (Asakura et al., 2009). Instead of meat, rice and fish constitute a major part of their diet (Asakura et al., 2009). Deficiencies of zinc, iron, calcium, and dietary protein increase the toxicity and absorption of Cd. Cadmium is divalent similar to the essential nutrients (Zn^{2+}, Fe^{2+}, Ca^{2+}) (Holdaway & Wuyi, 2018; Smolders & Mertens, 2012) . According to Blevik (2012), individuals with Fe and Zn deficiencies have a Cd retention rate 15 times that of individuals with sufficient Fe and Zn intake. This conclusion is supported by an epidemiological study of U.S. children also found an inverse relationship between the indicators of iron status and blood Cd levels (Silver et al., 2013).

Previous epidemiological studies in adults also reached the same conclusion, but they differed in that they found significant associations between iron levels and urinary Cd (Silver et

al., 2013). Silver et al. (2013) found that Cd in urine was correlated with age not iron level, which is consistent with the tendency of Cd to accumulate over time. Cadmium can accumulate in the long term because only small amounts of cadmium (0.01-0.02%) are excreted each day (Kim, 2018). Therefore, blood Cd is a better indicator of recent exposure, while urine Cd is a better indicator of long-term exposure (Silver et al., 2013).

However, studies of iron deficiency and Cd absorption in Japanese populations have found conflicting results. Studies suggest that menopausal status is the primary factor affecting Cd absorption. According to Asakura et al. (2009), there is no association between any dietary habit, including Fe intake, and Fe deficiency among Japanese women. The only variables that showed a significant association with Fe deficiency was menstrual condition such as menstrual cycle regularity and amount of menstrual flow (Asakura et al., 2009). Pregnancy may also result in enhanced cadmium absorption due to upregulated iron absorption during the late stages of pregnancy (Kim, 2018) . While premenopausal women show associations of high cadmium concentrations and low iron stores, postmenopausal women do not (Kim, 2018). Other studies suggest that iron deficiency (whether it be dietary or menstrual) does not impact Cd absorption. According to Tsukahara et al. (2003), the current level of iron deficiency does not have a significant effect on Cd body burden or kidney dysfunction among Japanese women in the general population. Women with anemia or iron deficiency did not have significantly elevated levels of Cd biomarkers in urine (urinary Cd, α_1-microglobulin, β_2-microglobulin) compared to healthy women (Tsukahara et al., 2003). Horiguchi et al., (2004) suggests that age, rather than iron deficiency, is an independent factor affecting Cd absorption, and that young women are at higher risk. Due to various conflicting studies on the effect of iron deficiency and Cd absorption, the consensus is unclear, and more studies should be conducted.

Evaluation of Nutritional Deficiencies in Residents

Based on literature research, all studies agreed that zinc deficiency increased Cd absorption. This section of my study examines the dietary intake of Zn to determine whether residents were at risk. For residents in the endemic area, zinc was present in the soils at high levels. A 1971-1976 survey by the Toyama Prefecture reported on Cd and Zn levels in rice and soil sampled from 31.3 km^2 of paddy fields in the Jinzu River Basin (Aoshima, 2016). The Zn levels in 1600 soil samples ranged from 5.3 to 865 ppm with a mean value of 59 ppm, which was 4 times higher than the mean value of 12.5 ppm from the 77 samples from uncontaminated areas (Aoshima, 2016) . As for Zn content in rice, the zinc content of unpolished rice samples did not differ between the endemic area and non-polluted areas (Zn: mean 25.2 vs. 24.9 ppm, range 9.8−78.3 vs. 19.7−40.3 ppm) (Aoshima, 2016). A report from the Ministry of Health and Welfare compared the nutritional intake of families with itai-itai disease, families in the endemic village of Fuchu Town, and families in rest of the Toyama prefecture (Tsuchiya, 1969). However, the study does not mention the duration over which intake was measured. Given similarities with other measurements, a unit of mg/day seems reasonable for the report.

With a typical serving size for rice of 1 cup (185 g), the single serving of rice should contain roughly 4.662 mg of Zn because the rice samples contained an average of 25.2 mg/kg of Zn (25.2 ppm). The 2005 Dietary Reference Intake (DRI) of Japan has a recommended daily allowance (RDA) of 9 mg for adults (MHWL, 2004) . There are newer DRIs available, but the 2005 version was referenced since it was released closer in time to the study period, and agricultural lifestyles have become less prevalent in modern times. A single serving of rice has over half the RDA. Based on these measurements, Zn deficiency is not a major concern.

Literature research found no papers that conflicted with the theory that calcium deficiency increases Cd absorption. So next I examine the question whether dietary intake of calcium placed residents at risk. Families with itai-itai disease had a mean calcium intake of 408.5 mg, families in Fuchu Town had an intake of 374.5 mg, and families in the rest of the prefecture had an intake of 331.0 mg (Table 3). While families with the disease had the highest calcium intake, this value is still well below recommended dietary intake. The 2005 DRI for Japan recommends a calcium intake of at least 600 mg/day (MHWL, 2004). This comparison suggests that residents of Toyama Prefecture may have experienced increased Cd absorption due to calcium deficiency.

Table 3 Comparison of nutritional intake (1955) (Tsuchiya, 1969)

	Family with Ouch-Ouch disease	Most endemic village	Total farming areas of Toyama prefecture
a. Calorie (Cal)	2139.0	2209.0	2236.6
b. Protein (g)	72.8	73.7	62.46
c. Fat (g)	14.5	17.1	16.6
d. Calcium (mg)	408.5	374.5	331.0
e. Phospate (mg)	1556.0	1432.0	1433.0
f. Iron (mg)	34.0	15.0	22.8
Vit. A (Int. U.)	1325.0	1754.0	1376.0
Vit. B_1 (mg)	0.84	1.08	1.05
Vit. B_2 (mg)	0.57	0.65	0.66
Vit. C (mg)	69.0	93.0	64.5

Public Health Impacts

Development and Effects of Itai-Itai Disease

Cadmium is extremely toxic to humans, even in small amounts. As chronic poisoning occurs from long term exposure, it can cause various symptoms and diseases. Itai-itai disease is the most severe form of Cd poisoning, which is characterized by renal tubular dysfunction and bone fracturing caused by osteomalacia and osteoporosis. The disease is considered to be a type of Fanconi syndrome since they share very similar characteristics (Tsuchiya, 1969). Other symptoms can include anemia, diarrhea, stomach pains, severe vomiting, reproductive failure and infertility, psychological disorders, immune system damage, DNA damage, and cancer (Fatima et al., 2019; Horiguchi et al., 2010).

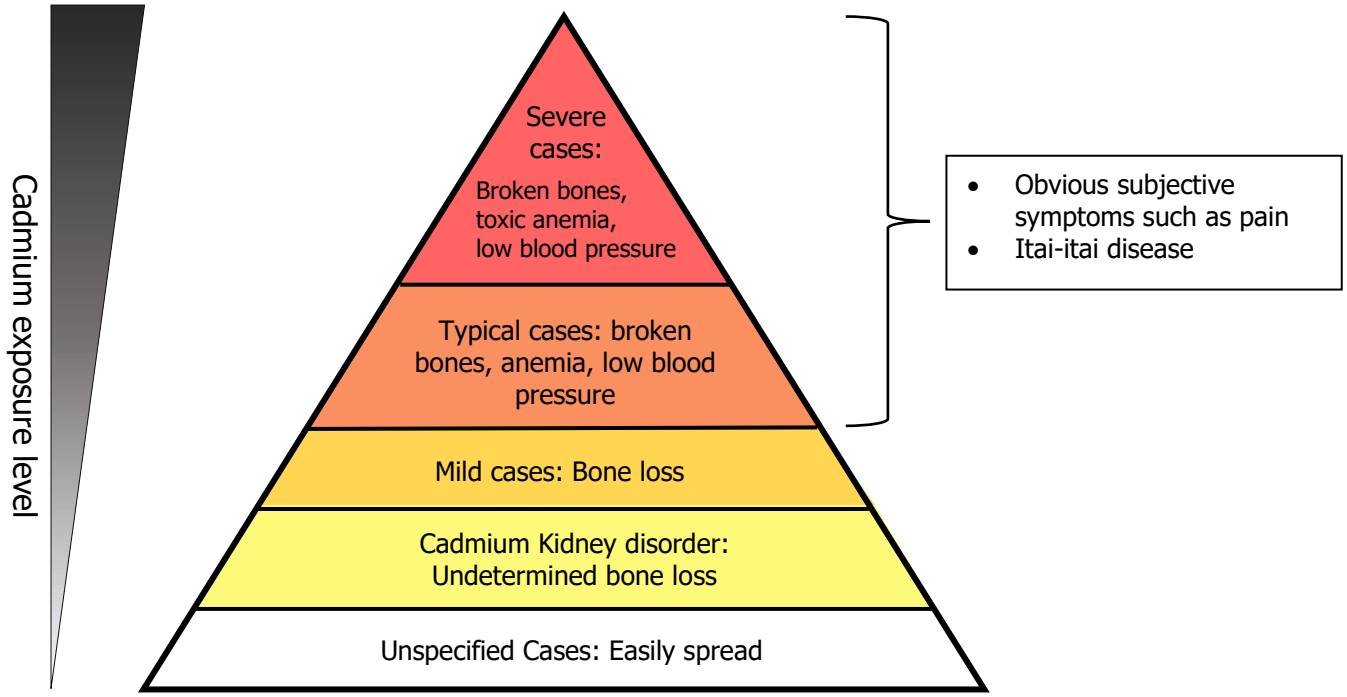

Figure 7 Sympoms of cadmium poisioning with increasing cadmium exposure. Figure remade from ICETT (2010)

As cadmium enters the body, it travels through the bloodstream to the liver and bonds with proteins to form complexes that are transported to the kidneys (Fatima et al., 2019) . With

chronic exposure, multiple proximal renal tubular dysfunction and renal glomerular dysfunction can develop in the kidneys, which affects the filtering mechanisms (Fatima et al., 2019). In the earliest stages of proximal renal tubular dysfunction, Cd damages the tubules in the kidneys, causing excessive urinary excretion and impaired reabsorption of essential nutrients: this includes phosphate, calcium, amino acids, low molecular weight proteins such as β_2-microglobulin, and bicarbonate (Aoshima, 2016; Fatima et al., 2019; Horiguchi et al., 2004). As the disorder progresses, renal glomerular damage occurs and eventually progresses to renal failure (Fatima et al., 2019). Due to the loss of calcium and phosphate from excessive excretion and alteration in renal metabolism of vitamin D, bone metabolism is disrupted (Faroon et al., 2012; Horiguchi et al., 2010). The resulting internal vitamin D deficiency causes calcium reduction in bones (Kido et al., 1990). Also, anemia can occur due to insufficient renal production of erythropoietin, an erythroid-specific glycol-protein hormone that promotes production of erythrocytes (red blood cells) (Horiguchi et al., 2010).

Eventually, chronic Cd exposure develops into itai-itai disease. This stage is characterized by osteoporosis and osteomalacia. Figure 7 shows the progression of cadmium exposure levels and the health effects; bone loss begins in the earliest stages of Cd-toxicity and continues to progress in severity. Osteoporosis is when the body loses too much bone tissue and/or cannot regenerate bone tissue fast enough, which results in bone thinning. Osteomalacia prevents bones from mineralizing or hardening (bone demineralization), which results in bone softening. As a result of these bone diseases, patients can form bone fractures, looser zones (pseudo-fractures), deformed spines, and severe generalized pain (Horiguchi et al., 2010). Figure 8 shows a patient with bone and spine deformation. The exact mechanism of Cd toxicity on bone is not fully understood, but studies suggest that bone changes are mediated through renal tubular

disorder: disrupted vitamin D metabolism results in imbalanced calcium absorption and excretion in the intestines and impaired bone mineralization (Faroon et al., 2012; Youness et al., 2012) . However, it is possible that there are other causes that mediate bone effects (Faroon et al., 2012). To emphasize the severity of itai-itai disease, patients experienced debilitating pain from even the simplest of actions such as walking, coughing, or laughing at late stages of the disease (Faroon et al., 2012).

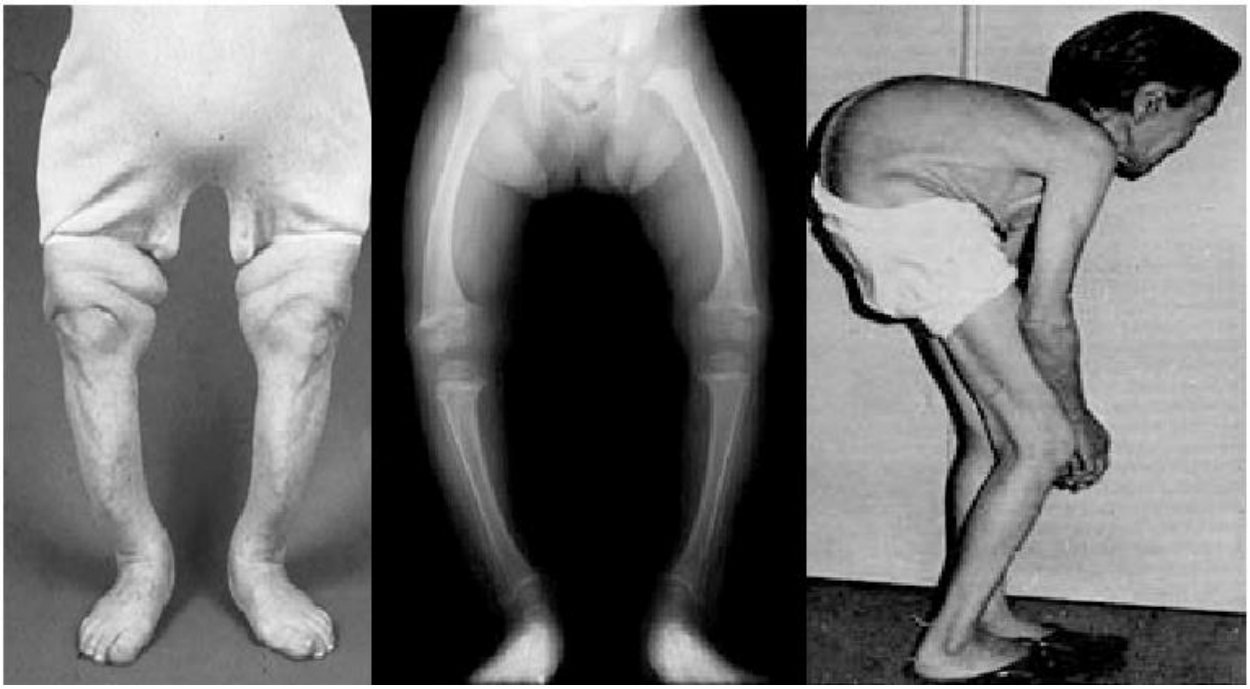

Figure 8 Effect of Cd toxicity on bone structure- Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Itai-itai-disease-and-bone-structure_fig3_273123192 [accessed 5 Mar, 2020]

Along with its debilitating effects, itai-itai disease can result in shortened lifespan for patients. Several studies reach the same consensus of high mortality and shortened lifespan for patients. Kawano et al. (1984) conducted a follow up study from 1967 to 1982 of 117 patients and 117 controls matched for age, sex, and residential area. Results showed 85 deaths (72.6%) in the patient group and 59 (50.4%) in the control group during the study period. After the 116 pairs (one pair was excluded) were evaluated, the higher number of deaths in patients was found to be

statistically significant ($p < 0.001$) (Kawano et al., 1986). Nakagawa et al. (1990) expanded the previous study by extending the observation period from 1967 to 1987 and included three subject groups: patients with itai-itai disease, subjects suspected of having the disease, and controls. There were 95 subjects in each group, and they were matched for age, sex, and residential area (Nakagawa et al., 1990). Results showed 84 deaths (88.4%) in patients, 76 deaths (80.0%) in suspected subjects, and 58 deaths (61.1%) in controls during the study period (Nakagawa et al., 1990). While there was not a significant difference in deaths between the patient and suspected subject groups, the number of deaths in the patient and suspected subject group were significantly higher than the control group ($p < 0.1$) (Nakagawa et al., 1990). At the end of the survey, the patient group and the suspected subject group had a lower survival time (life expectancy) than the control group by 2.2 and 1.6 years respectively (Nakagawa et al., 1990). Along with its debilitating effects, itai-itai disease can result in shortened lifespan for patients. Several studies reach the same consensus of high mortality and shortened lifespan for patients. Kawano et al. (1984) conducted a follow up study from 1967 to 1982 of 117 patients and 117 controls matched for age, sex, and residential area. Results showed 85 deaths (72.6%) in the patient group and 59 (50.4%) in the control group during the study period. After the 116 pairs (one pair was excluded) were evaluated, the higher number of deaths in patients was found to be statistically significant ($p < 0.001$) (Kawano et al., 1986). Nakagawa et al. (1990) expanded the previous study by extending the observation period from 1967 to 1987 and included three subject groups: patients with itai-itai disease, subjects suspected of having the disease, and controls. There were 95 subjects in each group, and they were matched for age, sex, and residential area (Nakagawa et al., 1990). Results showed 84 deaths (88.4%) in patients, 76 deaths (80.0%) in suspected subjects, and 58 deaths (61.1%) in controls during the study period (Nakagawa et al.,

1990). While there was not a significant difference in deaths between the patient and suspected subject groups, the number of deaths in the patient and suspected subject group were significantly higher than the control group ($p < 0.1$) (Nakagawa et al., 1990). At the end of the survey, the patient group and the suspected subject group had a lower survival time (life expectancy) than the control group by 2.2 and 1.6 years respectively (Nakagawa et al., 1990). shows mean survival time of subjects throughout the study period. As more elapsed, the gap between the control and the patient survival time significantly increased. Figure 10 displays

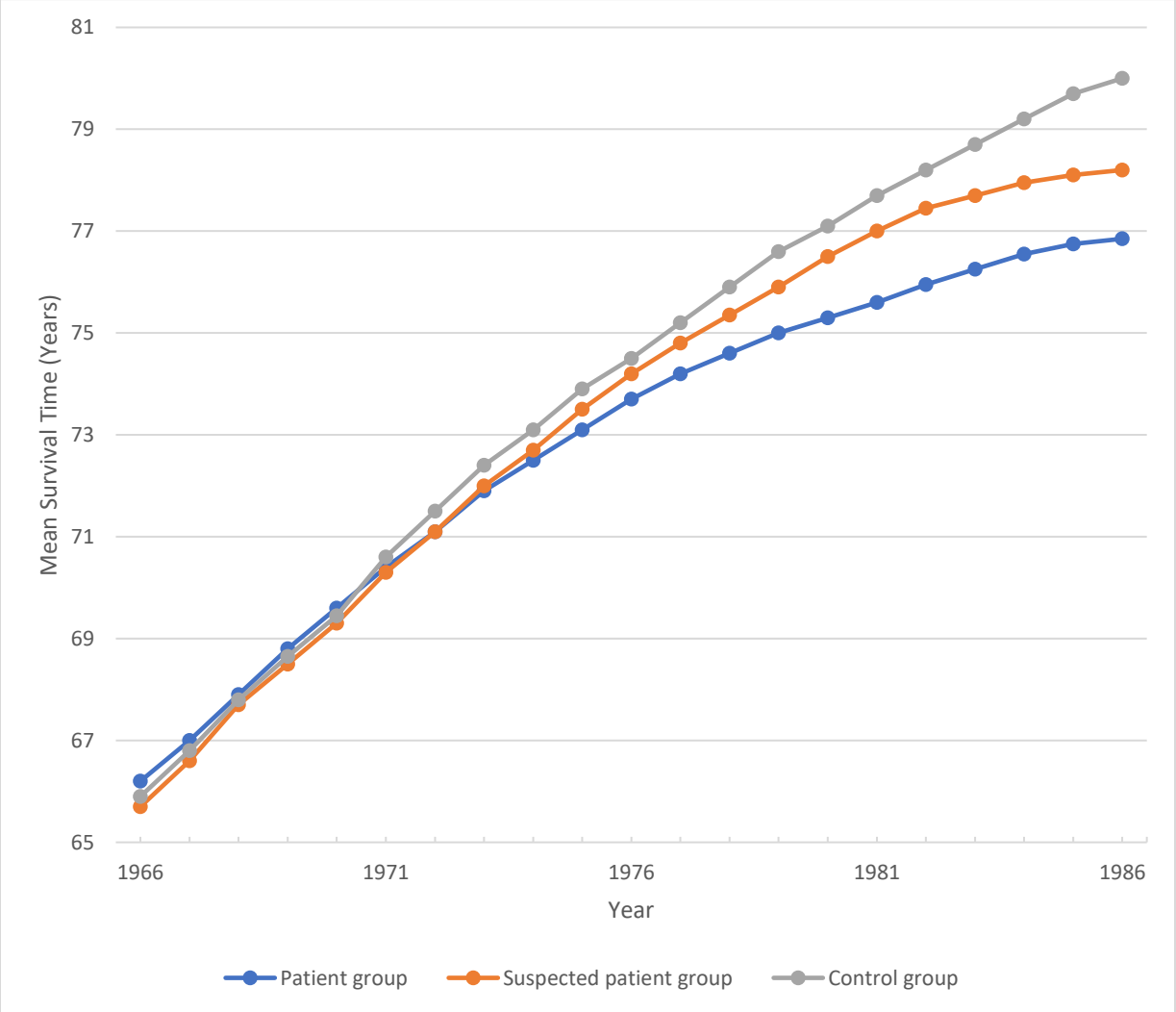

Figure 9 Mean Survival Time (mean ages of survivors and ages at death) each observation year in the patient, suspected subject, and control groups. Figure remade from Nakagawa et al. (1990).

the cumulative survival rates of the three subject groups. With increasing time, the cumulative survival rates of the three groups decreased. The rate of the suspected subject and the control group was the virtually the same for the first ten years, but after 12 years, the gap of the rate progressively increased.

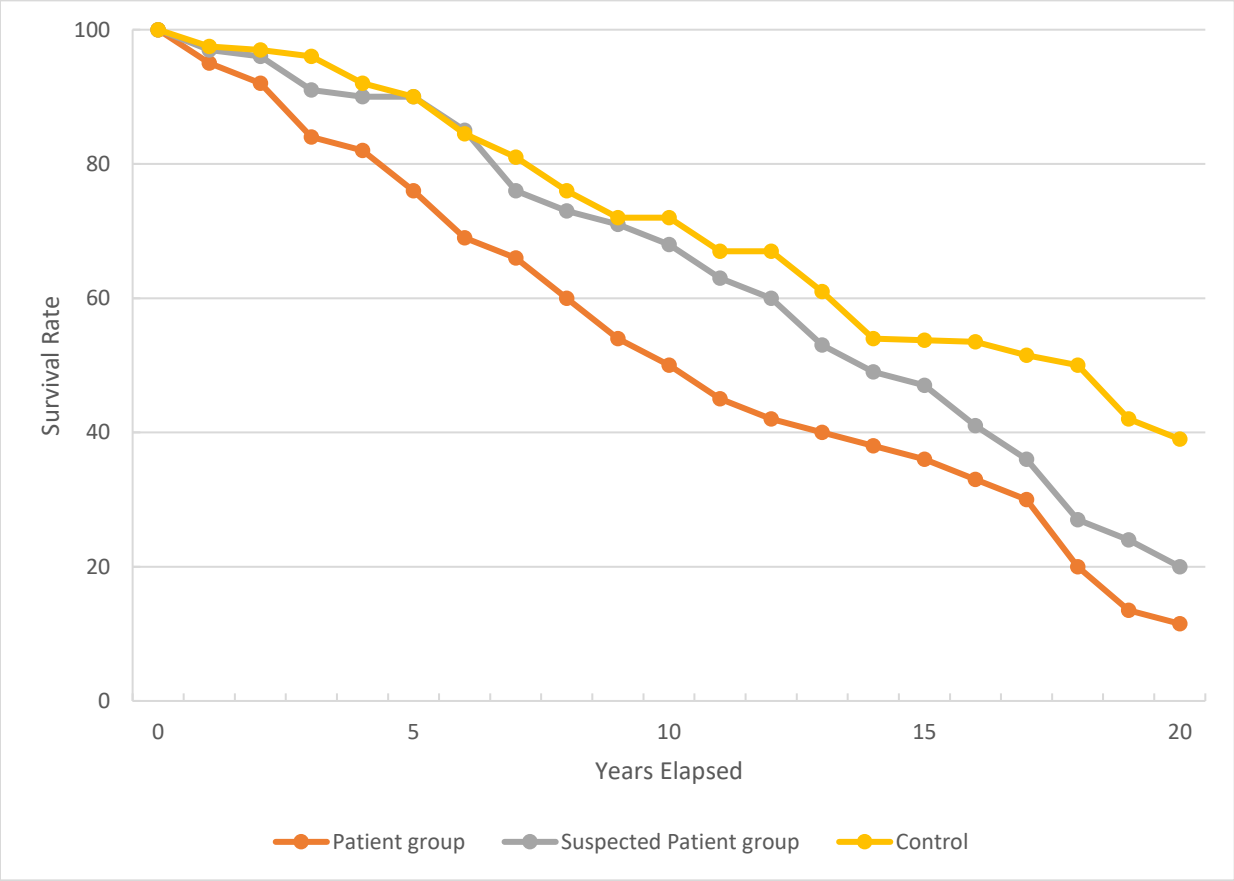

Figure 10 Cumulative survival rates for patient, suspected subject, and control groups. Figure remade from Nakagawa et al. (1990)

Starting in 1967, to be officially eligible for compensation by the Toyama prefectural government as a patient with itai-itai disease, the patient had to meet the following conditions: residence in an area heavily polluted with Cd, non-congenital development of renal tubular dysfunction, and development of osteomalacia and osteoporosis (which is confirmed by X-ray, biopsy, or bone autopsy) (Aoshima, 2016). As of October 2015, there have been 200 officially

recognized patients (195 women and five men) suffering from itai-itai disease (Aoshima, 2016). 97.5% of the patients were women. Only five patients were alive as of October 2015 (three women and two men) (Aoshima, 2016). Since systematic epidemiological surveys were not conducted by the government until 1962 and patient certification did not begin until 1967, there is not an accurate account of patients affected by itai-itai and the number of affected patients could be even larger (Aoshima, 2016). Several decades passed from the first initial appearance of the disease around 1912 to initial research. In the 1962 government survey, the survey recognized a total of 223 cases, including 150 suspected cases (Tsuchiya, 1969). The survey criteria for recognizing itai-itai patients was likely less stringent than the 1967 patient certification program. According to Kaji (2012), the number of affected patients between 1910 and 2007 is estimated to be roughly 400 people.

Gender-Related Differences

As shown in the official government count of patients, itai-itai disease occurred mostly in women, which can be explained by a few potential factors attributed to gender differences. It has been shown that populations with low body stores of calcium, iron, or other dietary components due to multiple pregnancies and/or dietary deficiencies could have increased cadmium absorption in the gastrointestinal tract (Faroon et al., 2012). With the high prevalence of the disease in women, they are thought to be at higher risk for bone diseases due to physiological changes during pregnancy and lactation (Nishijo et al., 2004). In the “Mechanisms of Cadmium Transport & Exposure” section, Fe intake of residents in the Jinzu River Basin was found to be adequate, however, premenopausal women may have Fe deficiency due to menstruation.

Increased disease prevalence and severity of effects on women can also be attributed to several other risk factors and mechanisms. A literature review of population-based research by

Nishijo et al. (2004) identified six risk factors in Cd health effects in women: (1) more serious type of renal tubular dysfunction, (2) difference in calcium metabolism and its regulatory hormones, (3) kidney sensitivity; difference in P450 phenotype, (4) pregnancy, (5) body iron store status, and (6)genetic factors. For the first factor, a study showed "hypo-phosphatemia [phosphate level in blood], hypercalciuria [calcium level in urine], and hypo-bacemia [calcium level in blood] were predominant in women despite a decrease in tubular reabsorption of Ca and P with increasing fractional excretion of β2-MG [microglobulin, a cell protein that is a urinary biomarker/indicator for renal tubular dysfunction]" (Nishijo et al., 2004). This suggests women experience more bone lesions and more severe renal tubular dysfunction compared to men (Nishijo et al., 2004). For the second factor, a population study in the Jinzu River Basin showed decreased bone density and increased levels of osteocalcin/bone Gla protein in women in a Cd-polluted area compared to controls (Nishijo et al., 2004). A study in the Kakehashi River Basin in Japan showed "a decrease in serum 1,25-dihydroxyvitamin D levels [measure of vitamin D body stores] in only women in concurrence with declining creatinine clearance [amount of blood per unit time cleared of creatine by the kidneys] and % tubular re-absorption phosphate (TRP) [percent of phosphate reabsorbed by the tubules]. In addition, "a decrease in serum 1,25-dihydroxyvitamin D and increase in serum parathyroid hormone (PTH) [blood calcium regulator] were more prominent in women than in men who had similar levels of renal tubular dysfunction" (Nishijo et al., 2004). These studies suggest that Cd-induced bone effects vary by gender (Nishijo et al., 2004). For the third and sixth factor, studies showed associations between Cd exposure and abundance of certain P450 enzymes in the liver and kidney (Nishijo et al., 2004). Cd exposure may influence the phenotype variation of the P450 enzymes, some of which affect vitamin D activation and blood pressure regulation (Nishijo et al., 2004). Also, phenotypes

are shown to vary by gender, but further research is required to explain gender differences between Cd body burden and phenotype variability of P450 enzymes (Nishijo et al., 2004). For the fourth factor, a 30-week study of uncomplicated pregnant women in a non-polluted area in Japan measured urinary excretion of proteins and enzymes indicative of renal tubular function (Nishijo et al., 2004). The means of β2-MG, α1-microglobulin (α1-MG), NAG increased, and a month after delivery, the values decreased to a normal range of non-pregnant women (Nishijo et al., 2004). The results suggest that Cd exposure enhanced changes in renal tubular re-absorption occurring during pregnancy (Nishijo et al., 2004). Contrarily, it may suggest the kidney is more sensitive to Cd during pregnancy (Nishijo et al., 2004). Another study was conducted on pregnant women with relatively low-blood Cd (<µg/l) in a non-polluted area in Japan (Nishijo et al., 2004). Blood samples were collected during pregnancy and five days after delivery – the blood Cd concentration was higher in the sample taken 5 days after delivery vs. the samples taken during the 30th gestational week (Nishijo et al., 2004).The change in blood Cd levels was pronounced for a 10 week period between the samplings, which supports pregnancy as a major factor in increased blood Cd (Nishijo et al., 2004). For the fifth factor, a study of Swedish women found that parity significantly influenced age-related increases in Cd body burden, which is thought to be due to increased iron absorption or increased Cd mobilization from liver to kidney during pregnancy (Nishijo et al., 2004). Another Swedish population study revealed higher blood Cd levels in non-pregnant women than in men, which is thought to be caused by increased iron absorption during menstruation (Nishijo et al., 2004).

Menopausal Differences

In addition to the gender differences, women with menopausal status show higher disease prevalence of itai-itai disease than young women, men, and children (Table 4) (Kakei et al.,

2013). This preferential distribution is reflected by the following findings. The age of disease onset is thought to range between 35 to 65 years and the severe stages of the disease tend to appear post-menopause – a report from the Ministry of Health and Welfare found in its study that clinically apparent cases of the disease only occurred in women over 47 years of age who had multiple pregnancies with the exception of a unconfirmed case of a 73 year old (Tsuchiya, 1969).

Table 4 Age, and sex distribution of patients, suspected subjects, and controls in 1967 (Nakagawa et al., 1990)

	Patients		Suspected subjects		Controls	
Age (y)	Men	Women	Men	Women	Men	Women
45–49		3		3		3
50–54		5		4		3
55–59		11		15		17
60–64		24		26		25
65–69		24		23		18
70–74		14		15	1	15
75–79	2	6	2	7	1	9
80–84		5		5		2
85–89		1				1
Total	2	93	2	93	2	93

Estrogen deficiency combined with Cd exposure is thought to be responsible for Cd-induced osteoporosis and increased prevalence of itai-itai disease in postmenopausal women, however, there is not substantial research on the topic (Kakei et al., 2013). Table 4 shows the preferential distribution of patients in a population study by Nakagawa et al. (1990). Of the 95 patients, 93 patients are women and all of them are over 45 years old, which is about the age that menopause generally occurs. Using ovariectomized rats as a model of postmenopausal women, Kakei et al. (2013) studied the combined effects of estrogen (Es) deficiency and Cd exposure on calcified hard tissues over a three-month period. Ovariectomized rats were divided into a control group and a Cd-exposed group (Kakei et al., 2013). Normal rats were also used and divided into a control group and Cd exposure group (Kakei et al., 2013). Concerning the effect of Es

deficiency on developing tooth enamel, electron micrographs of the enamel crystals showed partial defects in the crystal structure, like crystal perforations. Concerning the combined effects of Es deficiency and Cd exposure on the bone formation, soft x-ray radiographs revealed a labyrinthine pattern in the calvariae (top part of skull) of Cd-exposed, ovariectomized rats (Kakei et al., 2013). Electron micrographs of the calvariae revealed an increase of amorphous (shapeless) minerals in the calcified hard tissues. Also, the tibia of the Cd-exposed, Es deficient rats showed significantly greater distortion in the trabecular (spongy bone) architecture (Kakei et al., 2013). Figure 11 shows that the calvariae of the rat with combined effects had amorphous minerals and poorly developed lattice fringes, which indicates the failure of crystal nucleation in the calvariae.

These results revealed a couple key findings. When chronically exposed to Cd, amorphous minerals will increase in the bone due to the failure of crystal lattice nucleation, resulting in osteomalacia (Kakei et al., 2013). “After the menopause, Es deficiency may adversely affect osteoblast (bone synthesis cell) differentiation and thereby result in an

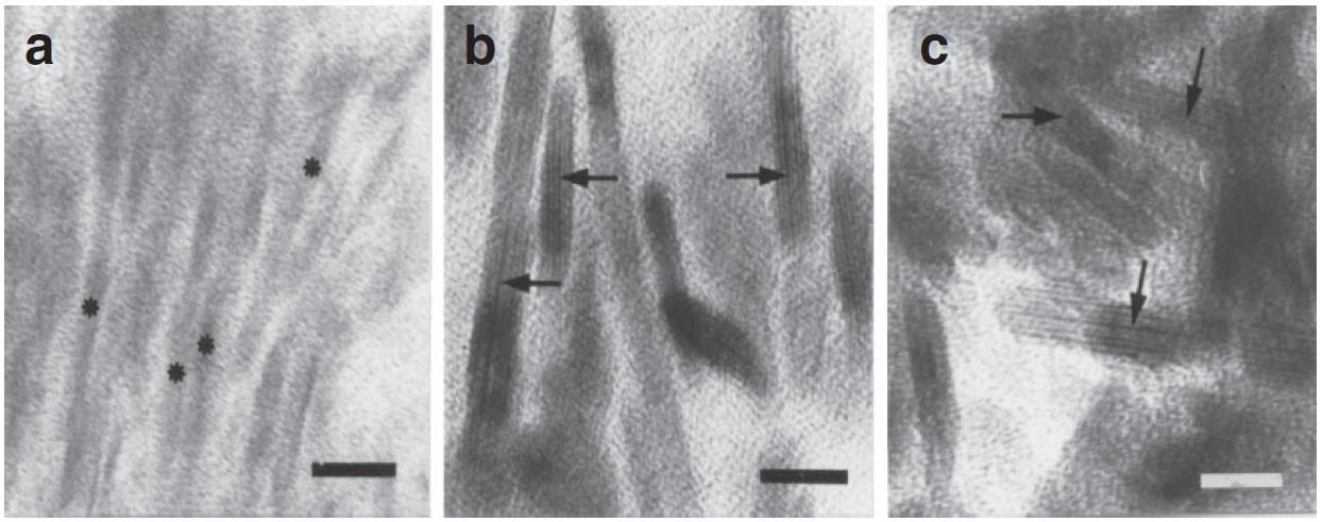

Figure 11 High magnification electron micrographs of minerals in the rat calvariae of the experimental (Es- deficient and Cd-exposed) rat and the control. a) Amorphous minerals in the experimental rat; b) crystals with lattice fringes in the experimental rat; c) crystal with well-defined lattice fringes in the control. Asterisks indicate amorphous minerals. Arrows indicate the lattice fringes (Kakei et al. 2013)

imbalance in bone remodeling" (Kakei et al., 2013). Therefore, the high disease prevalence in postmenopausal women may be due to deterioration of bone formation, not excessive bone resorption (Kakei et al., 2013). Further research is needed to confirm these effects in humans.

Public Health Solutions

After victims won a major lawsuit in 1972, Mitsui agreed to provide compensation and reparations. These pledges addressed some of the major public health consequences that resulted from cadmium pollution. Concerning health damages and high medical costs, Mitsui agreed to cover all medical expenses of patients. Mitsui also started treating wastewater from the mine and improving dust collection for industrial emissions (Yoshida et al., 1999). Between 1972 to 1997, the amount of cadmium discharged in the river was reduced from 35 kg/month to 5 kg/month and the amount of cadmium released via industrial emissions was reduced from 5+ kg/month to 0.4 kg/month (Yoshida et al., 1999). As a result, Cd pollution was drastically reduced. To address the Cd pollution already present in the environment, Mitsui and the local government of Toyama Prefecture conducted three soil remediation projects to remove the topsoil and the cadmium in the soil (Yoshida et al., 1999). By removing the polluted soil, residents are no longer at risk of high exposure to cadmium.

History of Legal Action and Compensation

Social Impacts and Legal Action

For the better half of the 20th century, pollution from the Kamioka Mine caused damage and suffering for residents of the Jinzu River Basin. In 1890, the first signs of pollution began manifesting as sulfur dioxide gas from rotary furnaces caused damage in the area surrounding the mine (Kaji, 2012). Beginning in 1896, damage to agriculture and fisheries appeared in the midstream and downstream areas of the basin, which reduced yield and stunted growth (Kaji, 2012). Some farmers had to stop farming altogether (ICETT, 2010). Around 1910, the first cases of itai-itai disease began appearing (ICETT, 2010). Victims with itai-itai disease suffered debilitating pain from osteoporosis and osteomalacia and a multitude of other symptoms. As a result, they became disabled and incurred high medical costs.

In response to complaints of air pollution and damages associated with agriculture and fisheries, the Mitsui Mining Company set up a furnace detoxification chamber, sedimentation basin, and sedimentation site (Kubota, 2020). However, most areas did not contain an adequate amount of lime to immobilize and solidify the harmful metals (Kubota, 2020). With the outbreak of World War II, zinc production and zinc waste increased fourfold, which caused pollution to spread more extensively across the Jinzu River Basin (Yoshida et al., 1999) . The waste facilities that were already inadequate before the war, became overwhelmed. The actions of Mitsui show that they prioritized economical solutions that would appease complaints rather than comprehensive solutions that would prevent pollution (Kubota, 2020).

After Japan's surrender in World War II, mine shipments reached their peak (Kubota, 2020). Moreover, the relationship between the cloudy river water and decreased agricultural productivity became obvious (Kubota, 2020).

Throughout the early 20th century, conflicts occurred in various parts of Japan between mining companies and farmers and fishermen; it was not uncommon for mining companies to pay them compensation (Kaji, 2012). The established dialogue allowed for farmers and fishermen in the Jinzu River Basin to gain compensation. “In 1948, two organizations with the same name, the Jinzu Mining Pollution Prevention Council (JMPPC), were established, one led by heads of local administrations and the other led by heads of agriculture cooperatives” (Kaji, 2012). After negotiations, the owners of Kamioka Mine agreed to pay money every year from 1949 to 1954 (Kaji, 2012). In 1951, the two organizations merged and pressed for further compensation from the mine (Kubota, 2020). In 1955, the three groups (JMPPC, Toyama Prefecture, and Kamioka Mine) came to a compensation agreement that would be revised every five years (Kaji, 2012). However, Kamioka Mine tried to decrease compensation in the next agreement and succeeded (Kaji, 2012).

To gain stronger evidence against the mine, JMPPC commissioned Dr. Kin-ichi Yoshioka to conduct research to assess damages from mining pollution (Kaji, 2012). The research of Dr. Jun Kobayashi, Dr. Noburu Hagino, and Dr. Yoshioka would eventually identify cadmium pollution as the cause of itai-itai disease in 1961; but proper compensation would not be won until a large lawsuit was pressed in 1968.

The dialogue surrounding health damages was not as established as it was for agricultural and fishery damage. For decades, patients suffered the effects of itai-itai disease with no compensation. The disease was limited to a small area in Japan, and medical research did not begin until the 1950’s. Researchers identified cadmium as the cause of health effects in 1961, but they were met with opposition from the prefectural government who were trying to promote industrialization in the area (Kaji, 2012). Toyama Prefecture created the Special Committee

Japan for Prevention of Local Diseases, which ran a patient survey to reinforce the malnutrition theory and draw attention away from mining pollution as the cause (Kaji, 2012). In 1963, the Ministry of Health and Welfare and the Ministry of Education assigned a research group to investigate (Kaji, 2012). While they admitted cadmium pollution was a cause, they claimed there also may be other reasons (Kaji, 2012). Official medical aid and compensation was offered to patients in 1967 by the prefectural government, but the inconclusive evidence and compensation was unsatisfactory (Aoshima, 2016; Kaji, 2012) .

In response to the lack of recognition and compensation from the government and Mitsui, victims took the matter to court. In 1968, the Itai-itai Disease Residents' Association filed a lawsuit against Mitsui with the help of 236 lawyers from all over Japan (Kaji, 2012). They based their lawsuit on Article 109 of the Mining Law, which covers a polluter's strict liability. The article permits liability without fault, so the plaintiffs did not have to prove the company's fault and intent (Kaji, 2012). They only had to prove that the Kamioka Mine polluted the river with cadmium. In 1971, the plaintiffs won the first trial. Mitsui appealed to the Nagoya High Court, disputing causality, but the verdict was upheld in 1972 (Yoshida et al., 1999). After the second trial, Mitsui admitted fault and began negotiations with the victims in 1972 (Kaji, 2012; Yoshida et al., 1999).

Compensation

It agreed to a few pledges, for example, medical compensation, compensation for agricultural damage and soil damage, and pollution prevention. Medical compensation included full compensation for treatment and medical expenses of victims, which included victims who developed the disease in the future (Kaji, 2012). At the time, there were over 200 victims of itai-itai disease (Kaji, 2012). The Pollution Control Agreement gave the Itai-itai Disease Residents'

Association the right to inspect the mines and factories at any time at Mitsui's expense (Kaji, 2012). Also, the Kamioka Mine had to install proper facilities to control and monitor mining waste and heavy metal concentrations in the surrounding environment (Yoshida et al., 1999). As for agricultural damage and remediation, 3130 hectares of farmland were examined; Of that, 1500.6 hectares had a rice cadmium concentration $\geq$1 ppm, and were designated for soil remediation (Figure 12) (ICETT, 2010; Kaji, 2012).

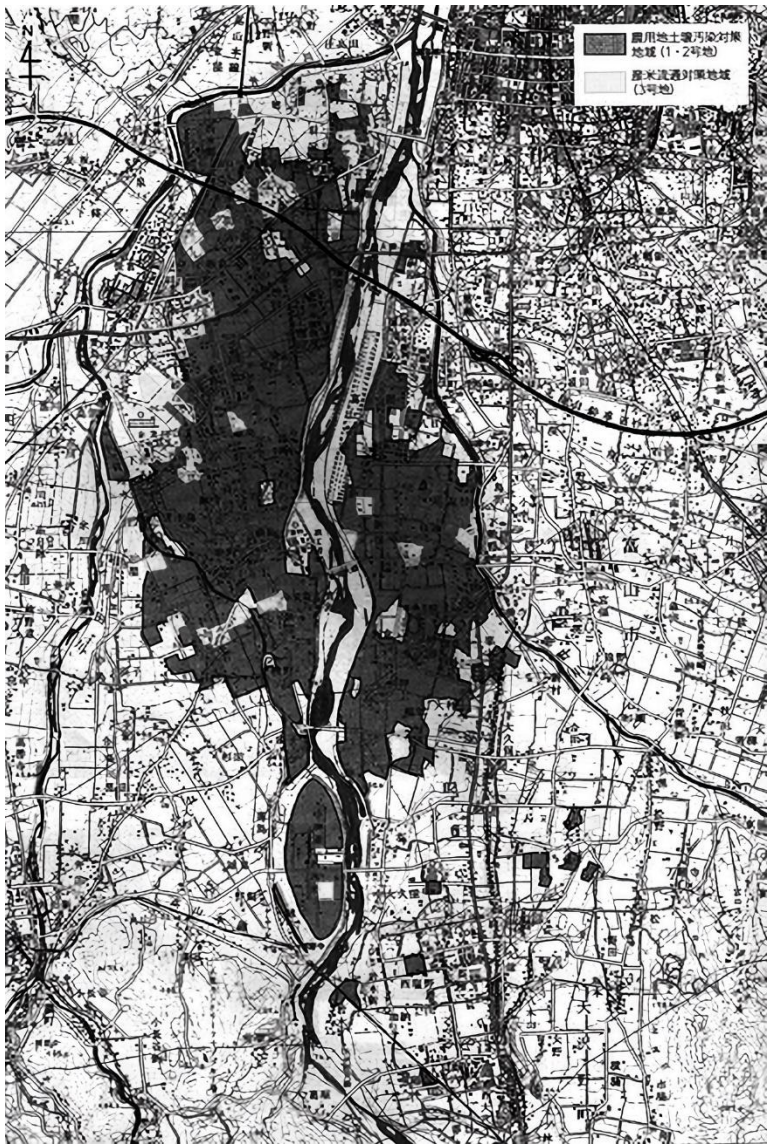

Figure 12 Remediation zones along Jinzu River for contaminated agricultural land (dark color) and rice-producing distribution zone (light color) (Kubota 2020)

Based on the pledges made in the 1972 lawsuit, the Mitsui Mining and Smelting Company paid major compensation and reparations (Table 5). For medical treatment and expenses, it spent ¥7.8 billion total: ¥3.7 billion in patient compensation, ¥1.5 billion for nursing allowances, and ¥2.6 billion for medical expenses (Yoshida et al., 1999). For spoiled rice production, it spent ¥11.8 billion total (Yoshida et al., 1999). For soil remediation, it spent ¥15 billion. For pollution prevention, it paid ¥12 billion (Yoshida et al., 1999). Figure 13 shows the

Table 5 Cost borne by Mitsui for Remediation and Reparations (Yoshida et al. 1999)

Project	**Cost**
Compensation for disease damage and medical care	¥7.8 billion
Compensation for spoiled rice production	¥11.8 billion
Restoration of polluted rice fields	¥15.0 billion
Pollution prevention investment	¥12.0 billion
Total	¥46.0 billion

yearly costs of pollution prevention investment for the Kamioka Mine from 1970 to 1992. The investment sum was divided among a few projects to improve wells and waste heaps, exhaust gas, and wastewater. Overall, it cost Mitsui ¥46 billion for remediation and reparations (Yoshida et al., 1999).

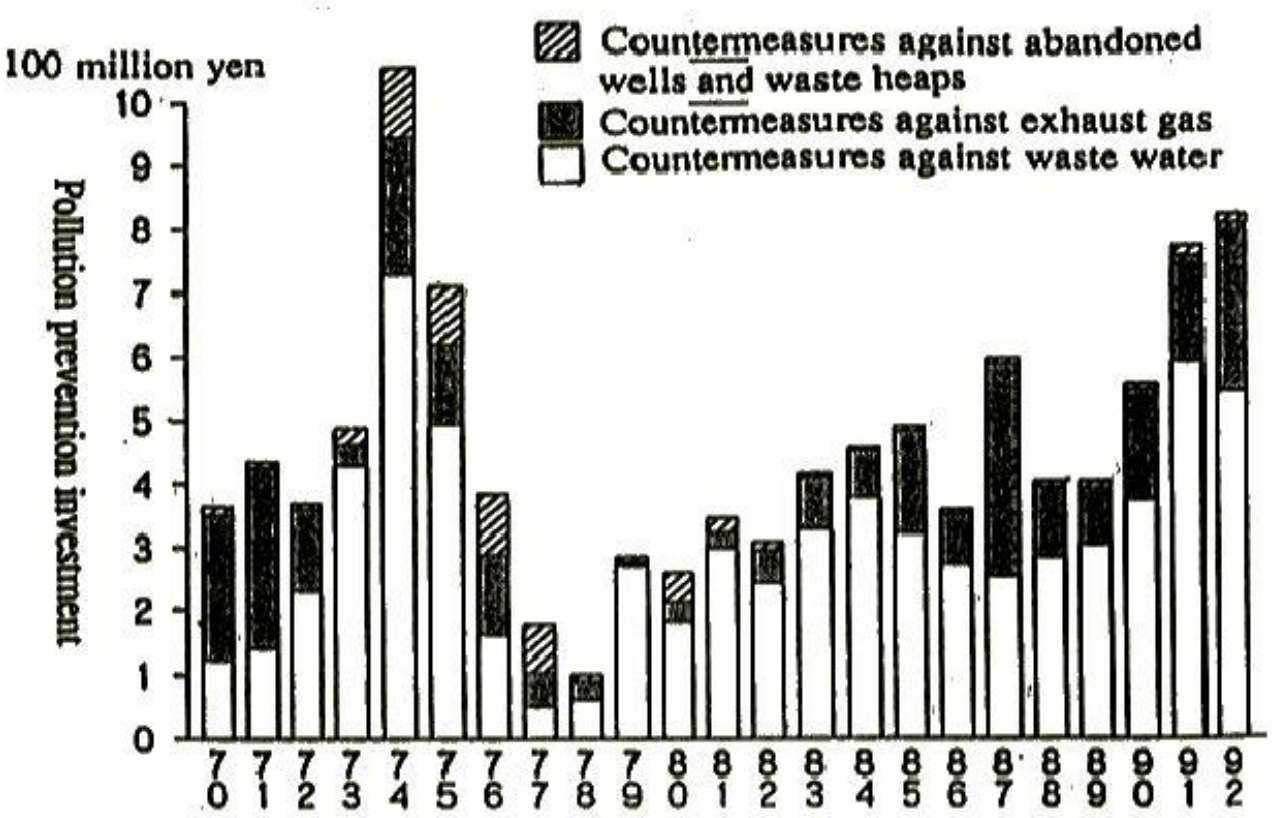

Figure 13 Yearly costs of pollution prevention investment and countermeasures for Kamioka Mine (ICETT, 2010)

DISCUSSION

This study demonstrates that mining pollution contributed to the development of itai-itai disease in the Jinzu River Basin and caused several public health concerns and social impacts. The Mitsui Company made negligent decisions concerning mining practices at the Kamioka Mine, which led to the introduction of cadmium waste into the Jinzu River. For over half a century, residents were exposed to cadmium and developed the devastating disease. Itai-itai disease disrupted the lives of many people by inflicting debilitating bone pain and deformation. However, the cause of the disease remained unknown until medical research began in the 1950's and cadmium pollution was identified as a potential cause in 1961. The lack of knowledge on the disease meant that victims suffered for several decades before any proper medical support and compensation was awarded in the 1972 lawsuit against Mitsui Company. After the lawsuit, the Kamioka Mine built adequate facilities to properly handle waste and monitor heavy metal concentrations in the surrounding environment. Despite the reparations and support, the damage was already done. The effects of cadmium poisoning on the human bone structure was irreversible. Life would never be the same for victims.

There are a few lessons to be learned from this study. Environmental regulations are necessary to protect the environment and the public health of nearby communities. Without any laws or incentives, companies like Mitsui will prioritize economical practices that may be detrimental to the environment and/or public health. Even the Toyama prefectural government prioritized the economy over the wellbeing of residents. They tried to suppress evidence of cadmium as the cause of itai-itai disease. To ensure such regulations are being followed, a higher authority like the Japanese government should establish environmental and public health agencies that have oversight of industrial operations. For any industrial project, public health

officials and environmental scientists should be involved to ensure the wellbeing of society and the environment is taken into consideration. Public health officials could have researched the effects of heavy metals like cadmium on the human body and determine guidelines for acceptable levels of exposure. Environmental scientists could have assessed the behavior of cadmium in the environment and devised solutions to monitor and control mining waste. Laws can be implemented to address potential problems. By taking a multidisciplinary approach, environmental disasters and pollution diseases like itai-itai disease can be prevented or minimized.

Also, public health should always remain a top priority in society. While many cases of the disease occurred around 1935, the outbreak was likely overshadowed by World War II and increased wartime production from industries like mining. To prevent the same from happening in the future, robust public health programs and organizations should be put in place to promote the wellbeing of society even in the event of a nationwide crisis. A dedicated public health organization can educate society on the importance of public health, inform people about potential concerns, and how to deal with such concerns. Devastating incidents in history, for example, the outbreak of itai-itai disease, can be used to emphasize and remind future generations of this importance. The same lessons should be taught in educational institutions as well. If the government fails to address public health issues, people should take matters into their own hands. Once research identified cadmium as the cause of itai-itai disease, residents mobilized into activist groups and gained the support of lawyers from all over Japan. In the present day, social media and mass media can be used to inform and mobilize people to act on environmental and public health concerns. Activism can involve people sharing educational

resources through social media, contacting government representatives, boycotting companies, pressing legal action, etc.

CONCLUSIONS

Mining pollution from the Kamioka Mine discharged into the Jinzu River due to insufficient waste facilities and heavy rains. Cadmium formed suspensions in the river and accumulated in the riverbed and was irrigated into the paddy fields. It accumulated in the soils for decades, where it was readily absorbed by rice crops. Inhabitations of the river basin consumed Cd-polluted rice grains and river water, which led to high Cd accumulation in the body. Also, their diet was insufficient in calcium, which may have resulted in increased Cd-absorption.

Mining waste overflowed into the Jinzu River and traveled downstream into the irrigated paddy fields of the Toyama Plains, especially in the fields near Fuchu Town. Cadmium adhered to suspensions and accumulated in river sediment and paddy soil for decades. During the draining stage of the rice growing season, cadmium mobilized and became available for rice crops to absorb into the root. Compared to other crops, rice readily bioaccumulates cadmium. Due to the lifestyle of the inhabitants, they were at high risk of exposure. The diet of the nearby inhabitants consisted largely of locally grown, Cd-polluted rice. Also, residents used water from the Jinzu River, which was also polluted. Certain nutritional deficiencies are thought to increase Cd absorption in the body. This includes iron, zinc, and calcium. The diet of residents did not indicate nutritional deficiencies expect for calcium.

Chronic exposure to cadmium caused toxicity in the body and resulted in multitude of symptoms. In the early stages, renal tubular dysfunction occurred. Eventually, itai-itai disease would occur, which was characterized by osteoporosis and osteomalacia. Patients experienced severe pain and disability from bone deformation. Also, patients had shorter lifespans as a result of the disease. The vast majority of patients were postmenopausal women. Research suspects

risk factors like estrogen deficiency, kidney sensitivity, pregnancy, genetics, enzyme differences, and lower iron stores are responsible for the preferential distribution.

For decades, inhabitants of the Jinzu River Basin suffered the consequences of mining pollution without proper compensation or support. Consequences included damage to agriculture and fisheries as well as health-related damages and disability. After victims won a major lawsuit against Mitsui Company, Mitsui agreed to a few pledges including medical compensation, compensation for agricultural damage and soil damage, and pollution prevention.

Recommendations for Future Work

The information and research in this study was limited by the sources available. While the risk factors of itai-itai disease, for example, gender and menopausal status, were investigated, the mechanisms behind the risk factors are still not fully understood. Also, the relationship between iron deficiency and Cd absorption is not elucidated yet. In order to study these mechanisms, further population studies must be conducted. While most itai-itai patients have passed away, studies could be extended to other populations at risk of Cd-exposure.

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