HEALTH EFFECTS FROM EXPOSURE TO ACUTE LEVELS OF
INDUSTRIAL CHEMICALS

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Keywords: Acute toxicity, MSDS, Dioxins, Non-regular work,

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1. Introduction

In modern society, chemical manufacturers endeavor to develop new chemicals for industrial use, and we enjoy benefits from many commercial products made of new and existing chemicals. When hazardous chemicals are manufactured in a poor work environment without adequate technical control, workers suffer acute and chronic poisonings from exposure to these industrial chemicals. Occupational diseases caused by exposure to hazardous chemicals have been a primary subject of concern for workers and occupational health specialists. Environmental health scientists are also concerned with the health consequences of releasing of hazardous chemicals into the environment outside an industrial plant. Such environmental release has caused catastrophes of acute poisoning among surrounding community residents. An accidental release of methylisocyanate from a chemical plant in Bhopal, India, killed two thousand community residents near the plant and caused acute poisoning in more than 2000 people. In a chemical plant, Seveso, Italy, 2,4,5-trichlorophenol (TCP) containing 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was discharged into the environment by a “runaway reaction” explosion of a reactor vessel for TCP production. The soil, water and air were contaminated with dioxins, to which nearby residents were exposed. They suffered from acute poisoning including chloroacne, followed by various chronic diseases. Acute poisoning has also been reported to occur among consumers exposed to commercial products including cosmetics and hair and water-repellant sprays. For example, an aerosol spray for leather protection caused acute pulmonary illness and deaths among the spray users, but its mechanism still remained unknown. Some sensitized consumers exhibit an acute allergic response to cosmetics. Deliberate misuse of industrial chemicals has resulted in suicides and homicides. Deliberate inhalation of organic solvents has also caused acute and chronic poisoning among young people.

Although cases of acute chemical poisoning are often observed under non-occupational
situations, a large amount of knowledge, based on clinical experiences and exposures of workers and community residents to the industrial chemicals, has been accumulated in the field of environmental and occupational health. In this article, we shed light on human acute toxicity of industrial chemicals to which workers and community residents are exposed in the workplace and the living environment, respectively. Also, the acute toxicity of dioxins is focused on in the final section of this article, because in Japan, public concerns have been raised over an environmental problem of dioxins from waste incinerators.

2. What is Acute Toxicity?

The term “acute toxicity of industrial chemicals to which workers are exposed” has frequently been used among occupational health specialists, including industrial hygienists, toxicologists and physicians. Workers are concerned with acute toxicity of industrial chemicals in their workplaces, and they have right to know basic toxicity information. Containers must be labeled and the Material Safety Data Sheet (MSDS) of the industrial chemicals must be made available. Human acute toxicity seems to be used without clear definition, because repetition and duration of occupational exposure to an industrial chemical and the health consequences of exposed worker are difficult to assess. According to a 1988 study, acute toxicity may be defined as the short-term biological responses and effects of a single exposure to a hazardous chemical on the whole body, organs, tissues or cells. For human acute poisoning, “short-term” is defined as less than 30 days, and “single exposure” can refer to as a small number of exposures over a week or less. There are, however, several cases of acute poisoning due to occupational exposure to a hazardous chemical, which do not fit the above-mentioned definition. The biological responses and effects may continue longer than 30 days, sometimes be irreversible, or appear after a latency of longer than 30 days. For example, anoxia produced by short-term exposure to carbon monoxide evokes acute and chronic neurological disorders as well as severe, and often delayed neurological sequelae. Also, a single brief exposure to high concentrations of inorganic mercury vapor in an industrial accident caused acute symptoms of fever, chills, chest pains and weakness, followed by chronic symptoms of nervousness, irritability, lack of ambition and loss of sexual desire long after the accidental exposure. Thus, long-lasting or delayed-onset responses and effects resulting from a short-term exposure to an industrial chemical may not simply be classified as acute poisoning in the field of occupational health.

In sharp contrast, animal acute toxicity of a hazardous chemical is more clearly defined in experimental toxicology. Acute toxicity can be defined as the adverse effects or responses appearing within a short time following administration of a single dose or multiple doses of a chemical given within a 24 hour period. The biological responses and effects can be classified into either lethal or non-lethal endpoints. The lethality is given by LD$_{50}$ and LC$_{50}$ which are dose and concentration of a substance, respectively, at which 50 % of test animal population dies of acute poisoning during a 14 days observation period after a single exposure. The exposure includes oral or dermal route for a chemical or 1-hr or 4-hr inhalation of gas, vapor or aerosol concentration of the chemical. These acute animal LC$_{50}$s and LD$_{50}$s of industrial chemicals have only limited predictive power for acute human mortality indices of hazardous chemicals. There is occasionally a marked interspecies difference in acute mortality indices between
animals and humans. In acute animal toxicity studies, non-lethal endpoints include changes in body weight, behavioral and various biochemical parameters, and postmortem histopathological observations of targeted organs. Non-lethal animal indices relate more directly to human morbidity due to acute chemical poisoning. Sensory irritation/corrosion has frequently been used for evaluating acute human discomfort due to industrial chemicals, but may not be classified strictly into a non-lethal endpoint acute toxicity. Irritation may be elicited by an acute physiological response in which the nociceptive chemical receptors and the peripheral and central nervous system are involved.

3. Occurrence of Acute Poisonings in Industries

In Japan, the incidence of occupational injuries and diseases, which exceeded 30 000 in 1970, has steadily been decreasing. This number declined to 8600 in 1997 (General guidebook on industrial health, 1997). Of these 8600 cases, there were 6000 cases of injuries, 1300 cases of pneumoconiosis and 364 cases of occupational diseases caused by exposure of workers to hazardous chemicals. The annual General Guidebooks (1991-1997) on Industrial Health edited by the Japanese Ministry of Labor summarizes the reported number of occupational diseases due to exposure to hazardous chemicals in every fiscal year. The Japanese Industrial Safety and Health Law asks employers to promptly report to the Labor Standards Inspection Office any industrial poisoning incidence in which a worker takes leave for 4 days or longer. Table 1 shows yearly changes in the reported number of Japanese workers who suffered from or died of chemical poisoning during the years spanning 1991 and 1997. These data, which are summaries of the reported poisoning cases, consist mainly of acute poisoning cases, rather than chronic poisonings (General Guidebooks on Industrial Health, 1991 – 1997). Table 1 reveals that the total number of acute poisoning cases in Japan have leveled off with a yearly mean of 234 cases and 26 deaths during a recent 7 years. A group of chemicals designated as specified chemicals in the Japanese Ordinance on the Prevention of Hazards due to Specified Chemical Substances caused the highest incidence of chemical poisoning. Among 63 of the most hazardous substances specified by the Ordinance, the number of chemical poisoning cases was greatest for chlorine gas, followed by hydrogen sulfide, sulfur dioxide and hydrogen fluoride. The incidence of carbon monoxide poisoning was ranked as the second, with an average number of 61 cases, including 6 deaths. The yearly averaged incidence of organic solvent poisonings are ranked as the fourth, and the number of solvent poisoning cases was greatest for xylene, followed by dichloromethane, trichloroethane and trichloroethylene in decreasing order. The number of acute poisoning cases due to oxygen deficiency coupled with, or without, exposure to hydrogen sulfide was ranked as the lowest, but the incidence of fatality was highest. Acute poisoning from oxygen deficiency with H₂S is reported to occur in confined spaces with sewage among cleaning-up workers, by combined exposure to the oxygen-deficient atmosphere and hydrogen sulfide emanating from rotten biological materials. It has been noted from the General Guidebook on Industrial Health, 1997, that some newly developed substitutes for the ozone-layer depleting substances caused acute poisoning among workers who were not informed of their chemical and toxic properties. Those substances were 1,1-dichloro-2,2,2-trifluoroethane, 1,1-dichloro-2,2,3,3,3-pentafluoropropane and 1,3-dichloro-1,1,2,2,3-pentafluoropropane, all of which are classified as Other Chemicals in Table 1.
Specified chemicals are compounds that are regulated by the Japanese Ordinance on Prevention of Hazards due to specified Chemical Substances, and include 63 hazardous chemicals such as chlorine gas, hydrogen halide, but does not include hydrogen sulfide. Organic solvents are those regulated by the Ordinance on Prevention of Organic Solvent Poisoning.

Table 1. Yearly changes in number of Japanese workers who suffered from or died of chemical poisoning during a recent seven year period (1991 – 1997). (Parenthesized numbers indicate number of deaths)

4. Non-regular Work as a Causative Factor of Acute Poisoning

Exposure of workers to hazardous chemicals in the work environment has been prevented by various control technologies, such as isolation of hazardous manufacturing processes by sealing, automation and remote control, substitution with less toxic chemicals, and installation of a local exhaust ventilation system. The implementation of such technologies has markedly decreased the number of occupational diseases due to exposure to hazardous chemicals. Workplace practices, such as wearing of personal protective equipment, and health care management, such as periodical medical examinations by industrial physicians have also contributed to a decrease in the number of occupational diseases. There is, however, a group of non-regular workers who are at higher risk of acute poisoning due to high-level exposure to hazardous chemicals. These non-regular workers keep the regular manufacturing process running safely by periodical inspection, overhauling, repair and cleaning-up of the processes in the chemical plant. Demolition of manufacturing processes in the chemical plant can also be categorized into this non-regular work. Such non-regular work is dirty, dangerous and temporary in many cases, and is usually undertaken by subcontractors who may be unfamiliar with the manufacturing process. Therefore, they have a greater chance of accidental exposure to high levels of hazardous chemicals. In Germany, an accidental explosion of an autoclave reactor for synthesizing 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) contaminated a work facility with TCDD and caused chloracne, a hallmark of acute dioxin toxicity among cleanup and overhaul workers in 1953. A mechanic inhaled a presumably high level of TCDD-contaminated polychlorinated aromatic hydrocarbon residues in 1958, 5 years after the German BASF explosion accident, when he was performing a welding work on the autoclave used for the 2,4,5-T production. He suffered from acute dermatological and neurological disorders, and died 9 months later. His autopsy revealed severe chloracne of the trunk, pancreatic necrosis, perforation of the stomach and liver abscesses. The acute and chronic toxicity of dioxins was not

<table>
<thead>
<tr>
<th>Fiscal year</th>
<th>Organic solvents</th>
<th>Specified chemicals</th>
<th>Carbon monoxide</th>
<th>Other chemicals</th>
<th>Hydrogen sulfide</th>
<th>Oxygen deficiency</th>
<th>Total</th>
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<tr>
<td>1991</td>
<td>58 (7)</td>
<td>36 (0)</td>
<td>36 (7)</td>
<td>57 (2)</td>
<td>1 (1)</td>
<td>14 (16)</td>
<td>202 (33)</td>
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<td>36 (7)</td>
<td>9 (2)</td>
<td>55 (5)</td>
<td>22 (0)</td>
<td>9 (2)</td>
<td>7 (12)</td>
<td>138 (28)</td>
</tr>
<tr>
<td>1993</td>
<td>32 (6)</td>
<td>97 (6)</td>
<td>49 (2)</td>
<td>47 (1)</td>
<td>1 (7)</td>
<td>9 (5)</td>
<td>235 (27)</td>
</tr>
<tr>
<td>1994</td>
<td>39 (5)</td>
<td>87 (3)</td>
<td>71 (11)</td>
<td>30 (0)</td>
<td>10 (2)</td>
<td>12 (7)</td>
<td>249 (28)</td>
</tr>
<tr>
<td>1995</td>
<td>23 (5)</td>
<td>115 (1)</td>
<td>42 (7)</td>
<td>57 (0)</td>
<td>7 (1)</td>
<td>7 (11)</td>
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</tr>
<tr>
<td>1996</td>
<td>25 (4)</td>
<td>53 (6)</td>
<td>62 (7)</td>
<td>36 (0)</td>
<td>9 (4)</td>
<td>12 (10)</td>
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<td>1997</td>
<td>41 (2)</td>
<td>187 (1)</td>
<td>70 (3)</td>
<td>53 (1)</td>
<td>4 (0)</td>
<td>13 (3)</td>
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<tr>
<td>Mean</td>
<td>36 (5)</td>
<td>83 (3)</td>
<td>55 (6)</td>
<td>43 (1)</td>
<td>6 (2)</td>
<td>11 (9)</td>
<td>234 (26)</td>
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</table>
known at that time. In another example of the increased risk of non-regular work, a case of acute mercury poisoning has been reported in which 4 contractors were accidentally exposed to high levels of mercury vapor while repairing a turbogenerator in a power station. Their acute symptoms were difficulty in breathing, tremor, restlessness and sweating. In Japan, a leakage of hydrogen sulfide gas occurred at a chemical plant, and 43 workers were seriously or slightly injured, three of whom later died. The plant was conducting an annual regular inspection of the hydrogen desulfurization equipment, which was not in operation at the time of the accident (Present status of Japanese industrial safety and health, 1996). As shown in the previous section, the number of acute poisoning cases in Japan has remained fairly constant during recent years. In order to further reduce the number of acute poisoning cases, effective risk management should be implemented for the protection of subcontracted, unexperienced workers from exposure to hazardous chemicals that are released during non-regular work. Such risk management should include dissemination of information to non-regular workers about the acute toxicity of chemicals, countermeasures against exposure, health consequences and first aid for acute poisoning. Of course, daily activities of work environment control, work practice control and health care management in the workplace by occupational health professionals are essential to reduce the risk of occupational chemical poisonings.

**MSDS and OECD’s Classification and Labeling of Acute Toxicity**

<table>
<thead>
<tr>
<th></th>
<th>Class 1</th>
<th>Class 2</th>
<th>Class 3</th>
<th>Class 4</th>
<th>Class 5</th>
</tr>
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<tbody>
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<td>Oral (mg/kg)</td>
<td>5</td>
<td>50</td>
<td>300</td>
<td>2000</td>
<td>5000</td>
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<tr>
<td>Dermal (mg/kg)</td>
<td>50</td>
<td>200</td>
<td>1000</td>
<td>2000</td>
<td></td>
</tr>
<tr>
<td>Inhalation Gases (ppm)</td>
<td>100</td>
<td>500</td>
<td>2500</td>
<td>5000</td>
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</tr>
<tr>
<td>Vapors (mg/l)</td>
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<td>20</td>
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<tr>
<td>Dusts &amp; Mists (mg/l)</td>
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<td>0.5</td>
<td>1.0</td>
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Table 2. OECD's classification of chemicals that cause acute toxicity.

The 1990 ILO session adopted Convention No.170 on the “Safety of Chemical Substance Usage in Workplaces”. Since then, the occupational health-related regulations of many countries have stipulated that employers must provide workers with information about all hazardous chemicals used in the workplace through packaging, labeling containers and distribution of MSDS. Chemical providers and transporters have to provide their customers with MSDSs in which toxicity information including acute toxicity and first aid are described. Labeling of chemical hazardousness on a container or a synthesizing process is effective for the prevention of acute poisoning through prior notice of hazardousness to workers who handle the chemical. In Japan, the standards for classification of acute toxicity of chemical substances are based on an LD<sub>50</sub> of 500 mg/kg body weight via oral and dermal doses, and an LC<sub>50</sub> of 2000 ppm via inhalation. The Organization of Economic Cooperation and Development (OECD) has been taking the initiative to standardize globally the setting of standards to classify and label acute toxicity of industrial chemicals. The methods for determining the lethal indices of hazardous chemicals are indicated by the OECD test guidelines, in which animal species, number of test animals, administration routes and observation period are described in detail. Use of rodents is recommended. Table 2 shows a recent agreement
reached in OECD countries on the classification of acute toxicity of industrial chemicals by different routes of exposure. Chemicals with the most severe acute toxicity are categorized as Class 1.

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**Biographical Sketch**

Heihachiro Arito, Ph.D., worked as an occupational toxicologist for the National Institute of Industrial Health, Ministry of Labor from 1965 to 2001. A visiting scientist in University of Washington, School of Public Health and Community Medicine in early 1970s and in Harvard School of Public Health in early 1990s. From 2001 to 2004, I moved to the Japan Bioassay Research Center, Japan Industrial Safety and Health Association as a toxicologist