SECTION

I

Introduction

CHAPTER

1

Toxicology and Its Roots as a Science

Introduction

It is clear that in our environments, we are routinely exposed to chemical agents. We justify their use to maintain and improve our own well-being and that of society in general. Unfortunately, we have seen, and may continue to see, incidents of chemically induced adverse events in humans and other species.

Bhopal, India, was the site of one of the largest industrial accidents of the 20th century. In 1969, Union Carbide Corporation built a carbaryl pesticide (trade name Sevin) factory there to support the emerging Indian agricultural market. The production process used by the Union Carbide India Limited (UCIL) plant combined methylamine with phosgene to form methyl isocyanate (MIC), which was then added to 1-naphthol to generate carbaryl. Poor economic conditions in India meant farmers were unable to afford Sevin, and as a result, the factory had a large quantity of unsold intermediates such as MIC in storage. In the early morning hours of December 2, 1984, water entered an MIC tank and the resultant exothermic reaction ruptured the tank and released more than 25 tons of MIC vapor. Many of the plant's safety features (flare towers, water curtains, and vent scrubbers) had fallen into disrepair and failed to work. Horribly, this

accidental discharge of methyl isocyanate into the air resulted in the overnight deaths of approximately 4,000 individuals, and over 100,000 more sustained injuries, some of which were so severe that many thousands later died. Prevailing winds carried the heavy gas over the densely populated shanties of Bhopal. The citizens of Bhopal woke with the onset of the initial effects of MIC exposure—coughing, air hunger, vomiting, and intense eye irritation. The primary cause of death was pulmonary edema; many survivors showed signs of compromised respiration (e.g., bronchoalveolar lesions and decreased lung function) and impaired vision (e.g., loss of vision, loss of visual acuity, and cataracts). Humans were not the only ones affected; thousands of animal carcasses were collected in the weeks following the release.

Recognizing the benefits of chemicals in general, we accept the potential risks related to their use until some undesirable event or additional information about any particular chemical forces us to reevaluate its benefit in light of the risk posed. As public health professionals, we further recognize that, at times, large numbers of individuals may be exposed to certain chemicals where there is often only limited information available about their effects on human health. This is especially true for chronic "low level" exposures. As we will see later, human safety is often inferred from laboratory data in animals as the source of toxicity information as, for example, in the case of satisfying the regulatory requirement for the safety of a new food additive by the federal Food and Drug Administration (FDA).

A simple yet comprehensive definition of toxicology is the study of the adverse effects of chemicals in biological systems. A biological system can be as complex as an entire organism or can be a less complicated in vitro cell culture system. As public health professionals, we direct most of our attention to human health effects; however, we must also recognize that we share our planet with other organisms, both plants and animals that are also affected by chemical agents.

Paracelsus, a German-Swiss Renaissance physician (1493–1541), expressed an early understanding of the conditions under which a chemical can become harmful Paracelsus hypothesized that all substances are potentially poisonous. The right dose differentiates a poison and a remedy. While this statement shows clear recognition of the very basis of toxicity, the dose, it further implies that concerns for a substance's toxicity are also a function of exposure, the conditions of exposure, the susceptibility of the host, and other factors and circumstances that may have bearing on evaluating the safety or hazard of a given exposure. All chemicals are toxic at some dose and may produce harm if exposure is sufficient; all chemicals produce their harm (toxicities) under prescribed conditions of dose or usage. It has been said that there are no harmless substances, only harmless ways of using them.

We must always remember that the evaluation of a chemical exposure as harmless or hazardous should not be viewed only as a function of the magnitude of the exposure (dose), or the types of toxicities that may produce at some given dose.

Toxic Chemicals

Terms commonly used to refer to toxic chemicals are as follows:

- Toxic chemical
- Toxic substance
- Toxic agent
- Poison
- Toxin
- Toxicant
- Xenobiotic

Although the terms toxicant and toxin are frequently used interchangeably, they have different meanings. A toxicant is any chemical that can potentially produce harm. Toxicants may affect specific tissues or organs (target tissues, target organs), such as benzene, which affects the blood and blood-forming tissues. Toxicants may also be relatively nonspecific, thus affecting the entire body. Sodium cyanide is an example of a systemic toxicant that has the ability to interfere with all body cell utilization of oxygen. A toxicant may be a heavy metal such as lead, a pesticide, an organic solvent, or even a toxin. The term toxin, on the other hand, must be reserved for those chemicals that are produced by living organisms. Rattlesnake venom or poisonous mushrooms contain toxins. Many toxins are extremely hazardous chemicals and can produce severe injury to tissues and organs, often to the extent that death may result from body system failure (**Table 1-1**).

A poison is generally defined as any substance that when ingested, inhaled, or absorbed or when applied to, injected into, or developed within the body in relatively small amounts may, by its chemical action, cause death or injury. A poison therefore could be any of the numerous synthetic chemicals or a chemical produced by a living organism (toxin). The commonly used term toxic substance does not describe whether one is speaking about a particular chemical or a

Table 1-1 Examples of Toxins

Toxin and Source	Example of Tissue/System Affected
Aflatoxin B (*Aspergillus flavus*)	Liver Necrosis and Cancer
α-Amanitin *(Amanita phalloides)*	Gastrointestinal Tract and Liver Cancer
Anatoxin (*Anabaena* spp.)	Nervous (anticholinesterase)
Sodium fluoroacetate *(Dichapetalum cymosum)*	Cardiac, Skeletal Muscle, Nervous
Ochratoxin A *(Aspergillus ocraceus)*	Kidney
Pyrethrin I *(Pyrethrum cinariaefolium)*	Nervous
Tetrodotoxin *(puffer fish, amphibians)*	Nervous

Table 1-2 Examples of Xenobiotics

Toxicant and Source	Example of Tissue/System Affected
Deltamethrin *(insecticide)*	Nervous
Ethylene glycol monomethylether *(solvent)*	Testis
n-Hexane *(solvent)*	Nervous
Methyl isocyanate *(used in insecticide manufacture)*	Lung and Eye
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) *(impurity in demerol)*	Nervous
Paraquat *(herbicide)*	Lung
Soman *(nerve gas)*	Nervous

mixture of chemicals that collectively have toxic properties. For example, whereas lead chloride is a discrete chemical that has toxic properties, asbestos is not a discrete chemical, but rather a mixture of various chemicals whose composition may vary.

The term xenobiotic literally means foreign to the body and can refer to any chemical that is not a natural component of the body (e.g., a synthetic antibiotic). The term, however, is typically used in the context of any synthetic chemical that has no beneficial effect on the body (**Table 1-2**).

The degree and nature of toxicity is not only related to which chemical one is exposed (the hazard) but to the conditions of exposure as well (e.g., the route and duration of exposure). For example, ethanol can acutely produce its effects on the central nervous system, but over the long term it produces chronic toxicity to the liver as well.

The practice of toxicology involves the application of toxicological principles that are focused on environmental, regulatory, industrial, clinical, or forensic issues, to name several. Indeed, any issue relating to health risks from chemicals is of concern to toxicologists. Toxicology is an applied science that has assimilated the theoretical and technical advances of disciplines such as chemistry, biology, physiology, pharmacology, pathology, epidemiology, and biostatistics. The duality of toxicology requires gathered and applied science. For this reason toxicology is often described as a "borrowing" science, and, indeed, this use of information from other disciplines is one of toxicology's greatest strengths. Toxicology can be considered one of the most interdisciplinary sciences of the modern age.

Epidemiological Studies

In toxicology, proof that a given chemical exposure resulted in change(s) in human health is established by a hierarchy of evidence. Students of public health toxicology must further recognize the importance of epidemiology in establishing toxicological causation. Epidemiological

studies are considered the highest level of scientific evidence for proving an association between a particular chemical exposure and human health effects. Studies are conducted using human populations to evaluate whether there is a causal relationship between exposure to a substance and adverse health effects. These studies can be based on literature that associates human illness with a particular exposure, as well as toxicological evidence from studies in which animals were exposed in a way that is likely to occur in humans. This scenario of experimentally induced production of adverse effects or even death in animals may or may not be similar to those effects that have been observed in humans. There are a number of aspects in designing an epidemiology study, the most critical being appropriate controls, adequate time span for the study, and statistical ability to detect an effect. The statistical ability to detect an effect should be based upon the study and control populations being as large as possible. The risk to the exposed population must be compared to that in an identical (e.g., same age, sex, race, economic status, etc.) unexposed population. Many epidemiology studies evaluate the potential of a chemical to cause cancer. Because most cancers have long latency periods (e.g., 20 years or more), the study must cover that period of time.

Types of epidemiological studies include:

- **Cohort study**—A cohort (group) of individuals *with exposure* to a chemical and a cohort *without exposure* are followed over time to compare disease occurrence.
- **Prospective cohort study**—Cohorts are identified based on current exposures and followed into the future.
- **Retrospective cohort study**—Cohorts are identified based on past exposure conditions and follow-up proceeds forward in time.
- **Case control study**—Individuals *with a disease* (e.g., cancer) are compared to individuals *without the disease* to determine if there is an association between the disease and prior exposure to an agent.
- **Cross-sectional study**—The prevalence of a disease or clinical parameter among one or more exposed groups is studied, for example, the prevalence of respiratory conditions among pesticide applicators.
- **Ecological study**—The incidence of a disease in one geographical area is compared to that of another area. For example, cancer mortality in areas with hazardous waste sites are compared to areas without waste sites.

Causality

Proof of causality, or the association of a particular exposure with a particular disease, is based on a variety of criteria. These criteria were first discussed by Hill in 1965. Using cigarette smoking as an example, the following criteria are considered:

- **Strength of association**—The stronger the relationship between the independent variable and the dependent variable, the less likely it is that the relationship is due to chance. The lung cancer rate for smokers is significantly greater than for nonsmokers.

- **Temporality**—It is necessary for a cause to precede an effect in time. Smoking in the vast majority of cases precedes the onset of lung cancer.
- **Consistency**—Multiple observations, under different circumstances with different observers, increase the likelihood of causation. In lung cancer, studies using both prospective and retrospective methods that provide a link between smoking and lung cancer have produced similar results in both males and females.
- **Biological plausibility**—It is easier to accept an association as causal when there is a rational and theoretical basis for such a conclusion. Does it make sense? The idea of smoking causing tissue damage, which over time results in cancer in the cells, was a highly plausible explanation.
- **Coherence**—Causality is clearest when it does not conflict with what is known about the variables under study and when there are no plausible competing theories or rival hypotheses. In other words, the association must be coherent with other knowledge. The conclusion (that smoking causes lung cancer) made sense given the current knowledge about the biology and history of the disease.
- **Specificity**—Demonstrating that an outcome is best predicted by one primary factor adds greatly to causality. Lung cancer is best predicted from the incidence of smoking.
- **Dose–response relationship**—There should be a direct relationship between the risk factor and the expression of the disease. There is a positive, linear relationship between the number of cigarettes smoked and the incidence of lung cancer.
- **Experimental evidence**—Any related research that is based on experiments will make a causal inference more plausible. Carcinogens have been shown to be present in tobacco tar and can induce cancer in laboratory animals.
- **Analogy**—Induced smoking in laboratory rats has showed a causal relationship to the development of cancer. By analogy, therefore, scientists made certain inferences and applied these scientific principles to humans.

Epidemiological study interpretations that deal with associations between particular exposures and human health effects must depend on the weight of evidence.

Toxicological causation often may not be readily apparent, but rather suggested based upon the weight of evidence (**Table 1-3**). As an example, consider the health effects from ozone exposures (see **Table 1-4**).

Additional causality evidence can be demonstrated in both experimental and epidemiological studies when there is a reduction in adverse effects that corresponds to the removal, reduction, or limitation of the exposure. This assumes, of course, that the injury produced is reversible in nature.

The Roots of Toxicology

Toxicology, from the ancient world and biblical times through medieval alchemy and the Renaissance, is a science that is rooted in a rich and interesting history. Reference to "poisonous" substances can be traced back to the use of natural poisons in hunting, "medicines,"

Table 1-3 Weight of Evidence for Causality

Causal

Evidence is sufficient to conclude that there is a causal relationship with relevant chemical exposures. That is, a chemical has been shown to result in health effects in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example: (1) controlled human exposure studies demonstrate consistent effects; or (2) observational studies cannot be explained by plausible alternatives or are supported by other lines of evidence (e.g., animal studies or mode of action information). Evidence includes replicated and consistent high-quality studies by multiple investigators.

Likely to Be Causal

Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant chemical exposures, but important uncertainties remain. That is, the chemical has been shown to result in health effects in studies in which chance and bias can be ruled out with reasonable confidence, but potential issues remain. For example: (1) observational studies show an association, but co-chemical exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent; or (2) animal toxicological evidence from multiple studies from different laboratories demonstrate effects, but limited or no human data are available. Evidence generally includes replicated and high-quality studies by multiple investigators.

Suggestive of Causality

Evidence is suggestive of a causal relationship with relevant chemical exposures but is limited because chance, bias, and confounding cannot be ruled out. For example, at least one high-quality epidemiological study shows an association with a given health outcome, but the results of other studies are inconsistent.

Evidence Is Inadequate

Evidence is inadequate to determine if a relationship exists with relevant chemical exposures. The available studies are of limited statistical power, quantity, quality, and consistency to permit a conclusion of causality.

Not Likely to Be Causal

Evidence suggests that with relevant chemical exposures, covering the levels of exposure that humans, including susceptible populations, would likely encounter, it is unlikely that a causal relationship exists.

Table 1-4 Health Effects of Ozone

Health Outcome	Causality Evidence
Respiratory Effects	Evidence *supports a causal relationship* to increased respiratory morbidity outcomes
Central Nervous System Effects	Limited evidence *is highly suggestive* of contributing to central nervous system–related morbidity, with alterations in system effects, neurotransmitters, motor activity, short- and long-term memory, sleep patterns, and histological signs of neurodegeneration
Cardiovascular Effects	Limited evidence *is highly suggestive* of contributing to cardiovascular-related morbidity

assassination, warfare, or other purposes. Early records show that humans did indeed use poisons rather effectively. The Ebers Papyrus (circa 1500 B.C.) contains the recipes of more than 800 "medicinal" and poisonous preparations. It describes poisons known at that time, including hemlock, later to be used as the state poison of the Greeks ("Socrates' nightcap"), as well as opium, aconite (a Chinese arrow poison), and heavy metals such as lead, copper, and antimony (**Figure 1-1**).

History has shown that it was not uncommon to retain the services of a poisoner to rid oneself of an inconvenient spouse or political rival, or the services of a poison "taster" to ensure that the food and drink to be consumed would not result in one's own demise!

Fortunately, the science has expanded well beyond only the poisoner's perspective, although poisoning (whether intentional or accidental) still remains an important focus area for the modern specialties of clinical and forensic toxicology. As toxicology began to more fully develop, it shed the unsupported superstitions of the past. The use of more objective methodologies and experimentation to produce or challenge ideas or to question unsupported but long held views about causality and nature became more firmly rooted as the best way to learn and advance the science.

FIGURE 1-1 The Ebers Papyrus. Kol I-II. *Source:* Courtesy of the National Library of Medicine.

Contributors to Toxicology

Contributors to the developing discipline of toxicology are numerous. The physician Hippocrates (circa 400 B.C.) is credited with being one of the first physicians to apply basic pharmacology and toxicology principles to the practice of medicine, including concepts of bioavailability and overdose.

Several early toxicological treatises stand out as noteworthy. In his work *De Historia Plantarum*, Theophrastus (371–287 B.C.) described numerous poisonous plants. Dioscorides (40–90 A.D.), a Greek pharmacist, physician, and botanist who served in the court of Roman emperor Nero, produced a pharmacopoeia to classify poisons according to their origin as animal, vegetable, or mineral. His work *De Materia Medica* is a five-volume systematic description of approximately 600 different plants and 1,000 different medications and has served as an important standard reference for almost 16 centuries. It is still considered a useful treatise even by today's standards.

The contributions of Moses ben Maimon, or Maimonides (1135–1204), to toxicology have survived through the years (**Figure 1-2**). He recognized that the bioavailability of many consumed toxins could be influenced by certain foods such as milk, butter, and cream, which appeared to impair their absorption. In addition to being a competent and well-respected physician, he was also a prolific writer. Of particular significance was his volume entitled *Poisons and Their Antidotes*, which was a guide to the treatment of accidental or intentional poisonings and animal bites. Maimonides recommended that suction be applied to insect stings or animal bites as a means of extracting the poison. He rejected numerous popular remedies of the day after testing them and finding them to be ineffective (e.g., the use of unleavened bread in the treatment of scorpion stings).

FIGURE 1-2 Commonly used image indicating one artist's conception of Maimonides's appearance. *Source:* Courtesy of the National Library of Medicine.

Philippus Aureolus Theophrastus Bombastus von Hohenheim (1493–1541) was a physician alchemist in the late Middle Ages who pioneered changes in the biomedical sciences. The importance of his contributions to the field cannot be underestimated; indeed, he changed his name later in life to Paracelsus (combining "para," or superior to, with Celsus) to reflect his own feeling that he should be regarded as superior to Aulus Cornelius Celsus, an early Roman physician. Paracelsus asked the question, "What is there that is not poison?" All things are poison and there is nothing without poison. Solely the dose determines that a thing is not a poison. Today, every student taking a first class in toxicology will hear his name and recognize the concept in one form or another, whether it is "The dose makes the poison," "All substances are poisons; there is none which is not a poison," or "The right dose

differentiates a poison from a remedy." Although he was an alchemist by trade, Paracelsus advanced several principles that formed the basis of the modern dose–response relationship:

- Experimentation is essential in the examination of the response to chemicals.
- One should make the distinction between the therapeutic and toxic properties of a chemical.
- One can ascertain a degree of specificity of chemicals and their therapeutic or toxic effects.
- Therapeutic and toxic properties are sometimes only distinguishable by dose.

Paracelsus recognized, for example, that although mercury is a poison, it can also be used to treat syphilis. Paracelsus additionally wrote a treatise *On the Miners' Sickness and Other Diseases of Miners*, which appears to have been one of the first major works of occupational toxicology (**Figure 1-3**).

Toxicological specialties began to emerge in the 18th and 19th centuries. In 1700, Dr. Bernardino Ramazzini (1633–1714) published the first edition of his most famous book, *De Morbis Artificum Diatriba* (*Diseases of Workers*), the first comprehensive work on occupational diseases outlining the health hazards of irritating chemicals, metals, dusts, and so forth that were encountered by workers in 52 occupations. This work became a standard reading in occupational medicine for the next 200 years.

Dr. Alice Hamilton, the first female professor at Harvard University, was also known as the "founder" of American occupational toxicology. Her book, entitled *Exploring the Dangerous Trades*, makes excellent reading for those especially interested in the history of medical and occupational toxicology.

FIGURE 1-3 Paracelsus. *Source:* Courtesy of the National Library of Medicine.

As communities began to shift from more sparsely populated agricultural societies to more densely populated town-centered societies, the incidence of some diseases was more easily detected. Some diseases could be causally linked to specific occupations. For example, a higher incidence of scrotal cancer in chimney sweeps was observed by Percival Pott (1714–1788), who recognized the relationship between the development of this disease and exposure to large amounts of soot and poor personal hygiene. Here we can see how perhaps a specific aspect of personal lifestyle in these individuals was an important contributing factor in the development of this disease. Ironically, if these workers had better attended to their personal hygiene, advances in the area of chemical carcinogenesis may have been significantly delayed!

Mathieu Orfila (1787–1853), a Spanish physician serving in the French court during the 1800s, essentially established the discipline of forensic toxicology. He used chemical analysis and

autopsy-related materials as proof of poisoning in legal proceedings. He developed a method for the analysis of arsenic that became the legal standard of the time. His book, *Traité des Poisons* (1814), went through several editions and is considered to be one of the most outstanding treatises in toxicology (**Figure 1-4**).

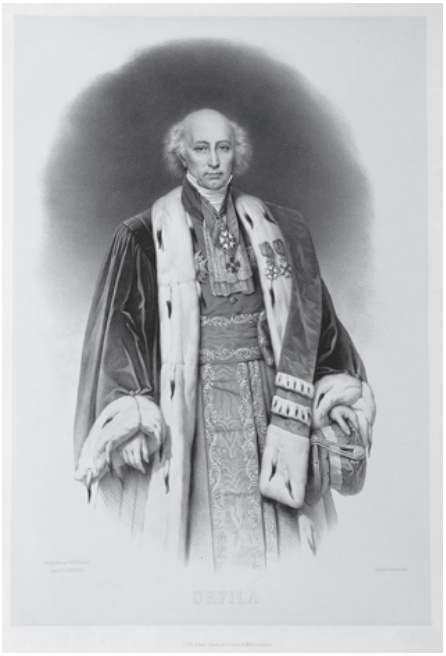

FIGURE 1-4 Mathieu Joseph Bonaventure Orfila. *Source:* Courtesy of the National Library of Medicine.

Early History: Intentional Poisonings

The early history of toxicology, as previously mentioned, contains numerous references to intentional poisonings. The "execution" of Socrates (470–399 B.C.) by drinking hemlock is one of the best known cases of suicide by poisoning, which was common practice in early Greek politics. Fear of being poisoned allegedly led Mithridates VI of Pontus (120–63 B.C.) to protect himself by consuming small doses of as many as 36 popular poisons of the day. As the story goes, his "self-inoculation" was apparently successful, because a later attempt at suicide by poisoning was completely ineffective and he was reduced to using a sword to accomplish his end. The term "mithridate" has been used to describe a concoction that possesses antidotal properties.

A contemporary of Paracelsus, Catherine de Medici (1519–1589), queen of France from 1547 to 1559, brought her poisoning skills from Italy to France, where she practiced her trade by "treating" poor sick people with poisons, carefully evaluating their responses, the effectiveness of the dose, the parts of the body affected, and the signs and symptoms of her victims. She was quite the descriptive toxicologist, and one must wonder if she was familiar with some of the principles of Paracelsus.

An Italian woman of the 17th century named Madame Giulia Toffana (1635–1719) developed a poisonous mixture and is reputed to have been responsible for greater than 500 killings. Her poisonous concoction containing arsenic was referred to as "Agua Toffana" ("the water of Toffana") or sometimes as "the Elixir of St. Nicholas of Bari," Bari being a town whose water was alleged to have healing properties. She sold it to individuals along with instructions concerning its proper use to get the job done. In 1719 she was executed in Naples; however, her "profession" was carried on by Heironyma Spara, a Roman contemporary who continued the training of young women in the art of how to murder their husbands by poisoning. She is said to have formed a local club of young wealthy married women, which soon became a club of eligible young wealthy widows. She was hanged along with other women, suspected to have been her aides.

In France, comparable activity was carried out by Catherine Deshayes (1638–1680), popularly known as La Voisin, who was also in the business of selling poisons to wives who wished to be rid of their husbands. The number of deaths that she may actually have been responsible for is claimed to be in the thousands. She was burned at the stake in 1680.

Not all poisonings are intentional, and, indeed, a lack of knowledge concerning the toxicity of even commonly used substances may contribute to the development of health problems. The early Romans, as an example, boiled wines to make them sweeter and thicker. Unfortunately, the pots that they used were made from copper and lead. The early Roman body burden of lead may have been higher in the more affluent Romans who had the financial means to obtain as much wine as their social and political position demanded. Today, of course, we all recognize the association between the body's accumulation of lead and the neurotoxicity that it can produce and even may be tempted, as have others, to speculate on the role that lead may have played in the decline of ancient Rome.

The Evolution of Toxicology

The development of toxicology as a science has been, like most other disciplines, a long process of slow and steady growth from the work and deeds of the good and the not so good as referenced here. A growth spurt in its development has occurred over the past century that has been remarkable and stimulated by the widespread use of dangerous "patent remedies," environmental pollution, adulteration of foods, occupational injuries, consumer illness, surge of pesticide use, and chemical production, just to name a few. The confluence of public concern, legislative action, and research has produced a flurry of legislation, journals, professional organizations, and regulatory agencies. Often decisions are initially made on the basis of public opinion, not the weight of evidence. Examples include the following:

- The Great Apple Scare of 1989 resulted from the use of Alar (Daminozide), a chemical used to prevent preharvest rotting that has been called the most potent cancer-causing agent in our food supply. It was removed from markets following public pressure without convincing evidence that eating apples placed any individual at excess risk for developing any cancer.
- Saccharin, an artificial sweetener discovered in 1879, was shown in a Canadian study to produce bladder tumors in male rats given artificially high doses, not especially relevant to human consumption. The FDA proposed its ban in 1977, but withdrew it in 1991; the National Toxicology Program and the National Institute of Environmental Health Science also removed it from their cancer threat lists.
- "Toxic Playgrounds" were believed by many to have resulted from the use of wooden play sets treated with chromated copper arsenate (CCA). Many believed that children exposed to this equipment were placed at excessive risk for cancer due to arsenic and hexavalent chromium leaching out of the treated lumber, and thus it was voluntarily removed by many public facilities.

In other instances, toxicity was clearly apparent, such as with the following examples:

- *An outbreak of jaundice in the Epping district of Essex, England, in February 1965*. Eighty-four persons ate wholemeal bread made at an Epping bakery. Biopsies of liver showed cholestasis. A sack of flour from which the bread was made had been contaminated with 4,4' diaminodiphenylmethane (an aromatic amine, dissolved in butyrolactone), which had been spilled

in the transporting van from a plastic container. This chemical was identified as the cause for the Epping jaundice.

- *The occupational exposure to mercuric nitrate (HgNO3) in the mid-1800s*. The chemical was used to shape wool felt hats, and exposed individuals developed psychotic symptoms including hallucinations, hence the term "mad hatter disease."
- *The industrial discharge of mercury in Minamata, Japan, from 1932 to 1968*. This resulted in severe nervous system dysfunction in individuals who consumed a regular diet of fish from the bay.
- *The oil spill at Prince William Sound in Alaska on March 24, 1989*. Exxon Valdez spilled over 11 million gallons of crude oil, resulting in an environmental disaster to birds, fish, and other wildlife.
- *Cult suicides by poison in Ghana on November 18, 1978*. Jim Jones of the Peoples Temple and hundreds died by suicide (cyanide-laced punch).

The first professional organization for toxicologists, the Society of Toxicology (SOT), held its first formal meeting on April 15, 1962, in Atlantic City, New Jersey. SOT is a professional and scholarly organization that represents a large number of scientists from academia, industry, and government who practice toxicology in the United States and around the world. The organization is dedicated to supporting the research and communication of sound scientific information that improves decisions regarding the health of humans, other animals, and the environment. The Society has established a number of specialty sections, including public health and regional chapters.

The official journal of the Society, *Toxicology and Applied Pharmacology*, was probably the first dedicated publication for the dissemination of toxicology research. Today, toxicology is well rooted, with numerous professional organizations, journals, and thousands of toxicologists internationally. The International Congress of Toxicology, composed of toxicology societies from the United States, Europe, Africa, Asia, South America, and Australia, provides an international forum through its meetings and publications to bring toxicologists together from all over the world.

Bibliography

Baron, S. L., & Brown, T. M. (2009). Alice Hamilton (1869–1970): Mother of U.S. occupational medicine. *American Journal of Public Health*, *99*(Suppl. 3), S548.

Hill, B. A. (1965). The environment and disease: Association or causation? *Proceedings of the Royal Society of Medicine*, 58, 295–300.

Klaassen, C. D. (2001). *Casarett & Doull's toxicology. The basic science of poisons*. New York, NY: McGraw-Hill.

Klaassen, C. D. (2007). *Casarett & Doull's toxicology. The basic science of poisons*. New York, NY: McGraw-Hill.

Klaassen, C. D., & Watkins, J. B. (2003). *Casarett & Doull's essentials of toxicology*. New York, NY: McGraw-Hill.

National Toxicology Program. (n.d.). Retrieved from http://ntp-server.niehs.nih.gov/.

U.S. National Library of Medicine, National Institutes of Health, Environmental Health and Toxicology Specialized Information Services (SIS). (2009, December 22). *Toxicology tutorial I*. Retrieved from http://www.sis.nlm.nih.gov/enviro/toxtutor.html.