Various Effects of Arsenic in Japan Depending on Type of Exposure
by Kenzaburo Tsuchiya*

Since 1955, a number of outbreaks of arsenic poisoning have occurred throughout Japan among industrial workers and the general population. The sources and types of exposure differ according to the incident, and the victims vary in sex and age. These incidents include arsenic poisoning in milk, soy sauce, and well water, pollution originating from the Toroku Mine on the island of Kyushu, the Matsuo Mine in Shimane Prefecture, and Saganoseki Smelter on Kyushu. The type, routes, and dose of exposure as well as major symptoms are given. The clinical signs and symptoms are discussed in relation to the various types of exposure which occurred in these incidents. Dose–response relationships will be considered where data are available.

Arsenic Poisoning in Powdered Milk

In early summer 1955, outbreaks of a disease characterized by anorexia, anemia, skin rash and/or pigmentation, diarrhea, nausea, vomiting, fever, and bloated abdomen occurred among infants, most of whom were less than 12 months of age. Three infants died at the beginning of August and the number of cases reported continued to increase. On August 20, it was confirmed that these cases were limited to those infants who were bottle fed. From the clinical symptoms, heavy metal poisoning was suspected, and arsenic was identified in Morinaga MF powdered milk by the Department of Legal Medicine of Okayama University. On August 24, the sale of this milk was banned. Extensive investigation and examinations of bottle-fed infants were carried out in the western part of Japan where the milk had been distributed. As a result of these investigations, the Ministry of Health and Welfare on June 9, 1956, announced a total of 12,131 victims, including 130 fatalities. An extensive review of this incident has been published by the Okayama prefectoral government (1).

The route of arsenic contamination was as follows: One plant of the Morinaga Milk Company located in the city of Tokushima on the island of Shikoku added sodium phosphate to the milk as a stabilizer. This sodium phosphate is a by-product of the process in which aluminum is produced from bauxite. This by-product consists of approximately 45% crystal water, 14% P2O5, 28% Na2O, 2% V2O5, and 6% As2O5. This by-product was recrystallized by another company which failed to completely remove the arsenic. The chemical formula of the compound found in the milk was later identified as: 2Na3(PO4 · AsO4 · VO4) · NaF · 18H2O, in which arsenic was pentavalent. The final product of MF milk contained 21–34 μg arsenic per gram; the concentration of arsenic differed by lot number. The first poisoned milk was produced on April 12, 1955 and the final contaminated lot on August 13 of the same year. Some lots produced within the same period contained no arsenic, so it is difficult to estimate just how much arsenic was ingested in each case, but it is assumed that a total of 2.5 mg arsenic was ingested by an infant one month old, 3.2 mg by those 2 months old, and 4.6 mg by those 6 months old. The poisoned infants were treated by BAL and other therapy. Although 130 infants died, the symptoms disappeared in the infants who survived. In June 1956 health examinations were conducted on the survivors, and it was diagnosed that most of the infants suffered no abnormality (2). It seemed that the incident had concluded.

However, 13 years later, a group of nurses, schoolteachers, and medical students visited the
families of the survivors and provoked discussion among scientists concerning the residual effects on those who had been poisoned in infancy. The nurses, teachers, and medical students reported that residual effects did exist. The reports from this time on become very complicated as politics and public opinion entered the picture.

More than 200 papers, including oral presentations in medical conferences, on clinical signs and symptoms and autopsy findings were reported in the period from 1955 to 1975. The main acute symptoms were fever, diarrhea, vomiting, and anorexia. Another characteristic symptom was melanosi. Miyata, Kosho, and Nagai (3) reported that the liver could be felt in most cases. Blood tests showed slight anemia, leucopenia, relative lymphocytosis, and leuconeutrophilia. However, no symptoms of the cerebral nervous system or the circulatory system were noted.

Other clinical symptoms as reported by Hamamoto (4) are shown in Table 1. According to Hamamoto, other reports of arsenic poisoning such as the beer poisoning incident in Manchester, England, had not cited fever, but in the Morinaga milk incident, fever was present in most cases. Furthermore, in the Morinaga incident, symptoms of neuritis were not observed. Even electromyelograms indicated no symptoms of the peripheral nervous system. Hamamoto mentions that the most remarkable effect of BAL treatment was the rapid gain in body weight. With regard to dose-response relationship, Hamamoto estimated that infants 3 months old or over developed symptoms after ingesting 90–140 mg arsenic oxide.

Fourteen years after the poisoning occurred, a series of follow-up studies were performed by groups of university researchers and practicing physicians. A great number of symptoms were noted in the children who had ingested the poisoned milk. However, all the records had not been kept over the 14 years. Other problems also complicated the investigations, as it appears that some parents desiring compensation indicated that their child had been poisoned, where in actuality he or she had not, and some other parents whose child had actually ingested the contaminated milk denied the fact for various personal reasons.

There are a number of reports on the youngsters who ingested the contaminated milk in infancy. The following discussion is based mainly on reports by Toyoshima and Sumi (5), Yamasaki et al. (6), Ohira and Aoyama (7), Yuwasa (8), Kawatsu et al. (9), Ohtori, Tsukamoto, and Bessho (10), and Nishida (11). Some of these studies discuss the relationship between arsenic poisoning and symptoms. It is not my intention here to discuss the cause–effect rela-

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### Table 1. Frequency of clinical symptoms.

| Symptom                                | Cases |
|----------------------------------------|-------|
|                                        | No.   | %    |
| Insomnia                               | 43    | 70.5 |
| Lack of energy                         | 41    | 67.2 |
| Ill humor                              | 40    | 65.2 |
| Pallor                                 | 38    | 62.3 |
| Loss of appetite                       | 37    | 60.7 |
| Weight loss                            | 33    | 54.1 |
| Fever                                  | 51    | 83.4 |
| Cough                                  | 31    | 50.8 |
| Eye discharge                          | 27    | 43.8 |
| Watery eyes                            | 22    | 36.1 |
| Salivation                             | 22    | 36.1 |
| Runny nose                             | 17    | 27.9 |
| Diarrhea                               | 14    | 23.0 |
| Hoarseness                             | 13    | 21.3 |
| Sneezing                               | 9     | 14.8 |
| Vomiting                               | 6     | 9.8  |
| Melanosi                               | 60    | 98.4 |
| Skin rash                              | 34    | 55.7 |
| Itching                                | 44    | 73.4 |
| Scaling                                | 46    | 72.2 |
| Leucodermia                            | 41    | 67.2 |
| Excessive sweating                     | 42    | 68.9 |
| Breath odor                            | 27    | 44.3 |
| Edema                                  | 23    | 37.7 |
| Hyperkeratosis                         | 16    | 26.2 |
| Loss of hair                           | 9     | 14.8 |
| Redness & swelling of the fingertips   | 3     | 4.9  |
| Pustules                               | 16    | 26.2 |
| Subcutaneous abscess                   | 8     | 13.1 |
| Ascites                                | 1     | 1.6  |
| Ascites                                | 1     | 1.6  |
| Liver swelling                         | 61    | 100.0|
| Bloated abdomen                        | 38    | 62.3 |
| Tympanic abdomen                       | 28    | 45.9 |
| Jaundice                               | 3     | 3.3  |
| Heart palpitation                      | 38    | 62.3 |
| Heart murmur                           | 15    | 24.6 |
| Accelerated jerk                       | 10    | 16.4 |
| Hyper- or hypo-sensitivity             | 9     | 14.8 |
| Joint pain                             | 3     | 4.9  |
| Encephalopathy                         | 4     | 6.6  |

*Data of Hamamoto (4).

### Table 2. Encephalogram findings by type of feeding.

| Type of Feeding               | Total No. | No abnormal findings | Suspected findings (suspicous of abnormality) | Abnormal findings |
|------------------------------|-----------|-----------------------|-----------------------------------------------|-------------------|
| Breastfed infants            | 48        | 36 (75.0%)            | 10 (20.8%)                                    | 2 (4.2%)          |
| Infants given milk other than Morinaga | 26        | 18 (69.2%)            | 7 (26.9%)                                     | 1 (3.8%)          |
| Arsenic-contaminated Morinaga milk | 33        | 17 (51.5%)            | 12 (36.4%)                                    | 4 (12.1%)         |

*Data of Ohira and Aoyama (7).
tionship of arsenic and these symptoms. One point I do wish to discuss is the possible effect of arsenic on the central nervous system, e.g., the paper by Ohira and Aoyama (7) reported the results of electroencephalograms as shown in Table 2. This table indicates a statistically significant difference in abnormal findings between the breast-fed group of infants and the Morinaga milk group. However, it is difficult to conclude from this study alone that arsenic was actually the cause of effects on the central nervous system because the number of cases of abnormal findings are too few. In his report in 1955, Hamamoto (4) found only four cases of encephalopathy (with convulsions) out of the 61 who suffered acute poisoning. It seems that these symptoms were caused by the inflammation of the cerebral membrane and not by disturbance to the cerebral parenchyma itself. Yuwasa (8) in 1970 and 1971 reported higher prevalence of epilepsy among the arsenic-poisoned children than in control children.

Tamura et al. (12) examined whether or not arsenic is transferred into the brain through the blood-brain barrier in animal experiments and found that arsenic in the brain and liver did not increase after 2 weeks of oral administration of arsenic in milk, whereas the content in the kidney increased. In this experiment 650 ppm As$_2$O$_3$ in milk was administered over a period of 35 days.

Tsutusmi (13) gave rats, mice, and rabbits sodium arsenate radioisotope by forced oral administration and reported the intake of arsenic by the brain. In rabbits the intake by the brain was lower than that by the other organs. In rats the brain intake was the second lowest after nails. In mice, however, it was the third highest, after the liver and kidney. The transfer of arsenic to the brain through the blood-brain barrier is an important subject for investigation in future studies.

**Soy Sauce Poisoning**

In 1956 approximately 400 persons ingested soy sauce contaminated by arsenic in Ube, a city in western Japan. Of these, 220 were examined by Mizuta (14). After two days of ingestion of the soy sauce, many victims developed edema and gastrointestinal symptoms followed by skin changes and later by symptoms of the peripheral nervous system (Fig. 1). Even though the ingestion of the contaminated soy sauce continued, the symptoms weakened after 5 to 6 days. The symptoms disappeared two weeks after cessation of exposure. Polyneuritis appeared in the third to fourth week of exposure. The liver was swollen and abnormal EKG findings were noted in 80% of those persons examined. (In the Morinaga incident, only about 40% showed abnormal EKGS.) Abnormal knee jerks developed remarkably after two weeks of exposure. As for eye symptoms, conjunctivitis, central scotoma, and retinitis of the optical nerve were observed. Many of the victims showed anemia with leucopenia, relative lymphocytosis, and basophilic

![Figure 1. Subjective symptoms.](image-url)
stippled red cells. No remarkable changes were noted in the bone marrow picture. Occult blood was noted in feces, stomach and duodenal juice. Increased excretion of arsenic in urine was noted two weeks after cessation of exposure. The duration of ingestion of contaminated soy sauce was 2-3 weeks. The arsenic concentration was 90-100 μg/ml. There was no fatality in this incident.

**Well Water Poisoning**

In 1959, about 60 cases of arsenic poisoning were identified by the Department of Dermatology, Niigata University School of Medicine. The source was found to be well water. In the town of Nakajo, Niigata Prefecture, there was a plant which had been producing arsenic sulfide for over 100 years.

![Figure 2. As concentrations in well water by distance from factory](image)

Waste water from the factory contaminated the well water drunk by inhabitants living near the factory. A number of the wells were connected to each other by ground water. The higher concentrations were evident in those wells closest to the factory, and the concentrations decreased with distance from the factory. It is important in terms of dose-response relationship to note that all 60 cases of arsenic poisoning were clustered within a distance of 400 meters from the factory where the concentrations were 0.05 ppm and over (Fig. 2). As levels in water from many of the wells in this area exceeded 1-2 ppm, with a maximum of 3 ppm. The patients complained of fatigue and some had fever. However, the most important chronic symptoms were skin changes, including keratosis, melanosis, scaling, and leucoderma. The actual number poisoned as determined by clinical symptoms was 60, but 90 were suspected cases, and of the 90, 48% showed anemia, 30% showed swollen liver, and fewer showed abnormal EKGs, proteinuria, accelerated knee reflex, pallor, joint pain, swelling of the lymph nodes, swelling of the spleen, and jaundice (16).

Terada et al. (17) discussed the nature of the anemia observed in many cases and 50% of the patients with anemia showed normochromic anemia and 30% showed hyperchromic anemia. There was no significant decrease of serum ion in those victims with leucopenia. Terada et al. concluded that the anemia observed resembled aplastic anemia. However, bone marrow pictures showed stimulation of the red cell system, thus contradicting the picture of aplastic anemia.

Another important finding in this study was that there was no relationship between skin symptoms and arsenic levels in hair, i.e., one case showed no skin symptoms, although arsenic level in hair showed 77 ppm, while another case showed advanced skin symptoms with arsenic level in hair of less than 5 ppm. It should also be pointed out that no case of cancer was reported in this incident.

**Toroku Mine Incident**

Toroku is a small village in the southern part of the island of Kyushu with a total population of less than 300. There is a mine located there which produced arsenic oxide until operations ceased about 15 years ago. In 1971, a schoolteacher raised the question that health of school children in the town may have been affected in the past by air pollution by sulfur dioxide and arsenic. The prefectural government began epidemiological investigations that same year with the cooperation of the medical community in the area. According to the investiga-

### Table 3. Relationship between the number of individuals with skin changes and place of residence.a

| Number of persons | Within 800 m from the roaster | 800-1200 m from roaster | Total |
|-------------------|-------------------------------|-------------------------|-------|
| Skin changes      | 17                            | 7                       | 24    |
| Without skin changes | 108                          | 109                     | 217   |
| Total             | 125                           | 116                     | 241   |

*aData of Kankyo Hoken Report, (18). $X^2 = 3.92 (p = 0.047)$.

### Table 4. Relationship between the number of individuals with skin changes and place of residence, excluding those employed at the mine or smelter.a

| Number of persons | Within 400 m 400-800 m 800-1200 m Total |
|-------------------|-----------------------------------------|
| Those with skin changes | 7 5 4 16                               |
| Those without     | 33 62 97 192                            |
| Total             | 40 67 101 208                           |

*aData of Kankyo Hoken report (18). $X^2 = 7.33 (0.02 < p < 0.05)$. 
tion of the environment, food and water were found not to be contaminated by arsenic, but a survey of the dust collected from ceiling boards in private homes showed high concentrations of arsenic in those homes which were located close to the roasting furnace of the smelter. From this it was concluded that while the factory was in operation, there did exist pollution by arsenic as well as by sulfur dioxide. A total of 24 persons living near the mine showed pigmentation, leucoderma, and/or hyperkeratosi the skin, which were assumed to have been caused by arsenic. However, a problem exists, in that some of those who showed skin changes worked for the mining company on a part-time basis, bringing ore and roasting it in their own homes. It was difficult to distinguish those who had practiced such work and those who had not, since for personal reasons, many did not wish to indicate the fact to investigators. However, as shown in Tables 3 and 4 it is evident that there exists a relationship between the prevalence of skin changes and distance from the smelter (18). The relationship between the two factors becomes more evident when those with confirmed occupational exposure are excluded, as shown in Table 5.

### Sasagadani Mine Incident

The Sasagadani mine located in Shimane Prefecture in western Japan which produced copper and arsenic trioxide started operations about 700 years ago and was closed down in 1949 due to insufficient production. Several rivers flow from the area near the mine, and the occurrence of agricultural damage was noticed as early as 1884. In 1950, four dams were constructed as a countermeasure against such damage. The hamlet closest to the mine was located about 1–2 km from the mine, so air pollution originating from the mine was most likely very slight. Extensive investigations of the environment,

| Occupation                        | Case group 19 lung cancer deaths | Control group 19 non-lung cancer deaths |
|-----------------------------------|----------------------------------|---------------------------------------|
| Welding                           | 0                                | 1                                     |
| Metal casting                     | 1                                | 2                                     |
| Petroleum refining                | 0                                | 0                                     |
| Quarrying, mining                | 1                                | 2                                     |
| Handling coke, coal tar           | 1                                | 1                                     |
| Asphalt paving                    | 0                                | 0                                     |
| Gilding                           | 0                                | 0                                     |
| Driving of steam and diesel locomotive | 1                    | 2                                     |
| Handling agricultural chemicals   | 3                                | 6                                     |
| Handling x-rays or radioactive substances | 0                    | 1                                     |
| Former employee of S copper refinery | 11                              | 7                                     |
| Smelting work at S copper refinery | 11                              | 3                                     |

*Data of Kuratsune et al. (21).*

The characteristics of exposure and effects in this area were as follow. The route of exposure was via the respiratory system. Chemical substances were not only As₂O₃ but also SO₂ from the stack, although the smelter closed down before determinations could be made as to just how much. The inhabitants, particularly those living near the smelter, had been exposed to those chemicals, but some of them had been exposed occupationally on either a full or part-time basis and the effects included mainly skin changes, such as pigmentation or particularly drinking water and house dust, and health examinations were performed on about 1000 inhabitants in 1970. Health examinations were conducted by the Tottori University School of Medicine (19, 20). Arsenic concentrations in drinking water of 200 families living within a 7–km radius of the mine were checked. The highest concentration found was 0.125 ppm in the well water of one family; 0.07 ppm was the next highest, and most wells showed As concentrations of 0.05 ppm or trace or nondetectable amounts. The arsenic con-

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centrations in vegetables consumed in the same hamlets were determined, but most showed less than 0.1 ppm and the majority 0.05 ppm or less. Thus it was assumed that environmental pollution was not very great in this area, and if it had occurred, the route of exposure was most likely via drinking water. The Tottori University Study Group determined seven persons as suffering arsenic poisoning and five other persons as suspected of such. However, among the seven, six persons had had a history of working in the mine. Those with occupational exposure showed skin changes such as pigmentation, leucoderma or keratosis, and in one case, lung cancer was also detected. This patient died of lung cancer at the age of 66 years. One person, 77 years of age without occupational exposure, had hypochromic microcytic anemia following an operation for stomach cancer and irritated seborrheic keratosis of the skin, slight neurogenic changes, and moderate hearing loss. Since these changes are usually seen after stomach surgery or in aged people, there was no confirmed evidence of arsenic poisoning.

Among the five suspected cases, there were three persons who had had no occupational exposure. Of these, two were a married couple, the wife was suspected as suffering Banti syndrome and the husband was diagnosed as suffering from liver cirrhosis. The study group suspected these two cases as suffering from arsenic poisoning because their drinking water contained 0.125 ppm arsenic, and arsenic concentrations in hair and nails of the husband were rather high, i.e., 1.4 ppm and 11.1 ppm, respectively. In the third person, a woman 46 years of age, the study group suspected arsenic poisoning because of increased eosinophiles in peripheral blood, hyposensitivity of the extremities, and hearing loss in the high frequency range. The arsenic concentrations in hair and nails of this woman were low and arsenic in drinking water was nondetectable. In this case, there were no skin changes.

Figure 3 shows the abnormal EMG findings among those persons of both observation and control areas, as well as among those with and without a history of occupational exposure in the observation area. Higher prevalences of abnormal EMG findings were observed in the observation area and in those with occupational exposure. Abnormal findings among control subjects were also found to increase with age. The prevalence of abnormal EMG findings between occupationally exposed and nonoccupationally exposed persons was greater among females than among males.

Most of the cases which were confirmed as suffering arsenic poisoning had been occupationally exposed, and the effects of arsenic on the general population are not very clear. If there were effects, they were very slight, with the exception of the case of the married couple whose drinking water showed a high concentration of arsenic. This case also indicated that the relationships between arsenic poisoning and Banti syndrome and arsenic poisoning and liver cirrhosis should be further investigated. Abnormal EMG findings or subclinical peripheral neuropathy due to arsenic exposure should also be closely studied in the future.

Saganoseki Copper Smelter Incident

This incident is a case of occupational exposure. Kuratsune et al. (21) in 1974 were the first to report lung cancer due to arsenic exposure in Japan. Another important aspect of this report is that high lung cancer mortality among males was discovered accidentally in a small town in the course of a routine vital statistics investigation by the local health department (Table 5). These men had been employees of the copper smelter. Based on this information, Kuratsune et al. performed a case-control study which also appeared in the same report in 1974.

Of a total of 19 cases of lung cancer, 11 persons had worked in the copper smelter. It was not confirmed whether these persons had perforation of the nasal septum, skin changes, anemia, or other typical symptoms of arsenic poisoning.

Discussion and Conclusion

In this presentation various effects due to arsenic exposure which occurred in Japan have been described and the dose, duration, and route of exposure are summarized in Table 6. In the Morinaga milk incident, the infants were exposed to relatively high doses of arsenic in powdered milk and the victims developed acute symptoms of the gastrointestinal tract, and in some cases, symptoms of the cen-
Table 6. Incident, type, route, dose of exposure and major symptoms.

| Incident              | Type of exposure | Route of exposure | Dose | GI tract | Nervous system | Skin changes | Skin cancer | Lung cancer | Perforation of nasal septum | Anemia | Fever | Liver disturbance |
|-----------------------|------------------|-------------------|------|----------|----------------|--------------|-------------|-------------|---------------------------|--------|-------|------------------|
| Morinaga, 1955        | General population (infants only) | Food (milk) | High | + | ± | a few cases | + | - | - | - | + | + | + |
| Ube, 1956             | General population | Food (soy sauce) | High | + | + | + | - | - | - | - | ± | + | ± |
| Niigata, 1959         | General population | Drinking High water | + | - | - | - | - | - | - | - | + | + | ± |
| Toroku mine, 1971     | General population | Air | Low | - | Peripheral | + | one case | ? | - | ± | - | ? |
| Sasagadani mine, 1972 | Occupational population | Air | Possibly water | Moderate | - | Peripheral | Subclinical | + | - | ? | - | - | - |
| Saganoseki smelter, 1974 | Mostly occupational | Air | Moderate | + | Peripheral | + | - | - | - | + | + | + | Liver cirrhosis |

*Residual effects on CNS are suspected.

One case.

tral nervous system, anemia, neuropathy, cardiovascular and skin changes, but no cancers. It is not clear whether the symptoms of the central nervous system were due to the stimulation of the cerebral membrane or to organic changes of the cerebral parenchyma. It is important to note that the development of some possible changes of the brain as indicated by EEG and possibly by the higher incidence of epilepsy occurred at a later stage—as late as 15 years after clinical changes had disappeared. No other study has reported the development of chronic encephalopathy among heavily exposed children or adults.

Cancer or Bowen’s disease due to arsenic poisoning among the Japanese people have not been frequently reported in spite of numerous reports of skin changes, including keratosis. It is noted that skin cancer occurs much less frequently among the Japanese population than among caucasian populations.

Another important question after having reviewed these episodes is whether arsenic is related to the causation of liver cirrhosis. In incidences reported in Japan, there is no increased prevalence of liver cirrhosis among those exposed to arsenic. In the Sasagadani incident, the married couple who had been drinking water containing 0.125 ppm arsenic showed liver cirrhosis (the husband) and Banti syndrome (the wife). However, since no cases of either disease have been observed among those who suffered heavier exposure, the relationship between these diseases and arsenic are still open to question.

In the soy sauce incident, it was noted that the symptoms improved even while the ingestion of the contaminated soy sauce was still in progress. The mechanism of this phenomenon should be further investigated.

The report on the increased prevalence of abnormality of EMG findings is also of interest, since prolongation of electric conduction velocity has been reported in persons whose blood lead level was lower than 70 μg/100 ml (22).

Since there have been no other reports on the increased risk of lung cancer due to arsenic among occupationally exposed workers in Japan, and also since the induction of lung cancer by arsenic in animal experiments has not been successful, the direct relationship between arsenic and lung cancer is still open to question. In the Saganoseki copper smelter incident, attention should be drawn to the fact that those workers of the smelter had also been exposed rather heavily to substances other than arsenic, including polynuclear organic substances, sulfur dioxide, and possibly to other chemical substances.

Future studies on arsenic poisoning are recommended to include the following: (1) transfer of arsenic to the brain through the blood-brain barrier, particularly in young organisms; (2) subclinical effects of arsenic in the peripheral nervous system; (3) relationship between arsenic or co-substance and cirrhosis or angiosarcoma of the liver; (4) cocarcinogenic substances or mechanism of the development of lung cancer due to arsenic; (5) adaptation mechanism; (6) difference of effects by type of inorganic compound.
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