An up-to-date treatment of the field which emphasizes both the *old* and the *new* potential killers

HERVEY B. ELKINS

the CHEMISTRY of INDUSTRIAL TOXICOLOGY

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HERVEY B. ELKINS

Director

Division of Occupational Hygiene

Massachusetts Department of Labor and Industries

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Preface
to the second edition

Since the first edition of this book was published, the number of substances which potentially menace the health of the industrial worker has materially increased. These substances include some inorganic materials and many organic compounds, especially pesticides. Very likely the most important, and certainly the best publicized, have been the radioactive isotopes.

During the past few years the control of the commoner hazards has improved to such an extent that occupational illness is now rarely encountered in this country from substances such as benzene and carbon disulfide. Moreover, industrial hygiene has developed rapidly in many countries outside the U.S.A., and the findings in these countries have confirmed broadly the earlier experience of America and Western Europe with the familiar industrial poisons.

Standards of permissible concentrations of toxic substances have found increasing acceptance and become increasingly severe. Also, many new analytical methods have been developed over the past decade, with particular emphasis on the analysis of body fluids.

In the second edition an attempt has been made to include the more important of these new developments in the field of industrial toxicology.

HERVEY B. ELKINS

December, 1958

Preface

to the first edition

Although the literature of industrial toxicology contains many papers dealing adequately with the chemistry of various industrial poisons, nearly all books on the subject are written primarily from the medical point of view.

Although the vital role played by the physician in controlling occupational disease is duly recognized, it is not amiss to point out that the most important single step in the prevention of many occupational illnesses is control of fumes or dust. Measurement of the effectiveness of such control, in the long run a medical problem, can best be made initially by chemical methods. Furthermore, responsibility for the protection of workers rests primarily with industry; and those most intimately acquainted with the industrial processes and materials involved are industry's own chemists and engineers.

In this book an attempt is made to treat industrial poisons primarily from the point of view of the chemist and engineer. This means that the harmful substances themselves will be emphasized, and the industrial processes in which they are used, rather than the symptomatology and pathology of their effects on the human being. Some mention of the nature of the injuries caused is essential; but emphasis is placed on the probable seriousness of such effects, rather than on their complete physiological characterization.

It is hoped that this volume will provide a convenient source of information on the basic properties of the common industrial poisons;

that it will stimulate the interest of the industrial chemist in problems of occupational illnesses of toxic origin; and that it will encourage employers to utilize the knowledge and training of their chemists and chemical engineers in protecting their workers from harmful substances to which they are exposed.

HERVEY B. ELKINS

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I.

Fundamentals

INTRODUCTION

Poisons have long been of interest to mankind. Primitive man encountered toxic substances in plants, insects, and reptiles. In time he learned to prepare poisonous brews of organic origin. As the arts of mining and metallurgy were developed, inorganic poisons such as compounds of arsenic and mercury became known. The effects of toxic gases, such as carbon dioxide, found in caves and wells, and carbon monoxide and sulfur dioxide, from fire, were no doubt known long before the existence of gases was discovered.

With the development of the science of chemistry dozens of new elements, hundreds of inorganic substances, and thousands of organic compounds were discovered and studied. The effects of many of these substances when ingested or inhaled by animals, and even by man, were investigated. Medical science, in quest of new drugs, has sponsored the largest part of these investigations. Most effective medicines are somewhat toxic, and the importance of knowing the limiting safe dosage and physiological effects of substances which are to be swallowed by or injected into sick persons is obvious. The use of such toxic materials as mercury compounds and morphine in the treatment of disease is based on a thorough knowledge of their toxicology.

The need for control of insect pests, which consume vast quantities of foodstuffs and spread many infectious diseases, has resulted in further study of the properties of toxic compounds. Insecticides and fumigants, which can be effective without greatly endangering human lives, have been developed; but the need for new and improved agents and methods is still great. Some of these materials, such as the pyrethrum extracts, are relatively non-toxic to man; but others, such as many of the organic phosphates, are very poisonous to humans.

The occurrence of poison gases in warfare has been highly sporadic, the most important being in World War I. Their employment at that time, and the ever-present possibility of later use, have stimulated further exhaustive researches on toxic materials.

Thus far we have considered poisons which have been deliberately used for their effects upon some form of life. There is another host of substances which are employed for other purposes entirely but which may constitute an incidental poisoning hazard. Thus lead water pipes, cadmium-plated ice trays, and arsenic-pigmented wall-paper have all been responsible for numerous poisonings. Accidental poisonings from carbon monoxide gas occur almost daily; and children have contracted lead poisoning by sucking lead-painted toys.

Industrial toxicology deals with still another phase of poisoning—that suffered by workers in the course of their employment in mining, manufacturing, and mercantile establishments. Although the fundamental principles of toxicology apply whenever poisonous substances are absorbed, in practice there is a great difference in emphasis between the study of industrial poisons and the study of war gases, or general public health hazards.

Thus drugs are usually taken through the mouth or by injection into the blood stream, the dosage is carefully controlled, and medical supervision is close. Most industrial poisonings, except for dermatoses, result from inhalation of the toxic agent, medical supervision, if any, is at best remote, and dosage is determined with difficulty. War gases are often inhaled, but they are intended to give immediate effects, whereas most industrial poisonings are typically gradual in their development.

In spite of the long history of mercurial drugs, the maximum safe dosage of mercury vapor was not known until determined by the United States Public Health Service and the Connecticut Department of Health in a study of felt-hat plant workers. The limiting safe concentration of lead dust was similarly determined by investigations of storage-battery workers and bears little relationship to allowable lead concentrations in drinking water. In spite of the hundreds of soldiers exposed to chlorine gas in World War I, the effects of long-continued inhalation of small concentrations of chlorine are still unknown.

In short, industrial toxicology has properly been developed to a large extent independently of other branches of toxicology. Although its medical aspects are obviously of great importance, the chemical and industrial phases are equally significant. This book seeks to outline those aspects of industrial toxicology which are the primary concern of the chemist, engineer, and factory manager.

AVENUES OF ABSORPTION

Systemic industrial poisonings usually result from inhalation of the toxic agent. This fact is fairly obvious as far as gases, like carbon monoxide, and dusts which attack the respiratory system, such as silica, are concerned. With volatile liquids there is a possibility of absorption through the skin, and occasionally this is important. As a rule, however, skin absorption is secondary to absorption by inhalation when systemic effects are considered. Local injury to the skin, due to direct contact with a liquid or solid, is, of course, common.

With solid substances, inhalation and ingestion are the most important avenues of intake. Industrially, inhalation is again the most important, and toxic solids are most dangerous when dispersed in the air as dusts or smokes. This fact is frequently not recognized in the trades affected. Evidence of the major importance of inhalation as a source of metal poisoning is conclusive, however.

Ingestion of toxic substances along with food, in workrooms where the housekeeping is not good, or where workers are careless about washing, no doubt occurs to some extent. As a general rule, however, there is also a considerable dust inhalation where such conditions exist.

The classical cases of industrial poisoning via ingestion were those of radium dial painters, who absorbed radium mainly from the practice of using their mouths to point the brushes wet with radium-bearing paint.[1] Another group involved shinglers, who contracted lead poisoning from lead-coated nails, owing to their habit of holding extra nails in their mouths.[2] These, of course, are isolated instances of exceptional practices. In the majority of situations the toxic dust carried into the body is suspended in the air breathed by the worker.

Absorption through the skin is still less common with solids but may occur with certain liquids, especially those of low volatility. Phenol, cresol, nitrobenzene, aniline, lead tetraethyl, and many of the organic phosphate insecticides, such as parathion and TEPP, are liquids that present an equal or greater hazard through skin absorption than through inhalation. Other liquids and vapors, however, have been shown to pass through the skin to such a degree that gas masks or respirators do not give complete protection against high concentrations. Hydrogen cyanide, for instance, passes through the unbroken skin if enough is present in the air. Animals have been poisoned experimentally through the skin by certain of the chlorinated hydrocarbons. This fact should be borne in mind where very high concentrations of vapors or gases are present and individual respiratory protection is provided.

ELEMENTS OF RESPIRATION

An excellent discussion of respiratory processes is given in Henderson and Haggard's *Noxious Gases.*[3] Only a few fundamental principles will be outlined in this volume.

The respiratory system is divided into two main parts: the upper respiratory tract, consisting of the nose and throat; and the lower respiratory tract, or lungs. The nose, throat, bronchi, and bronchioles are essentially air passages leading to the alveoli, the minute cell structure of the lungs. In the alveoli the gases in the lungs are separated from blood capillaries by very thin walls, and, since the total surface is very great (90 square meters), diffusion of the lung gases into the blood stream is rapid. Ordinarily the blood receives oxygen and gives up carbon dioxide, which is discharged to the air upon exhalation.

If the air inhaled contains other gases or vapors, they ordinarily reach the blood in a similar fashion. However, if the gas is water-soluble, much of it may be deposited on the moist walls of the throat, bronchioles, and other passages of the upper respiratory system, and very little may enter the alveoli. Nevertheless, it finds its way into the blood stream, although less rapidly than via the alveoli. Since the latter cells are the most sensitive portion of the respiratory system, a corrosive gas may vary greatly in its effects, depending on where it is absorbed. Thus the water solubility of a gas or vapor, especially one whose action is primarily irritation, is an important property from the toxicological standpoint.

With a dust, smoke, or mist, the particle size may determine whether it is absorbed mainly in the upper or lower respiratory tract. As a general rule, the smaller the particle size, the greater the proportion which reaches the alveoli of the lungs, and the faster and more severe the action.

Rate of Breathing

Unless voluntarily controlled, the rate of respiration is determined primarily by the concentration of carbon dioxide in the blood, and secondarily by the blood-oxygen concentration. Since both values are affected by the rate of oxygen consumption, it follows that physical exertion, which creates an immediate demand for oxygen, stimulates breathing. The degree of this effect is very great, as shown in Table 1 (from *Noxious Gases*).[3]

TABLE 1

RATE OF BREATHING FOR AN AVERAGE MAN

Activity	*Air Inhaled* (l/min)
Resting in bed	6
Sitting	7
Standing	8
Walking—2 miles per hour	14
Walking—4 miles per hour	28
Slow run	43
Maximum exertion	65–100

Thus the volume of air breathed per minute varies nearly fourfold when one changes from a light sedentary occupation to moderately severe exertion (walking 4 miles per hour). The rate of inhalation of any toxic impurity in the air increases by the same ratio. It is apparent that this factor must be considered in interpreting data regarding the effects of toxic fumes in the air.

CIRCULATION

The blood, which has approached equilibrium with the lung gases, passes through the arteries and eventually deposits its load of oxygen in the body tissues, at the same time picking up carbon dioxide resulting from the combustion of carbohydrates. If the blood contains dissolved gases or other substances not normally present, these also are deposited to some extent in appropriate tissues, according to the fundamental laws of physical chemistry.

The rate of circulation is increased by physical effort, although to a somewhat lesser extent than is respiration.

RATE OF ABSORPTION

1. Non-Reactive Gases and Vapors

Gases and vapors which do not react immediately with the body fluids or tissues to form non-volatile compounds are progressively dissolved in the blood until equilibrium is reached. With a gas that is relatively insoluble in blood and body tissues, such as helium, equilibrium is approached rapidly. With highly soluble vapors, like methanol, equilibrium is approached very slowly, and in practice it is probably never even approximately attained. Thus any immediately apparent toxic effects, such as narcosis, result more rapidly from a gas of low solubility in blood and tissue than from one that is readily soluble.

2. Reactive Gases and Vapors

If the gas reacts irreversibly in the body to form a non-volatile product, equilibrium is not reached, and the amount of gas absorbed is proportional to the total amount inhaled.

3. Dusts and Smokes

Similarly, all the dust of a non-volatile compound which is trapped by the respiratory system is retained. Not all the particulate matter retained by the respiratory passages is absorbed directly into the blood stream, however. According to some estimates more than half is deposited in the upper respiratory passages and subsequently swallowed. If the particles which reach the lungs are insoluble, many of them may be eliminated from the lungs, raised by ciliary action, and finally swallowed.[4]

ELIMINATION

Removal of waste matter from the body takes place mainly through the respiratory tract, the intestinal tract, and the bladder and urinary tract. Toxic substances are eliminated through these same channels. Gases, such as carbon monoxide and radon, are removed mainly through the lungs.

Vapors of lower volatility, especially water-soluble compounds such as methanol, may be eliminated mainly through the urine. Other vapors, such as those of benzene and toluene, are converted to non-volatile oxidation products, which in turn are excreted in the urine.

Many metals, such as lead, manganese, and radium, are excreted chiefly through the intestines in the feces. Relatively large proportions of certain metals, however, notably mercury, uranium, and arsenic, are found in the urine.

Reactive compounds of elements commonly found in the body in large amounts, like hydrochloric acid or hydrogen sulfide, may be neutralized or destroyed, and the resulting products enter into regular metabolic processes.

Ingested material usually passes directly into the intestines from the stomach and is often eliminated without being taken into the blood stream. For this reason many substances, e.g., lead compounds, are more toxic when inhaled than when ingested.

Minor avenues of elimination of toxic compounds include perspiration, hair, and nails.

The excretion of most toxic organic compounds, and of gases, is usually a matter of hours, or at most of days. Many of the poisonous elements, however, can be stored for long periods of time in the body. Metals with chemical properties similar to those of calcium (radium, lead, and plutonium, for example) may be deposited in the bones. Mercury is also stored in various parts of the body for long periods. Fluorine, too, is stored in the bones. If further absorption of the toxic element is discontinued, excretion of the stored portion is begun and continues until it is virtually eliminated from the system.

Conversely, if there is a long continued intake of some toxic element, excretion may increase until it balances absorption. This is a condition frequently found in chronic poisoning.

HARMFUL EFFECTS

The pathological changes induced by toxic materials will not be discussed in detail in this volume, since such a discussion belongs properly to the medical consideration of toxicology. Some appreciation of the organs and processes injured by various poisons is desirable, however, even in a purely chemical approach.

There are three types of acute effect which may result from the inhalation of any toxic fume, but particularly from gases and vapors. These are asphyxiation, irritation of respiratory organs, and narcosis. In addition there are other responses which may be acute but are more typically chronic. These include damage to blood, nervous system, liver, kidneys, bones, etc. Many of these effects are exerted independently of one another, but sometimes one predominates, often to the virtual exclusion of all others.

Asphyxiation

Oxygen is necessary to sustain life, and, as we have already seen, an increased amount is needed if work is being done. Table 2 indicates the result of reduction in the oxygen content of the air.[3]

TABLE 2

EFFECT OF REDUCED OXYGEN

Partial Presure of Oxygen (mm mercury)	*Oxygen in Atmosphere at Sea Level* (%)	*Response*
120–160	16–21	No notable effect
90–120	12–16	Increased respiration, slight diminution of coordination
76– 90	10–12	Loss of ability to think clearly
45– 76	6–10	Loss of consciousness, death

Asphyxiation may be brought about by mechanical obstructions, by reduction of air pressure, by dilution of air with another gas until the concentration of oxygen is reduced by reduction of the oxygen content of the air, or by chemical action which prevents access of oxygen to, or inhibits use of oxygen by, the tissues.

The simple asphyxiants, gases which act only by diluting the air, include most of the inert gases, also hydrogen, methane, ethylene, nitrogen, and carbon dioxide. In order to reduce the oxygen content to a fatal degree, a vapor concentration of about 50 per cent must be attained. This is possible only with a gas or a very volatile liquid; and in such concentrations the direct effects of most gases are in themselves fatal.

Chemical asphyxiants are relatively few in number. They include carbon monoxide, the cyanides, and possibly hydrogen sulfide.

Asphyxiation may also result from the inhalation of irritant gases, which injure the respiratory system so that it is no longer able to convey oxygen from the air to the blood stream.

Irritation

Direct irritation of the respiratory tract, the eyes, and the skin is frequently produced by toxic materials, characteristically by strong acids, alkalies, and oxidizing agents. Some degree of irritation is also caused by many solvent vapors.

The most pronounced irritation is produced by substances readily soluble in water, such as ammonia and hydrochloric acid. Such gases, however, affect mainly the upper respiratory passages. Injury to these organs is less serious than damage to the lungs, which is likely to occur when gases with similar chemical properties but only slightly soluble in water are inhaled.

The influence of water solubility, which in general parallels solubility in body fluids, is shown in Table 3.