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Fundamentals of Industrial Toxicology

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Preface

The growth of technology has generated new chemicals at a rate never before experienced. The safety of these new materials is a major concern. Furthermore, for chemicals which have long been in use, we have become aware of previously unsuspected toxicity problems such as carcinogenesis, mutagenesis, and teratogenesis. The challenge to the toxicologist is to assess the hazard of chemicals and to recommend the safe conditions under which we may come into contact with them. Creation and enforcement of regulations based on these recommendations has given rise to not one, but several government agencies. In a bewilderingly brief period of time, practically everyone in industry has become aware of the regulations generated by these agencies and the need to conform to them. Consequently, a new vocabulary has been thrust on many engineers and plant managers—for most, their chemistry and biology backgrounds have faded a bit with the passage of time. *It is no consolation that much of the vocabulary of toxicology would be equally foreign to a recent chemistry or biology graduate.*

It is primarily to assist people in industry that this book has been prepared. Here we introduce the basic concepts of industrial toxicology in a compact fashion, designed particularly for people whose background did not prepare them in this area but who now find they must deal with it. A reference that serves those already employed in industry, this book will also

prove valuable to those about to enter industry. Students can use this book either as the basis of a short course at a university or for self instruction. In summary, the principles and vocabulary of toxicology are introduced. Many problem compounds are singled out for specific discussion. Extensive lists of references allow those who require more depth in some aspect of the field to locate more detailed sources. The whole is presented in a compact, convenient format.

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Ronald M. Scott received a PhD in Biochemistry from the University of Illinois and a BS in Chemistry from Wayne State University. Since 1959 he has lectured in biochemistry and, more recently, in toxicology, at Eastern Michigan University. Professor Scott has consulted on problems of metal ion toxicity, and has guest-lectured at the University of Warwick, England. He has published papers in professional journals on topics of chromatographic methods of trace analysis; techniques for clinical analysis; and work relating to the use of freshwater clams as environmental monitors of industrial effluents. Professor Scott has written three chromatography reference books and a biochemistry textbook, and was technical editor of a reference book on trace analysis.

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Definition and Scope of Industrial Toxicology

Many substances utilized, formulated and manufactured in the industrial environment possess the ability to adversely affect humans. The National Institute for Occupational Safety and Health (NIOSH) annually publishes its *Registry of Toxic Effects of Chemical Substances*[1]. The 1978 edition lists almost 28,000 different substances which meet this definition:

> A toxic substance is one that demonstrates the potential to induce cancer, tumors, or neoplastic effects in man or experimental animals; to induce a permanent transmissible change in the characteristic of an offspring from those of its human or experimental animal parents; to cause the production of physical defects in the developing human or experimental animal embryo; to produce death in animals exposed via the respiratory tract, skin, eye, mouth or other routes in experimental or domestic animals; to produce irritation or sensitization of the skin, eyes, or respiratory passages; to diminish mental alertness, reduce motivation, or alter behavior in humans; to adversely affect the health of a normal or disabled person of any age or of either sex by

producing reversible or irreversible bodily injury or by endangering life or causing death from exposure via the respiratory tract, skin, eye, mouth or any other route in any quantity, concentration, or dose reported for any length of time.

While the definition is long and encompassing, it reflects the variability of toxicology. Toxicology is a science that combines and requires the knowledge of other sciences. Biology, chemistry, biochemistry, pharmacology, physiology and pathology are all utilized in industrial toxicology. The toxicologist investigates the harmful actions of chemicals on biological tissue, but usually has a specific and practical goal. In the course of exploring the potential harm chemicals may have, testing is performed chiefly to determine the conditions under which chemicals may be safely used.

The science has developed three main branches: forensic toxicology (dealing with the medical and legal aspects of human poisoning); economic toxicology (dealing with the harmful effects of substances which are deliberately administered to biological organisms to achieve some specific purpose, e.g., drugs, food additives and pesticides); and environmental toxicology (dealing with the harmful effects of substances to which people are unintentionally exposed, as in the environment, food and the workplace). Industrial toxicology is part of this last division, and is concerned with the harmful potentials of the raw materials, intermediates and finished products encountered by workers[2].

This book will divide industrial toxicology into component parts, and explore the significance and interrelationships of these parts. In order to identify the advancement of industrial toxicology, a review of historical events is necessary. Chapter 2 will briefly review the historical progression of industrial toxicology.

2
Historical Review of Industrial Toxicology

Before proceeding with a detailed study of industrial toxicology as it exists today, it would be wise at this point to examine the word "toxicology" and to review the historical development of man's interest in the adverse effects of various substances on man and body.

Toxicology is the study of the nature and actions of poisons[3] The term is derived from the Greek word referring to the poisons in which arrows were dipped. Archaeological research has provided knowledge of the poisons used by primitive man. Venoms, poisonous herbs and toxic materials were known to primitive man. Myth, legend and history indicate the growth of toxicological knowledge[4]. For example, the African Bushmen used a mixture of various species of herbs as poisons for arrow tips. Periodically, snake and black spider venom was added to this mixture. Other African tribes used seeds for poisons. Poisons were emphasized in early times.

Each succeeding age had its own toxins and methods of administration. As early as 1552 BC, Egyptian scrolls listed spe-

cific diseases and/or remedies. Mention is also made of the toxicity of lead, antimony and copper. In 460 BC the Greek scholar, Hippocrates, had advanced the knowledge of poisons considerably. Arsenic, antimony, mercury, gold, copper and lead were all identified as toxic by Hippocrates. By 980 AD the Arabs had translated Greek works into Arabic and had developed their own system of medicine. They were advanced chemists and developed novel analytical methods for processing medicines. Numerous agents were identified as toxic by Arab physicians. Our knowledge of poisons from the ninth to the fifteenth centuries (the Middle Ages) is derived from manuscripts which have come down to us from these periods[5]. A number of toxic agents were identified in the Middle Ages. During the sixteenth and seventeenth centuries, poisoning became a serious menace. As more toxic agents were discovered they were utilized in heinous ways. Occupational exposures to toxic agents were then being considered. The nineteenth century saw the development of tests for identification of poisons. In the 1880s Orfila published a classic text on toxicology, *Traite' de Toxicologie*, which provided a major breakthrough in toxicology. Orfila's works provided a needed stimulus to toxicology[8]. Within a short time numerous researchers were devoting considerable effort to the study of toxic agents. Since about 1900 increasing social concern for the health of workers exposed to chemical agents has proliferated[6]. Intensive investigation and research of the toxicity of industrial materials has been precipitated by social concern. The emphasis on safe and healthful work environments and proper precautionary measures for the utilization of toxic materials has been addressed by industrial toxicology.

Some industrial hazards have been known for centuries. In the first century AD the symptomatology for lead intoxication was identified[7]. The Romans used only slave labor in the Spanish mercury mines at Almoden, and a sentence to work

there was considered equivalent to a death sentence. Mercury intoxication was identified in the hat industry in France in the seventh century, and became so widespread that the expression, "mad as a hatter," became a colloquialism[8]. Exposure to other hazardous substances is an outgrowth of modern technology. In addition to newly developed chemicals, many materials first synthesized in the late nineteenth century have found widespread industrial use. The hydrides of boron, for example, have been known since 1879, but the first report on their toxicity appeared in 1951 as a series of case histories of people, mostly young chemical engineers, who had been exposed to boron hydrides in the course of their work.

Numerous other cases of occupational poisonings have been reported. Catastrophic events have resulted from worker exposures to benzene, lead, leptophos, vinyl chloride, dibromochloropropane (DBCP) and Kepone in the late 1970s. Toxicological research is of paramount importance in assessing the safety of new chemicals. If proper and timely research activities are conducted, hopefully the social and legal obligations of providing a safe and healthful workplace, free from recognized hazards for our populace, can be met.

In summary, it is interesting to note that despite the fact that developments in the history of toxicology began more than 3000 years ago, a large percentage of knowledge in this area has been developed in the last 15 years. What is happening is almost an explosion of interest in the subject in contemporary times. Questions which will be addressed in later chapters involve this increase in toxicological research and will focus both on the analysis of the problems and their solutions.

3
Role of Industrial Toxicology

In Chapter 1 industrial toxicology was defined as a specific segment of environmental toxicology concerned with the harmful potential of the raw materials, intermediates and finished products encountered by workers. Environmental toxicology is primarily concerned with the harmful effects of chemicals encountered by man in the total ecological system. Human exposures to atmospheric pollutants are generally incidental, whereas exposure to chemicals in industry is directly influenced by working conditions and hygienic practices of the specific industry. With the current diversification of industrial operations and chemicals of today, few occupations are entirely void of exposure to chemical pollutants. When the toxic potential (e.g., cancer, irreversible damage, genetic changes and death) of many chemicals is also considered the significance of the problem is compounded.

Industrial toxicologists are actually involved with investigative research of chemicals utilized and produced by industry. Evaluations are being conducted at an ever increasing rate in the attempt to define toxic substances. Laboratory animals, as well as humans, are utilized as test specimens in these research efforts. Due to social concerns, however, human subjects are

rarely utilized in U.S. research efforts at the present time, whereas in nations such as the Soviet Union, research in which humans are exposed to toxic agents is common[9]. Most human research which is conducted in the United States relates to dermatologic exposures. However, industrial retrospective studies are now being conducted to identify substances to which humans have been exposed. The validity of such retrospective studies is somewhat questionable unless human exposures are explicitly defined. These studies are essential in the identification and recognition of industrial agents which are toxic. For example, if retrospective studies had not been conducted on the vinyl chloride incident at Goodrich Rubber in Akron, Ohio, the correlation between angiosarcoma (liver cancer) and vinyl chloride monomer might have been neglected. This is one example of numerous retrospective studies which have been utilized to identify and define toxic agents. The toxicologist must take into account the specific toxic properties of substances as they reveal themselves in experimental animals during laboratory tests. Only then can toxicologists calculate the likelihood of harm to humans who encounter the substance in a specified operation and concentration.

The likelihood of damage or harm is defined as hazard. Data obtained from experimental laboratory studies are considered in conjunction with actual exposures humans will encounter. Adequate "hazard evaluation" of toxic substances will utilize experimental data, susceptibility of workers, physical characteristics of substances, warning properties of substances and conditions of exposure. This must be done in conjunction with experimental data from both human and animal studies.

The susceptibility of workers who face potential exposure to substances is addressed by toxicologists. Different worker groups are particularly susceptible to certain toxic actions. For example, female workers of child-bearing age should not be exposed to teratogenic or mutagenic agents. The expected frequency and duration of worker exposure is also significant. For