Chapter 5
Yokkaichi Asthma: Health Effects of Air Pollutants in Japan

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Abstract Yokkaichi asthma from the 1960s to the early 1980s involved the onset and exacerbation of asthma, chronic bronchitis, and chronic obstructive lung disease, which was attributed to sulfur dioxide (SO_2). Inhaled SO_2 easily dissolves in the epithelial lung lining fluid of the nose and upper airways and generates secondary reactive compounds, such as sulfurous acid and sulfuric acid. These derivatives increase the level of prostaglandin D2, inducing the constriction of airway smooth muscle, inflammatory responses, and oxidative stress. As a result, exposure to SO_2 causes bronchoconstriction in asthmatic subjects and exacerbates asthma. Many epidemiological studies found that exposure to SO_2 was associated with mortality and incidence of asthma and chronic obstructive pulmonary diseases for adult, and prevalence of persistent cough/phlegm, asthma-like attack for schoolchildren. These scientific evidences played an important role to support the causal relationship between ambient SO_2 and chronic obstructive pulmonary disease in individual patients who filed a lawsuit against the petroleum industry group.

Keywords Air pollution · Health · Respiratory diseases · Sulfur dioxide · Asthma

5.1 Introduction

Yokkaichi asthma was one of the four major pollutant-based diseases in Japan during the high economic period, i.e., from the 1960s to the early 1980s. It involved the onset and exacerbation of asthma, chronic bronchitis, and chronic obstructive lung disease in Yokkaichi City that were attributed to the excessive emissions of sulfur

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dioxide (SO_2). Serious health issues associated with similar air pollution were observed in other areas of the Pacific Belt from the Kanto plain to North Kyushu, where the coastal areas were occupied by oil refining and petrochemical industries [1]. Nine patients in the Isozu district filed a lawsuit against the companies operating the complex in Yokkaichi in 1967, and the plaintiffs won the case in 1972. Scientific evidence was used to establish a causal relationship between SO_2 and respiratory diseases. The following text describes the health effects of SO_2 based on both toxicological and epidemiological evidence.

5.2 Toxicological Evidence on the Health Effects of SO_2

The major sources of SO_2 include anthropogenic activities, especially the combustion of coal and oil containing sulfur, and metal smelting. Toxicological studies using human epithelial cells and animals have elucidated the mechanism by which exposure to SO_2 causes harmful effects on the respiratory system. Inhaled SO_2 easily dissolves in the epithelial lung lining fluid of the nose and upper airways and generates secondary reactive compounds, such as sulfurous acid (H_2SO_3) and sulfuric acid (H_2SO_4), which are subsequently converted to bisulfite and sulfite derivatives. These derivatives increase the level of prostaglandin D2, inducing the constriction of airway smooth muscle, inflammatory responses, and oxidative stress [2]. In addition, SO_2 oxidation contributes to the formation of secondary particles of various sizes, including fine and ultrafine particles. These secondary products and particles are also responsible for oxidative stress and inflammation in the respiratory tract [3].

Previous studies have shown that exposure to SO_2 alters mucociliary clearance, a defense mechanism of the respiratory system that removes inhaled particles and infectious agents. Sulfuric acid also affects mucociliary clearance and causes respiratory irritation [4]. Clinical and epidemiological studies have shown that asthmatics are more sensitive to SO_2. Genetic polymorphisms may enhance the susceptibility to respiratory effects of SO_2 [3]. A review of several controlled exposure studies, in which asthmatic volunteers were exposed to SO_2 during 5–10 min, has shown that exposure to SO_2 causes bronchoconstriction with increasing SO_2 between 0.2 and 1.0 ppm [5]. Another review reported that the response of lung function to SO_2 decreases in forced expiratory volume in the first second (FEV1), and an increase in airway resistance was induced within a few minutes. Although the concentration that causes acute responses varies according to each individual, exposure to SO_2 (>0.5 ppm) generally triggers bronchospasm in asthmatic patients [6].

5.3 History of Yokkaichi Asthma

After World War II, petroleum and petrochemical industries acquired the site of the former Japanese Navy Fuel Depot in the Yokkaichi area and developed petrochemical industry complexes (Table 5.1). A few years after its operation began in 1955,

Table 5.1 Timeline of air pollution-related events in Yokkaichi from World War II until 1973

Year	Events in Yokkaichi area	Events related to national and local government
1939–1945		World war II
		Petroleum and petrochemical industries started operation of its factory.
1955	Complaints about offensive odor in fish caught off Yokkaichi coast	Postwar high economic growth period in Japan policy for petroleum industry development by Ministry of International Trade and Industry. The petroleum industries used the ruins of the navy fuel deposit to build a petroleum complex.
1959		Several petroleum and petrochemical complexes started its operation.
Early 1960s	The complaints about noise, soot, malodor/irritating odor significantly increased in Shiohama complex areas	
1960	There was an increase in residences who complained asthma-like symptoms in Isotsu area.	Yokkaichi City pollution control committee was established. The monitoring of SO_2 (lead dioxide methods), and soot started.
1962		Soot and smoke regulation law was promulgated.
		Yokkaichi city pollution control committee reported that the level of soot was lower than Kawasaki city but SO_2 level was higher, especially in Isotsu area in the interim report.
	The health survey for residents was initiated.	Mie medical university carried out free health checkup to examine the possible health effects of air pollutants. They found a remarkably high prevalence of bronchial diseases.
1963		Yokkaichi pollution control council was established.
1965		Yokkaichi City started the certification system of pollution-related diseases. The Ministry of Health and Welfare initiated a health survey of air pollution effects on school children in Yokkaichi (until 1969).
1967	Nine patients in Isotsu filed a lawsuit against 6 companies.	The basic law for environmental pollution control was enacted. Several petroleum industries installed tall stacks.
1969	Several researchers testified on the causal association between air pollution and asthma at the trials.	The national government enacted the Act on Special Measures Concerning Relief of Pollution Related Disease.
1970	There were several public rallies against environmental pollution in Yokkaichi.	The national government started the support of medical expenses on the air pollution-related diseases.
1971		The environmental agency was established.

(continued)

Table 5.1 (continued)

Year	Events in Yokkaichi area	Events related to national and local government
1972	Judgment was issued. The court ordered the companies to pay compensation for the patients.	
1973		Environmental quality standards for SO_2 was established in Japan

This timeline was adapted from the table "the history of Yokkaichi pollution" with permission [in Japanese] (Yokkaichi Pollution and Environmental Museum for Future Awareness. https://www.city.yokkaichi.mie.jp/yokkaichikougai-kankyoumiraikan/pdf/pollution/nenpyo1-13.pdf. These are copyrighted materials)

there were claims about "petroleum odor" emanating from the fish caught near Yokkaichi harbor; this resulted in a huge economic loss for fisheries and was recognized as a social problem [7]. It was proved that aromatic hydrocarbons in seawater containing the petroleum industrial waste caused the offensive odor in fish [7, 8]. There were also resident complaints regarding noise, dust, and odors around the petroleum complex. In the 1960s, emissions of soot and sulfurous acid gases from the petroleum complex in Yokkaichi increased. Concurrently, a number of patients with asthma were reported in the Isozu district, the most polluted area, and its surrounding districts; this received wide public attention.

In response to the unusually high prevalence of asthma in these districts, a series of epidemiological studies have been conducted by national and local governments, and local universities [9]. From January to March 1963, the average SO_2 concentration measured by Thomas' volumetric method was 0.3 ppm, approximately 786 μg/m^3 in mass concentration, much higher than the WHO air quality guidelines [10] and the Japan Environmental Quality Standards [11], which are 20 μg/m^3 and 105 μg/m^3 for 24-h average, respectively, (Table 5.2). Moreover, the peak concentration often ranged from 1 to 2.5 ppm.

Studies using the National Health Insurance Billing data of over 10 districts with various SO_2 levels within the city found that the incidence of asthma and chronic obstructive pulmonary diseases for those aged 50 years and older was over 5 times higher in the polluted district than in the nonpolluted district [12]. A significant correlation was observed between the prevalence of bronchial asthma and SO_2 concentration. The correlation was evident among those aged 50 years and older [13]. Another study using data of Yokkaichi from 1961 to 1970 found that the mortality rate due to obstructive respiratory diseases, especially bronchial asthma and emphysema, was higher in polluted areas than in nonpolluted areas. The district-specific mortality rate due to obstructive respiratory diseases was strongly correlated with the concentration of sulfurous acid ($r = 0.76$ in 1971) [14]. A questionnaire survey on schoolchildren showed that the concentration of sulfurous acid was correlated with the district-specific prevalence of persistent cough/phlegm, asthma-like attack, and wheezing during a cold [15].

The evidence obtained from many epidemiological studies led by the local government and universities was used to support the causal relationship between

Table 5.2 Standards for SO_2 concentration in Japan and WHO

	Averaging time	Standards
Japan		
Environmental Quality Standards (1973)	24 h	105 μg/m^{3a}
	1-h	262 μg/m^{3a}
WHO		
Air quality guideline (2000)	24 h	20 μg/m^3
	10 min	500 μg/m^3
Interim target-2	24 h	50 μg/m^3
Interim target-1	24 h	125 μg/m^3

[a]Applying conversion factor of SO_2 for ppb to μg/m^3: 2.62
Source: Ministry of the Environment, Japan. Environmental quality standards in Japan - Air quality. Available from: https://www.env.go.jp/en/air/aq/aq.html
World Health Organization. WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide. Global update. Global update 2005. Available from: https://apps.who.int/iris/bitstream/handle/10665/69477/WHO_SDE_PHE_OEH_06.02_eng.pdf

ambient SO_2 and chronic obstructive pulmonary disease (COPD) in individual patients who filed a lawsuit against the petroleum industry group [16]. After the plaintiffs won the case in 1972, Mie prefecture imposed total emission control of SO_2 for the entire Yokkaichi area based on the Mie Prefecture Ordinance that was more stringent than the national regulations [17]. SO_2 concentration decreased dramatically by one-third, 0.75 mg/100 cm^2/day with PbO_2 method in 1976 compared to 2.58 mg/100 cm^3/day in 1970. SO_2 is correlated with chronic obstructive lung disease, including bronchial asthma, chronic bronchitis, and emphysema, after accounting the area-level socioeconomic status [18].

Yokkaichi City was the first city in the country to establish a certificate system for pollution-related diseases in 1965. The city supported the medical expenses of patients who developed air pollution-related asthma, chronic bronchitis, and pulmonary emphysema regardless of the severity of the conditions [15]. Between 1965 and 1970, over 700 patients were acknowledged by this city-specific system. In 1969, the national government enacted the Act on Special Measures Concerning Relief of Pollution Related Disease and supported the certificate system. In 1987, the law changed to the Law Concerning Pollution-Related Health Damage Compensation and Other Measures.

Based on the statistics of 2018, over 2000 patients were officially designated as victims of Yokkaichi asthma. In 2018, 358 patients were said to have survived, although no new certified cases have been reported since 2012. Half of these cases included the elderly, aged 60 years and older. Approximately 80% of the patients were diagnosed with bronchial asthma, while the remaining were diagnosed with chronic bronchitis (Yokkaichi City Office, Report on environmental conservation, https://www.city.yokkaichi.lg.jp/www/contents/1543551934253/files/h30kankyo-uhozen.pdf).

5.4 Current Studies Related to Yokkaichi Asthma

Although many epidemiological studies conducted in the Yokkaichi area accumulated evidence supporting the adverse health effects of SO_2 on the respiratory system, most of them, especially those conducted before 2000 opted for an ecological study design because of limited access to individual data and rudimentary statistical methodologies. Since 2000, time-series analysis and case-crossover design have been used for air pollution epidemiology. These statistical methods account for confounders and have yielded more validated effect estimates of air pollutants. A study examined the association between SO_2 and mortality using daily data from 1972 to 1991 in Yokkaichi and its neighboring cities. The mean SO_2 level decreased dramatically from 32.9 ppb in 1972 to 7.8 ppb in 1991. A case-crossover design was applied in this study. After adjusting for relevant confounders, including seasonality, long-term trends, and meteorological factors, the results showed that an elevated level of SO_2 was associated with an increase in all-cause mortality [19]. The association between SO_2 and mortality was pronounced during the second half of the study period (1982–1991). In particular, the strongest association was observed between SO_2 and mortality due to COPD and asthma. The association continued even after adjusting for suspended particulate matter or nitrogen dioxide. Although an association between SO_2 and mortality from cardiovascular or cerebrovascular disease was also observed, it was not robust.

Air pollution has lifelong and acute effects. A study compared the mortality rate and life expectancy of 1354 patients who were certified as victims of air pollution-related diseases in Yokkaichi City during 1965–1988 with that of the entire population of Mie prefecture. Surprisingly, the mortality rate from COPD and asthma in the patients of Yokkaichi City was more than 10 times higher than that of the general population in Mie prefecture. Similarly, the life expectancy of patients in Yokkaichi was much shorter than that of the general population in Mie prefecture for any age group [20]. The average difference in the life expectancy for each age group ranged from 1.9 to 8.5 years for males and 4.5 to 8.5 years for females. Moreover, the reduction in life expectancy was larger for the younger age groups.

5.5 Conclusion

The case of Yokkaichi asthma shows that scientific evidence plays an important role in demonstrating the causal relationship between SO_2 and respiratory diseases in polluted areas. Japan's experience in environmental pollution is a lesson that unsustainable development will engender a huge public health burden arising from environmental pollutants.

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