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INDUSTRIAL TOXICOLOGY

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PREFACE TO THE SECOND EDITION

Advantage has been taken of the demand for a second edition of this book, not only to make several minor changes, but also to write a number of new sections and to introduce new material in order to bring the book thoroughly up to date. The great advances in chemical technology, the manufacture in large quantities of new chemical substances, and the increasing accumulation of toxicological data have collectively imposed an obligation to contribute further information on those new substances which have received substantial toxicological investigation.

It is a great pleasure to express my thanks to my colleagues here and abroad who, by sending me reprints of their scientific papers, have greatly eased the burden of library search. I wish to record especially my appreciation and gratitude to many friends and associates who have rendered me most valuable aid with material, assistance, and suggestions. Acknowledgment is also made to publications of the U.S. Tariff Commission, the Manufacturing Chemists Association, and the U.S. Bureau of Mines for use of certain data.

It is to be hoped that the inclusion of the various tables in the Appendix will increase the usefulness of the book.

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INTRODUCTION

In an earlier period of our industrial development workmen were exposed to smoke, dust, fumes, and gases without regard to the possible injurious nature of many of these substances. Certain occupations, such as the mining of mercury, were formerly notorious in this respect. Furthermore, this condition was recognised in only very few instances and exposure to fumes or dusts of a deleterious type was generally recognised as a somewhat disagreeable and accepted condition of many occupations. The fact that some workers in mines, mills, or factories sickened, were forced to leave their occupation, and later died, did not always bring with it the realization that the nature of their work was a factor. In some occupations where industrial disease was prevalent there were often individuals who had been immersed in such an environment most of their working life and yet remained apparently strong and healthy. Such cases would be cited as indicating the general harmlessness of their occupation and those who sickened were regarded as weaklings. Many industrial diseases, such as phosphorus poisoning, were undetected for years, or, as in the case of manganese poisoning, were undetected for generations. The scrutiny of occupation as a factor in disease, although emphasized long ago by Ramazzini, is a comparatively modern development. Industrial physicians only a generation ago were largely concerned with the more external factors of employment—hernia, lumbago, cataracts in the case of glass workers, deafness in boiler-makers—or in incidental disease, such as ankylostomiasis among miners or tuberculosis among cotton spinners. The latter were, of course, related to poor sanitation and poor nutrition, respectively, and were by no means peculiar to the occupation of the worker.

Knowledge, however, of the existence of occupational disease became more and more evident and, although locally confined at first, gradually spread. Thus, such terms as "grinder's rot", "phossy jaw", "painter's colic", "chrome itch", and "miner's phthisis"

gradually appeared in industry and in the literature. Within the past generation industrial physicians have been alerted to the danger of much of the smoke, dust, or gases to which workers were exposed, scientists have actively investigated the effects of many of these aerial contaminants on animal life, and engineers have instituted control measures in industry to reduce the hazard of exposure.

Poisoning familiarly occurs as the result of ingestion of toxic substances and this doubtless influenced much of the earlier industrial hygiene thought. As a result, stringent sanitary measures were advocated and adopted in certain industrial processes in order to prevent possible entrance of industrial poisons by mouth. These precautionary measures included such matters as a complete change of clothing on entering a shift, careful scrubbing of the hands and face before eating lunch, and a thorough washing and shower at the end of the work period. While excellent in themselves, these measures do not include the sanitation of breathing and instances of industrial poisoning have occurred where workers had observed strict cleanliness yet were exposed to dangerous concentrations of dust, fumes, or gases. Inhalation is now recognized as one of the most dangerous routes of entrance of industrial poisons.

Gases, Fumes, and Dust

While the greater part of industrial smoke consists largely of carbon and is relatively harmless, it frequently contains gases which are dangerous if continuously breathed or if breathed in high concentration and, in addition, it may contain noxious fumes or toxic dusts from certain processes.

From the point of view of industrial hygiene a gas may be considered to be any aeriform or completely elastic fluid which does not become liquid or solid at ordinary temperatures. Fumes or vapors consist of material in the near-gaseous, or extremely fine particulate form which condense to liquids or solids at room temperature. Dusts,

on the other hand, consist of larger particulate matter suspended in air. It must be realized that these definitions are not rigid and that they merely indicate somewhat roughly different stages of attenuation of matter. It is possible, for instance, to have mercury dust suspended in the air of a workroom, due to constant attrition of mercury spilled on the floor and carried into the air as extremely minute droplets following mechanical agitation. At the same time, mercury fume may be present as the result of heating this substance and finally the vapor tension of mercury is such that true, gaseous mercury may also be present to a slight extent. It is important for the industrial hygienist to keep these distinctions in mind. The detection and estimation of mercury gas in air by means of the photoelectric mercury detector depends upon the absorption of ultraviolet light of a wave length of 2537 Å and the degree of absorption is a measure of the amount of gaseous mercury present. However, this instrument would not indicate the total mercury present in an atmosphere where particulate mercury or dust from any of its compounds was also present.

While dusts have been classified as particles or aggregates of particles of from 150 microns to 1 micron in diameter, fumes of from 1 micron to 0.2 micron in size, and smokes as particles less than 0.3 micron in diameter, size alone represents at best only a rough separation of these three classes. The mode of formation must also be considered. Thus, dusts ordinarily result from mechanical attrition and distribution, while fumes and smokes are formed and carried into the air usually as the result of chemical reaction or the sudden dispersion of a chemically active substance by release of pressure or by explosion.

The disperse systems, or aerosols, in which the dispersion medium is a gas, differ from other disperse systems in the great disparity that exists between the density and structure of the disperse phase and the dispersion medium. The mere fact that two such disperse systems contain amicroscopic particles similar in magnitude does not necessarily mean that the properties of the two

systems are identical, although they may have many points of similarity. In the case of dust, a great deal of work is required in order to reduce a solid to fine dust, i.e., to overcome the forces of cohesion that originally held the particles together in addition to the work required in distributing the particles throughout the dispersing medium. Even though a certain degree of uniformity finally is attained by settling or other means, dispersed dust of the finest order of magnitude is less uniform in structure than aerosols produced by the condensation of vapor. These factors have some weight in devising means of sampling and analysis of aerial contaminants.

The evaluation of aerial contaminants is very frequently a matter of importance to the industrial hygienist and a knowledge of the properties of such disperse systems as those indicated above, as well as the properties of gases and vapors in relatively low concentrations, is of particular value with reference to the analytical detection and determination of the constituent contaminants.

The composition of the aerial contaminant to which workmen in a given plant are exposed is of course of paramount importance to the industrial hygienist. This is usually known, or information may be obtainable from the management. In some cases, however, an unknown or unsuspected factor may be present and careful investigation may be necessary before the culprit is revealed. Cases have occurred, for example, where arsenic, cadmium, or selenium existing as unsuspected impurities in the material being fabricated have caused illness and death. An unrecognized by-product of manufacture may cause difficulty, or a change in the formula of basic material used in manufacture may bring about an unhygienic situation. The industrial hygienist is required not only to ferret out the occupational disease hazard but also—very necessarily—to know its characteristics, a proper method of sampling, and the most reliable method of analytical evaluation in terms of air content. His study includes the weighted or average exposure of employees at various stations and occupations. Furthermore, he

is required to know something regarding the toxicity of the aerial contaminant in order to define the conditions under which employees are to be permitted to work in such an environment.

The toxic effects of many hazardous materials in industry are well known and it is comparatively easy to define safe working concentrations. There exist many substances in common use in industry, however, which are toxicologically not well defined. Unfortunately, toxicity cannot be evaluated with the ease with which a chemical constant, such as a boiling point, melting point, or index of refraction, may be determined. Even with arduous investigation extending over many months, the toxicologist can at best give only a very general answer regarding the poisonous nature of a given substance. It would be of inestimable benefit of course, if one could—knowing the composition and molecular structure of such a substance—predict its physiological properties.

Chemical Constitution and Physiological Response

The possibility of relating chemical constitution and physiological activity has long proved a fascinating field of speculation. The advantages of defining the toxicity of a substance from its constitution or structural formula are, as indicated above, obvious. Unfortunately, however, the matter is not simple. Certain relations exist, it is true, between structure and toxicity. For instance, ethyl and methyl alcohol, although differing in one important respect, are very similar in many of their other physiological properties, and propyl, butyl, and amyl alcohols might be assumed to act similarly. These latter alcohols do, in fact, resemble the lower members but with a progressive increase in toxicity. An analogous increasing toxicity might therefore be anticipated in the higher members of the alcohol series. This reasoning, however, is nullified by the changing physical properties of the higher members. In spite of a similar chemical structure, the higher alcohols become increasingly insoluble in body fluids and as a result there is an overall decreasing toxicity beyond a certain point. A similar increase in toxicity with an

increasing number of carbon atoms is noted with sodium acetate, propionate, butyrate, and valerianate. Many other such relationships have been pointed out as more toxicological information has become available.

The replacement of a hydrogen atom with chlorine in the saturated hydrocarbons results in an immediate change in toxicity; the entrance of such a halogen group in the organic sulfur compounds greatly intensifies the toxicity of the resulting compound. When one chlorine group is introduced into ethyl sulfide, which is a weak poison, the resulting monochloroethyl sulfide is found to be markedly toxic, while the introduction of a second chlorine atom results in dichlorodiethyl sulfide, or mustard gas, which is a very strong poison indeed. However, no such general rule can be applied in other cases. The successive replacement of hydrogens by chlorine in the methane molecule, which of itself is not toxic but merely an asphyxiant, results in monochloromethane, CH_3Cl , dichloromethane, CH_2Cl_2 , trichloromethane, CHCl_3 , and tetrachloromethane, CCl_4 , respectively. These substances, however, do not follow a pattern of increasing toxicity. For instance, chloroform with its excellent narcotic properties, as well as the attendant possibilities of liver and heart damage, is less toxic in general than carbon tetrachloride on the one hand and much less toxic than methyl chloride on the other hand. Yet dichloromethane, which occupies an intermediate position, is far less toxic than any of the other members of this group. It does not follow therefore that there is any direct correlation between the number of chloro groups and the toxicity.

The relatively inert and inoffensive hydroxyl group when introduced into an organic molecule frequently results in an increase in toxicity. Thus, methanol, CH_3OH , has pronounced toxic properties compared with the parent substance and monohydroxybenzene, $\text{C}_6\text{H}_5\text{OH}$, or phenol, has marked poisonous properties over and above those of benzene. Increasing the number of hydroxyl groups may also increase the toxicity of the aromatics. For example, the introduction of a second hydroxyl group in the benzene ring yields resorcinol, $\text{C}_6\text{H}_4(\text{OH})_2$,

which is more toxic than phenol, while the introduction of a third group yields pyrogallol, which is the most toxic of the three.

The entrance of an alkyl group into the molecule of a substance may also intensify its poisonous quality. Dimethyl resorcinol, $C_6H_4(OCH_3)_2$, is more toxic than resorcinol, $C_6H_4(OH)_2$. On the other hand, an alkyl group may diminish the toxic effect in other substances. Dichloromethyl arsine, $As(CH_3)Cl_2$, is very toxic, while the introduction of a second methyl group, as in dimethyl chloroarsine, $As(CH_3)_2Cl$, yields a substance of weaker toxicity.

While the introduction of a chlorine group in aliphatic hydrocarbons increases the toxicity in general, this is not necessarily true in the case of the aromatic hydrocarbons. Thus, monochlorobenzene is less toxic than benzene itself and has been of no particular significance as an industrial poison.

It appears to be a general rule that *iso* compounds are somewhat less toxic than normal compounds. *iso*Propyl alcohol has a somewhat lower toxicity rating than normal propyl alcohol; *isobutyl* alcohol than normal butyl alcohol. A most interesting difference in toxicity has been found to exist in the benzene hexachlorides which have recently received attention as insecticides. In this case, the gamma derivative of 1,2,3,4,5,6 hexachlorocyclohexane, $C_6H_6Cl_6$, has been found to be especially lethal in action compared with the other four known isomers (1). Woodard and Hagan (2) found the gamma isomer to be as much as 60 times as toxic for certain warmblooded animals as other isomers of benzene hexachloride. In the case of many other optically isomeric substances, great differences may also be found in toxicities. For instance, 1-hyoscyamine is twice as active physiologically as *dl*-hyoscyamine (*atropine*) and moreover the *laevo* compound is 12 to 20 times as active as the *dextro* compound (3). Usually, but not invariably, the *laevo* compounds are more active than *dextro* compounds. Thus, Cushny found 1-hyoscyne to be 16 to 18 times as active as *d*-hyoscyne and twice as active as *dl*-hyoscyne. Similarly 1-adrenaline was 12 to 15 times as active as *d*-adrenaline in its

vasoconstrictor action and twice as active as *dl*-adrenaline. On the basis of rather indirect evidence, it is possible that the difference in physiological behavior of such stereoisomers is due to the ability of one or the other to combine with some protein or other constituent of the cell. However, sufficient quantitative data are not available to define clearly the mechanism of physiological activity and stereochemical configuration. The problem of relating chemical constitution and physiological action is even more confusing when it is recalled that substances of diverse chemical nature may produce similar physiological effects. The aliphatic narcotics, for example, include a large variety of structural type, such as hydrocarbons, alcohols, ethers, amines, and sulfones. According to Ing (4), these substances appear to achieve their effect by modifying the physicochemical conditions of the cells due to certain physical properties shared by all classes of these compounds and not by the presence of certain pharmacodynamic groups.

It will be apparent therefore that while the temptation to rationalize regarding the prediction of toxicities may be great, the evaluation of toxicities of new substances is fraught with considerable uncertainty. Since no great rational scheme is available to aid, except rather sketchily, in deciding upon the toxicity of a given substance, it is inevitably necessary to carry out experimental work with animals.

Experimental Toxicology

Experimental industrial toxicology does not differ widely from that of experimental pharmacology, since they both use the resources of chemistry, physics, physiology, and pathology to achieve their purpose. However, the pharmacologist is primarily interested in therapy rather than toxicity. Furthermore, he is interested in the effects of administration of a substance by mouth, or by intravenous or subcutaneous injection and rarely in the effects of inhalation, except in the case of inhalation anesthetics. The refinements of approach to certain physiological reactions adopted by the pharmacologist, however, often yield data of fundamental importance within a relatively short

space of time. The toxicologist on the other hand may be compelled to follow an intricate procedure which is arduous and time consuming in order to define a given physiological response. Moreover, toxicological studies frequently depend upon pathological changes following the administration of small amounts of such toxic materials as gases, fumes, or dusts and these changes usually occur very slowly.

Toxicological investigations are in general based upon animal experimentation for human experimentation is, of course, indefensible. It is true that animal experiments provide only indirect evidence of the probable action of toxic substances on man, yet they are nonetheless of the greatest value. They not only afford information regarding upper toxic limits, but by long-continued study, reveal changes in lower concentrations which are of the greatest importance. In experimental work of this character, a considerable amount of interpolation is necessary and evaluation of the experimental results requires both acumen and careful judgment. Moreover, there are many poisons which produce completely different effects in different species of animals. Mice and guinea pigs, for example, are more sensitive to poisoning by trichloroethylene (acetylene trichloride) than cats, while rabbits are less sensitive than cats. On the other hand, cats are more sensitive to lead poisoning than dogs and the latter more so than rats. Although such qualitative and quantitative differences may exist, nevertheless there can be no doubt that animal experiments are of value since they give an indication of the type of toxic action, as well as the relative toxicity of the substance under investigation.

The great advantage of animal experimentation is, first of all, the control of dosage and secondly, the degree to which poisoning can be carried. This yields most useful information in tracing similar effects in humans accidentally poisoned and in warning against human exposure beyond a certain degree.

Although the effects of exposure by inhalation are of paramount importance, animal studies also usually include other forms

of administration, such as ingestion, intravenous injection, intraperitoneal injection, and subcutaneous injection. The latter form of administration is perhaps the least used as absorption is frequently slow and has less significance than the other forms. Intravenous injection provokes the most immediate response and is often useful in studying the immediate effects of substances upon the hemopoietic system. Intraperitoneal injection is one means of following the slow absorption of relatively insoluble substances, but is of particular value in studying the physiological response of various substances. For instance, when pure silica suspensions are intraperitoneally injected, a reaction occurs which is typical and fairly constant (5). Sayers and Miller found three types of reaction occurred with various dusts—absorptive, inert, and proliferative. The absorptive reaction occurs when fine dusts, such as calcite, limestone, gypsum, and cement, are injected. After sufficient time, this material disappears from the peritoneal cavity without the formation of any scar tissue. In the case of the inert reaction, the dust remains distributed about the peritoneum by the action of phagocytes, sometimes forming flat nodules, which do not tend to progress or form fibrous scar tissue. Soapstone, carborundum, and coal dusts exhibit this inert reaction. In the proliferative reaction, nodules form which continue to increase in size with the formation of fibrous or scar tissue. Quartz, chert, and flint dust produce this reaction. These three types of reaction correspond very closely with the results obtained by the inhalation technique. While this method perhaps requires further exploration, it is useful in the approximate classification of dusts.

The inhalation technique with reference to dusts, fumes, and gases is by far the most useful method used in experimental toxicology. In the case of gases, the various concentrations to which animals are exposed may be regulated with accuracy. Hence, the exposure may be clearly and accurately defined. With fumes and dusts, the concentration of fume or dust in the air may be determined by exact chemical analysis. Whether or not the animals always breathe

in the amount in the atmosphere may not be so accurately defined in many cases as small animals, such as guinea pigs, tend to huddle together and may be able to filter out some of the dust or fume to which they are exposed.

For the purpose of exposure, gas-tight or dust-tight exposure chambers of large size are usually used and animal cages may be placed directly in the exposure chamber. The gas may be introduced in known amounts and rapidly distributed throughout the exposure chamber by means of small fans. Substances which are sufficiently volatile, such as solvents, may be introduced in known amount into a constant current of air and the breathing concentration may be accurately calculated. In addition, of course, samples of the exposure atmosphere may be taken in most cases and analyzed chemically.

Fumes, such as metal fumes, may be generated by arcing between electrodes of the metal carrying 110 a.c. current and an appropriate resistance. In order to prevent the formation of metallic oxide fume, it is usually necessary to generate this fume in an atmosphere of inert gas, such as nitrogen or helium, and "bleed" it into an incoming air current. Oxide fumes are readily formed by arcing in air or in an atmosphere of oxygen. Fumes of many organic substances may be formed by heating the material to the volatilization temperature in the incoming air stream.

Dusts must be suspended in air in very finely divided form in order that they may remain in suspension as long as possible and so that the material is of sufficient degree of fineness to be carried deeply into the animals' lungs. An elutriating device is useful for this purpose (6), since it permits a constant flow of very finely divided dust of more or less uniform size. In the case of dust exposures, it is difficult to control the amount of dust in the exposure atmosphere and hence it is necessary to draw small samples from time to time for analysis. Even though the dust concentration is accurately known, the amount carried into the animals' lungs is questionable, as a variable amount is removed by the filtering action of the nose,

part of the dust remaining in suspension is removed before the air enters deeply into the lungs. The ciliated epithelium found throughout the extent of the air-passages and their prolongations constantly sweeps out air-borne particles and only the very finest material penetrates to the lung alveoli.

The evaluation of exposure and the localization of toxic material in the various animal tissues, and the determination of its excretion metabolites, are of course dependent upon exact analytical procedures. Toxicological analysis frequently involves the isolation, identification, and determination of quite minute amounts of poison. In cases of metal poisoning the application of emission spectrography is of invaluable assistance. With organic substances, especially when only minute amounts may be isolated and purified, identification may prove more difficult. Indeed the original poison may have become metabolized so that it may no longer be identifiable, and above all the metabolic fate or the nature of its breakdown products may be unknown. However, where this field has been sufficiently explored the determination of the end-products of metabolism has been of great value. Thus, it is possible to trace benzene poisoning by the urinary excretion of phenol and conjugated ethereal sulfates, picric acid by the urinary excretion of 4,6-dinitro-2-aminophenol, methanol by formic acid and formaldehyde, acrylonitrile by thiocyanate excretion and trichloroethylene by the urinary excretion of trichloroacetic acid.

Modern methods of detection and identification have enormously facilitated this type of investigation. Just as emission spectrography in the ultraviolet region has proved of great value with reference to inorganic substances, absorption spectrophotometry both in the ultraviolet and the infrared regions has been a most valuable tool in the hands of the analyst with reference to structure as well as identification and determination of toxic substances. The development of chromatography and the availability of radioactive tracers have also served to facilitate analytical investigation. X-ray diffraction technique presents a particularly useful means of identification, and

the more recent type of equipment registers the position and intensity of radiation graphically, so that more rapid examination is possible. X-ray diffraction analysis not only has the great advantage of identification, but requires only a very small amount of substance. Moreover, this substance is not destroyed or changed in any way. Furthermore, as with spectrography, a visual record is obtained. The electron microscope has proved useful for the analysis of airborne particulates and in the investigation of the role played by quartz particles in initiating fibrotic changes in the lungs.

Those who are interested in the field of toxicological analysis will find the publications of Fabre (7), of Turfitt (8), and of Kirk (9) of particular value.

Description of the means of evaluating the effects of various industrial poisons will be found given in detail in the various publications referred to in the succeeding text. It will be noted that a considerable latitude of experimentation is necessary in order to study the effects of a given industrial poison.

The degree of exposure (that is, the total amount of substance to which an animal has been exposed for a given time) is, of course, only preliminary to the evaluation of the toxicity of the substance. The behavior of the animal must be observed for this is an index of the manner in which the poison acts. Some substances may cause death immediately or within a few minutes—for example, hydrogen cyanide, hydrogen sulfide, or carbon monoxide. Other substances may act as irritants with symptoms of pain, salivation, vomiting, and purging. Ammonia gas, cadmium oxide fume, and chloropicrin, respectively, produce these effects. Other substances affect the central nervous system and produce characteristic symptoms, such as narcosis, convulsions, and paralysis.

The various symptoms, in general, serve at best only as a rough classification of toxic substances. The effects of poisons are often subtle and a variety of symptoms may be displayed. In chronic poisoning, or in the case of a cumulative poison, anatomical changes may be produced in certain organs or tissues which are characteristic for the

poison. Blood changes may occur with an increase or decrease in hemoglobin, in red or white cells, and often with characteristic morphological changes in either or both the erythrocytes and leukocytes. All these and many other effects must be studied with care in the evaluation of the toxicity of a substance. It will be apparent therefore that the term *toxicity* does not refer to a fixed quantity, such as, say, a constant of nature. On the contrary, it is a descriptive term and is often more clearly understood when applied in relation to other analogous substances. When the toxicity of a substance is evaluated in the broad sense described above, however, the industrial toxicologist is able to advise somewhat definitely the limitation of possible exposure of human beings to industrial poisons.

A further element of caution should be exercised with reference to attempts to evaluate the toxicity of a given substance by any mathematical relationship between the quantities of poison administered and the routes of administration, for it is still necessary to consider the species of animals used. Furthermore, in attempting to apply such a relationship to man, a number of other factors must be considered, not the least of which are age and physical condition. However, in order to satisfy those who must know "how toxic" a substance is, a table of usual industrial poisons is appended (Table IV) which gives the LD₅₀ values for one species of animal (the rat) and one mode of administration (oral), which have been gathered from the literature and to which I have assigned various groupings and designations. It affords a rough means of comparison and avoids the confusion experienced when one is confronted with a variety of species and methods of administration. Even so, it will be recalled that rats are more sensitive to certain toxic substances, for instance alpha-naphthylthiourea, than other animals. However, in the light of acute poisoning the table is presented for what it is worth and disclaims any effort at finality.

It should be clearly indicated that, while such procedures as those briefly indicated above serve to establish useful limits with regard to industrial poisons, the more funda-

mental aspects of toxicology involve far more extensive and difficult physicochemical and physiological investigation. Various physical factors such as surface activity, solubility, dispersibility, polarity, partition coefficient, particle size, and electrophoretic properties may require study. The mechanism whereby many substances produce toxic effects in man is important and requires careful exploration. The fate of these substances in the body—the changes which organic compounds undergo and the metabolites formed—serves to indicate the means by which the body attempts to reduce their toxicity and thus protect itself against their poisonous effects. This is especially true of organic compounds completely foreign to the body. In their passage through the animal organism these substances interact with the normal biochemical systems which they encounter. The enzymic systems which carry out the oxidations, reductions, hydrolyses, and syntheses in the body may be variously affected. The metabolic processes involved reflect an attempt to reduce or abolish the toxic action or damage to the organism. However, it is not true that the product or products formed are invariably less toxic than the parent substance. For example, Channon and his associates (10) found that 2,4,6-trinitrotoluene (α -TNT) is partly converted in the animal organism to 2,6-dinitro-4-hydroxylaminotoluene which is excreted as such in the urine. Furthermore, the biological reduction product of picric acid is picramic acid. In both these cases the end-products are more toxic than the original substances. Nevertheless in the case of many other poisons the toxic substance is converted to harmless metabolites and eliminated. Fundamental investigation of the toxicity of a given substance therefore includes study of the course of the toxic agent through the body, its effects on various organs and tissues during its passage, and the changes produced in the substance by the detoxicating mechanism of the body as indicated by the metabolites formed.

Investigation of toxic substances and in particular of the mechanism of detoxication may ultimately prove to be one of the most fruitful fields of biochemistry, inas-

much as it provides specific knowledge of processes that are not obvious nor come to light except as the need for meeting an unusual or critical situation arises. Enzymatic action which can bring about hydroxylation, conjugation, acetylation, or methylation of substances foreign to the body is not only interesting *per se*, but may also give a clearer insight into living processes in general (see Appendix, Table II). The minor metabolic changes which occur with certain toxic substances not only follow curious paths, as for instance in the formation of unusual or unexpected metabolites—such as the partial transformation of benzene to *trans-trans*-muconic acid and aniline to *ortho*-aminophenol in addition to its well-known transformation product, *para*-aminophenol—but may have considerable significance. Furthermore the pattern of biological oxidation is frequently different from that of *in vitro* experimentation, for apparently biological oxidation and other processes do not invariably attack those portions of the molecule which are familiar to the chemist as the most reactive centers. Investigation in this field is at best difficult, frequently slow, and occasionally unrewarding, yet a surprisingly large amount of useful information has been accumulated. Interesting as this is, it is beyond the province of this book to discuss the biological significance of the changes which foreign organic substances undergo in the body. The following pages therefore relate to the direct toxic effects of industrial poisons.

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of arsine is related to its affinity for the hemoglobin of the red blood corpuscles and the symptoms of acute arsine poisoning result from hemolysis of the red blood cells with resulting anemia and jaundice. It has been suggested that arsine is carried unchanged to the various tissues by loosely combining with the erythrocytes (13). Fatal termination is frequent.

Analysis

The great importance of arsenic from a toxicological point of view and the extreme sensitivity of the various methods has resulted in the accumulation of immense amounts of literature devoted to the analytical detection and estimation of this substance. The conventional Marsh and Gutzeit methods which depend on the formation of arsine and its detection are convenient and satisfactory within certain limits. The gold chloride test paper method of Turfitt (14) is a particularly useful test for arsenic. Of the various colorimetric procedures for the micro-determination of arsenic, that of Sandell is both accurate and sensitive (15). In this method, the material, freed from substances that prevent complete evolution of arsine, is so treated that the arsenic is quantitatively evolved as arsine. This, in turn, is absorbed in an acid solution of mercuric chloride containing permanganate and the arsenic thus oxidized to arsenate can be determined by the addition of an excess of ammonium molybdate-hydrazine sulfate reagent which yields molybdenum blue in proportion to the amount of arsenic present. This method is particularly applicable to amounts of arsenic within the range of 1 to 15 micrograms with an accuracy of 5 per cent. Arsenic may also be detected qualitatively by *n*-ethyl-8-hydroxy-tetrahydroquinoline hydrochloride, which gives a reddish-brown color in spot tests in the presence of ferric chloride (16). The arc spectrum for arsenic is very poor and there are a number of interfering lines. However, the following lines—2860.5, 2780.2, and 2349.8—are useful for spectrographic identification.

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ASBESTOS

Characteristics

Asbestos, amianthus, earth flax, stone flax, mountain cork, is a characteristically silky, fibrous mineral, the composition of which varies with its source. The form known as chrysotile is derived from serpentine and is a hydrous magnesium silicate containing from 12.5 to 14 per cent water of crystallization.

About 95 per cent of commercial asbestos is chrysotile. Chrysotile has the silkiest and strongest fiber and can be spun. The fibers may be as long as 6 inches in length. Asbestos derived from amphibole occurs as a variety of minerals consisting of iron, calcium, and magnesium with little water of constitution. The latter type of asbestos consists of short fibers and is usually inferior to that derived from serpentine. Amphibole asbestos (anthophyllite) while not so suitable for spinning is more stable chemically than chrysotile and more resistant to acids and heat.

Canada has been an important source for the chrysotile asbestos used largely in the United States. The Canadian asbestos industry is centered in the Thetford Mines area of the Province of Quebec. A new source for chrysotile type asbestos is a large quarry on the eastern shoulder of Belvidere Mountain in Vermont which was opened in the summer of 1944. This deposit is of importance because it represents the only large source of long-fibered chrysotile so far found in the United States. Deposits of amphibole asbestos are mined in Georgia and North Carolina.

Industrial Uses

Asbestos is an important substance in industry and consumption in the United States for 1951 amounted to 796,992 short tons (1). Due to its fibrous nature, flexibility and heat-resistant properties, it is used extensively for valve packings, gaskets, boiler lagging, and pipe covering in industrial plants and as friction material in the automotive industry. A considerable market exists in the building industry for asbestos-cement products, heat insulation, and fire-proofing. The utilization of asbestos for fibers for spinning in the manufacture of asbestos clothing for fire fighting is an important use for asbestos. The largest single outlet for asbestos in manufactured products in 1944 was for clutch facings, and next in quantity of output were brake linings. Asbestos roofing consumed the third largest amount of asbestos in that year.

Industrial Injury

The inhalation of asbestos dust produces a condition known as asbestosis. While cer-

tain other minerals of minor importance have been shown to produce lung fibrosis, asbestos is the only important silicate apart from talc and mica which does not contain free silica and yet produces pulmonary lung fibrotic changes leading to disability and death. Asbestosis occurs chiefly in industrial plants where asbestos is fabricated. The spinning and weaving of asbestos in combination with other textiles results in exposure of workmen to asbestos dust. The long-continued inhalation of asbestos dust results in a form of pneumoconiosis. The primary effect of inhalation of asbestos dust is an interstitial pulmonary fibrosis. On an X-ray film the shadows cast by this type of fibrosis resemble ground glass in appearance and usually extend over the lower portions of the lung fields, frequently being heavier on the right side (2). Unlike silicosis, nodular fibrosis has not been detected in asbestos workers (3). The fibrogenic action differs from that of silica in that the effects are produced only by long asbestos fibers while the very short asbestos fibers appear to have little or no effect. The long fibers apparently block the finer bronchioles and produce fibrotic changes as a result of irritation. A progressive dyspnea, variable cough, substernal chest pains, decreased chest expansion, weakness, emaciation, clubbed finger tips, and curved fingernails are the chief symptoms of asbestosis, as in silicosis. A characteristic finding in asbestosis is that of asbestos bodies in the lungs and in the sputum (4). The so-called asbestos bodies are apparently formed only in the lungs and may be demonstrated microscopically on sectioning lung tissue or in the sputum. The core of the body is an asbestos fiber which is surrounded by protein deposits. Unstained specimens are golden yellow or golden brown. They are not stained with ordinary histological stains but may be demonstrated by the Prussian blue staining procedure. The reaction to the fibrous needle in the tissue which becomes manifest in exudate cell infiltration is accompanied by numerous giant cells containing foreign particles and an increase of diffuse interstitial connective tissue and fibrosis. While the essential reaction to asbestos particles is considered to be chemical by many investigators others consider the

pathogenesis of the disease to be mechanical (5) in nature. For instance, the investigations of Vorwald and his associates (6) indicate that the mode of action of the long asbestos fiber is mechanical rather than chemical in nature. When the lungs are examined by the naked eye after death, they are large and densely fibrotic. Often the lung is completely adherent to the chest wall and, in advanced cases, to the diaphragm with the formation of a thick and extremely dense layer of fibrous tissue. Four main complications and sequelae of pulmonary asbestosis are purulent bronchitis, bronchial pneumonia, pulmonary tuberculosis, and emphysema (7). Several cases of asbestosis have been reported which progressed to a fatal termination with heart failure and without evidence of infection or other complicating disease (8). Any appreciable decrease in the amount of asbestos dust will cause a decrease in the incidence and severity of asbestosis (9). In a recent study of 40 cases of asbestosis at necropsy, Lynch and Cannon (10) found support for the belief that fibrosis does not progress indefinitely after cessation of exposure. It would appear that if the dust concentration in asbestos factories can be kept below 5 million particles per cubic foot, new cases of asbestosis would not arise (2). Cartier (11) has found cases of asbestosis only in those employed for at least 14 years and exposed to air containing at least 5 million fibrous particles varying in length from 10 to 250 microns per cubic foot of air. Doll (12) has concluded from a study of 105 necropsies of individuals employed at an asbestos works that lung cancer is a specific hazard of asbestos workers.

Analysis

While the analysis of asbestos dust as an aerial contaminant is not of particular importance, its microscopy and above all the evaluation of the number of particles per cubic foot of air is of paramount importance. Air samples may be secured by the impinger method using 25 to 50 per cent alcohol as a collecting medium and dust counts made by the usual method. Microscopic examination of the dust reveals typical asbestos fibrous particles which may be accompanied also by cotton or other textile fibrous materials in

samples taken from the air of weaving factories. The index of refraction being only slightly greater than that of Canada balsam, the relief is low. Other forms of asbestos than chrysotile have somewhat higher indices of refraction. Extinction is parallel except in the case of tremolite which has oblique extinction. The birefringence of chrysotile is moderate $n_p - n_a = 0.013$. The maximum interference color is bright yellow of the first order. The air sampling of asbestos dust both by the impinger method and by the electrostatic precipitator method is discussed in detail by Fehnel (13).

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BARIUM

Characteristics

Barium, Ba, atomic weight 137.36, density 3.5, melting point 850° C., and boiling point 1140° C., is a yellowish-white, slightly lustrous, soft metal which is somewhat malle-

SILICA

Silica (SiO_2) or silicon dioxide, is the most abundant of all the minerals and rocks that form the earth's crust. It is characterized by its hardness and chemical resistance to reagents. It is slightly soluble in alkalies but the finely particulate material is only very slightly soluble in water (1, 2). Silica fractures into very minute particles. In the crystalline form it occurs as quartz but two other forms are known. These are tridymite and cristobalite, and each of these exists in a number of modifications. Sand, flint, and agate are familiar forms of silica and diatomaceous earth, which is occasionally found in nature in large deposits, is composed of the silicious skeletons of diatoms. In view of what is known about the disease called "silicosis", it is important to distinguish between silica in the free state, as SiO_2 , and silica in the combined state, such as the various silicates. The silicates are still considered innocuous when inhaled as dust, with the exception of talc, mica, and the fibrous silicates which are known as asbestos (3). The percentage of free silica in the various dusts which have been analyzed in connection with health studies of workers in dusty trades has been shown to range from 54 per cent to a trace (4). Silicosis is a chronic disease caused by the inhalation of particulate matter containing free or uncombined silica. It is characterized anatomically by generalized fibrotic changes with miliary nodulation in the lungs. Clinical signs are shortness of breath, a lowered vital capacity, a lowered capacity for work, increased susceptibility to tuberculosis, and a characteristic X-ray appearance of the lungs.

Silicosis is found to occur in such occupations as mining, the cutting of sandstone and granite, the coal industry, the smelting, refining, and grinding of metals, the manufacture of certain abrasives, the pottery industry, and the processing of the various forms of free silica. The number of workers exposed to dangerous amounts of silica dust has been estimated at more than 1 million (5).

Because of the disabling nature of silicosis (6), the extent to which exposure occurs in

industry and the number of workers involved, many surveys have been made and these investigations have resulted in the setting up of efficient protective measures in working establishments. Dust control measures, taking into consideration the chemical composition of the dust and the size of the silica particles, as well as the concentration of the dust in the air, have been instituted. There is more or less general agreement that it is desirable to avoid concentrations of more than 5 million particles per cubic foot of air in working places where the dust contains a high percentage of free silica. Granite dust, which contains about 35 per cent free silica, when in concentrations of 10 to 20 million particles per cubic foot has been found not to cause disabling silicosis in a working lifetime, while anthracite dust, containing less than 5 per cent free silica, has been found not to cause anthracosilicosis in concentrations of less than 50 million particles per cubic foot (3). Because airborne dust may differ markedly from that of the source material from which it arises, it is common practice in appraising dust hazards to determine the free silica content of samples. Furthermore, it has been indicated that toxicity increases sharply with silica dust below 3 microns in size (7). Since particles too large to be significant in silicosis production often contain a much higher percentage of free silica than fine particles of significant size, Holden and his associates (8) describe a procedure to eliminate the oversize particles before analysis.

Silicosis is occasionally found to occur under unusual or unexpected circumstances. While workers at the face in coal mines may be much less affected, silicosis has been found to be more prevalent among the mine locomotive operators in certain mines. This has been attributed to sand used as traction material. The spinning and grinding action of the wheels produces dust which, in the confined space of entries or tunnels, may rise to high atmospheric concentration. Laboratory study of substitute materials by Fairhall, Highman, and Perone (9) showed that iron ore tailings, metallurgical slags, and trap rock produce far less peritoneal reaction in guinea pigs than sand or quartz,

yet possess the requisite hardness to serve as traction material.

The mechanism and pathology of silicosis have been very adequately described. It is well recognized that very fine particulate silica is carried to the air sac or alveolus which represents the terminal dilatation of the bronchioles in the lungs. The alveoli are in intimate contact with blood vessels through which the oxygen-carbon dioxide interchange phenomena of respiration occur and they are also in contact with lymphatics which are important for the removal of foreign or irritant material. This defense mechanism is motivated by the activity of phagocytic cells which carry off the minute silica particles to the lymph nodes. There an ineffective accumulation of this material occurs and fibrotic changes take place resulting in areas which constitute the silicotic lung marking revealed by the chest roentgenogram. Just why the phagocytic cell is affected by the silica—whether, in fact, silica has a direct toxic action, or whether it initiates other effects—is still in the realm of speculation.

Certain substances, such as aluminum, iron and magnesium dusts, as well as coal and cement dusts, when used with quartz have been found to decrease the pulmonary changes associated with free silica itself. This has been attributed to a decreased solubility of the particulate silica and Denny, Robson, and Irwin (10) have shown that small quantities of metallic aluminum powder almost completely inhibit the solubility of siliceous material. While aluminum dust therapy has represented an interesting phase of the silicosis problem, it should be mentioned that Rüttner and Willy (11) have found aluminum dust itself to be fibrogenic and state that caution should be exercised in regarding it as antidotal. Furthermore, King (12) reports that, while a mixture of aluminum hydroxide with silica lowers its solubility, it does not prevent fibrosis in animals. Heffernan (13) proposed the theory that only freshly fractured quartz is biologically active and that the surface activity of the silica particles is the important factor in the production of silicosis rather than the solubility of the silicon di-

oxide. However, this theory has been vigorously criticized by Wright (14), who has attacked the various hypotheses on which this theory is based. Moreover, comparative animal experiments by Rüttner (15) have demonstrated that pure, freshly fractured quartz is no more active than "old" quartz. Vigliani *et al.* (16) have stated that measurement of the blood serum globulins can assist in both the diagnosis and the prognosis of silicosis. More recent experimental work by Baldi and Boselli (17) and by Proyard and Nizet (18) has failed to substantiate this finding. The application of the electron microscope to the examination of particulate quartz obtained from the lungs of workers has revealed a process of disintegration, according to Beintker and Meldau (19). These investigators state that the disintegration of the particle is revealed in the form of very minute droplets on the surface of the particle and that these droplets appear to be silicic acid in colloidal form. It is thought that this colloidal material may play an essential role in initiating silicosis. The more recent piezoelectric theory of fibrogenic activity of quartz has been disproved by the experimental work of Pratt and his associates (20) who found that highly piezoelectric substances other than quartz do not produce fibrosis or silicosis in guinea pigs, while tridymite and vitreous silica, both of which are not piezoelectric, do produce fibrosis.

Since free silica or quartz is the important factor in causing silicosis, the identification of this substance and its quantitative evaluation as a dust constituent are of prime consideration. The microscopic examination of such dust yields especially valuable information. Of the six distinct silica minerals, quartz, chalcedony, and opal are the more common. Tridymite and cristobalite are more or less of volcanic origin and are also found as constituents of silica bricks, while lechatellierite is exceedingly rare. Quartz and chalcedony have refractive indices near that of Canada balsam and a birefringence of about 0.009. The other silica minerals have lower indices of refraction and weaker birefringence. The microscopic examination of such industrial dusts as are known to contain free silica can only be satisfactorily

accomplished by the use of the petrographic microscope and a considerable amount of experience is necessary. Quantitative evaluation of the quartz content of a dust may be made microscopically by examining the dust and counting the dust particles in two different immersion media (21) having different indices of refraction. In one of these media all the particles are visible; in the other, having the same index of refraction as quartz, only the nonquartz particles are visible. The difference between these two estimations gives some approximation of the silica content of the dust. The method is not suitable for very fine particles and estimation based on particles of less than 10 microns in size is not good petrographic practice. Chemical methods for the estimation of free silica, such as the hydrofluosilicic acid method (22) and the fluoboric acid method (23), are tedious, time-consuming, and frequently yield information of no more quantitative value than less lengthy procedures. The X-ray diffraction method of dust analysis has become of increasing importance and is especially commendable from the point of view of speed, while it appears to yield results of as great accuracy as is obtainable by other methods of analysis. Fraser (24) has presented a method that permits for the first time an absolute procedure for the analysis of airborne solid particulates. The method makes use of the combined high efficiency of the molecular filter membrane for sampling and of the electron microscope for measurement.

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TABLE IV

Comparative Toxicities of Various Substances Based upon the LD₅₀ Value
for Oral Administration to Rats

Substance	Mgs./Kg.	Toxicity*	Substance	Mgs./Kg.	Toxicity*
Acetic acid	3310	IV	2,4-Dinitrophenol	30	I
Acetic anhydride	1780	IV	1,4-Dioxane	5325	IV
Acetanilide	800	III	Ethanol	13600	IV
Acetone	9750	IV	Ethylacrylate	1020	IV
Acetonitrile	3800	IV	Ethylamine	400	III
Acetosalicic acid	1360	IV	Ethylenediamine	1160	IV
Acridine	2140	IV	Ethylene glycol	6122	IV
Acrolein	48	I	Formaldehyde	800	III
Acrylonitrile	93	II	Furfuryl alcohol	275	III
Aldrin	67	II	Hexanal	4520	IV
Allyl alcohol	64	II	1-Hexanol	4870	IV
m-Aminophenol	1000	IV	2-Hexanone	2590	IV
Aminothiazole	480	III	Hexylamine	670	III
Ammonium sulfamate	3900	IV	Hydroquinone	320	III
tert-Amyl alcohol	1000	IV	Hydroxyethyleneimine	74	II
Aniline	460	III	isoBornylthiocyanosac-	1000	IV
Antabuse	8600	IV	tate		
Arsenic trioxide	138	II	isoPropyl alcohol	5840	IV
Benzene hexachloride	125	II	Lead arsenate	825	III
Benzoic acid	1714	IV	Malathion	1400	IV
Benzyl alcohol	3100	IV	Mercuric chloride	37	I
Biphenyl	3280	IV	Methoxychlor	6000	IV
Boric acid	2660	IV	Methyl carbitol	9210	IV
Butyl acrylate	3730	IV	Methyl iodide	150	II
n-Butyl alcohol	4360	IV	Methylmethacrylate	9360	IV
n-Butylamine	500	III	Morpholine	1600	IV
Butyl ether	7400	IV	α-Naphthylthiourea	6.9	I
p-tert-Butyltoluene	1543	IV	Nicotine	50	I
Butyric acid	2940	IV	Parathion	6	I
Carbitol	6500	IV	Pentachlorophenol	125	II
Chloroacetamide	3100	IV	Phenol	530	III
Chloral hydrate	800	III	Phenothiazine	5000	IV
Chlordane	470	III	o-Phenylphenol	2700	IV
Chloroacetic acid, mono-	76	II	Phenylthiourea	20	I
Chloroacetic acid, tri-	3320	IV	o-Phthalic acid	7500	IV
1-Chloronitropropane	50	I	Piperonyl butoxide	11500	IV
p-Cresol	1800	IV	Propanol-1	1870	IV
Crotonaldehyde	300	III	Propionaldehyde	1410	IV
2,4-D	666	III	Pyrethrins	1500	IV
DDD	3400	IV	Pyridine	1580	IV
DDT	420	III	Pyrolan	90	II
Dehydroacetic acid	570	III	Quinoline	460	III
Dicumarol	541	III	Rotenone	132	II
Dieldrin	87	II	Salicylamide	1400	IV
Dimetan	150	II	Sodium azide	46	I
Diethylamine	540	III	Sodium fluoride	200	II
Diethyl sulfate	880	III	Sodium fluoroacetate	2.5	I
Dimethyl phthalate	8200	IV	Strychnine	16.2	I
Dimethyl sulfate	440	III	Tetraethylpyrophosphate	2	I
4,6-Dinitrobutylphenol	60	II	Thiourea	1830	IV
4,6-Dinitro-o-cresol	30	I	Toxaphene	69	II
4,6-Dinitrocyclohexyl-	180	II	Triethylamine	460	III
phenol			Thallium sulfate	15	I

* I, extremely toxic; II, very toxic; III, moderately toxic; IV, slightly to nearly nontoxic.

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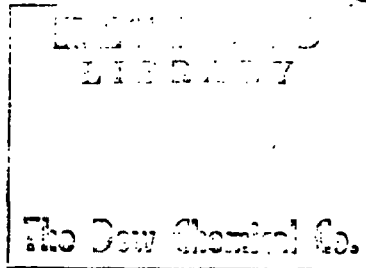
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