CHAPTER 7

INDUSTRIAL TOXICOLOGY

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INTRODUCTION

Toxicology is the study of the nature and action of poisons. The term is derived from a Greek word referring to the poison in which arrows were dipped. Mythology, legend and history indicate the growth of toxicological knowledge. The early emphasis was on ways to poison people. The 19th century saw the development of tests for identification of various poisons, such as the Marsh test for arsenic. These found use in legal medicine and criminology, the area known as forensic toxicology. Since about 1900, there has been increasing social concern for the health of workers exposed to a diversity of chemicals. This has led to intensive investigations of the toxicity of these materials in order that proper precautions may be taken in their use. This is the area of industrial toxicology which concerns us here.

Some industrial hazards have been known for centuries. For example, clinical symptoms of lead poisoning were accurately described in the 1st century A.D. The Romans used only slave labor in the great Spanish mercury mines at Almaden, and a sentence to work there was considered equivalent to a sentence of death. French hatters of the 17th century discovered that mercuric nitrate aided greatly in the felting of fur. Such use led to chronic mercury poisoning so widespread among members of that trade that the expression "mad as a hatter" entered our folk language. Exposure to other hazardous substances is an outgrowth of modern technology. In addition to newly developed chemicals, many materials first synthesized in the late 19th 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.

Toxicological research now has its place in assessing the safety of new chemicals prior to the extension of their use beyond exploratory stages. Information on the qualitative and quantitative actions of a chemical in the body can be used to predict tentative safe levels of exposure as well as to predict the signs and symptoms to be watched for as indicative of excessive exposure. An elucidation of the mechanism of action of the chemical can hopefully lead to rational rather than symptomatic therapy in the event of damage from excessive exposure. Both in the application of newer refined research techniques of toxicology and in his communication of knowledge vital to the public health, the toxicologist considers old as well as new hazardous substances. This point was well made by Henry Smyth[1] who said "Most people are careful in handling a new chemical whether or not they have been warned specifically of its possible toxicity. Despite the potential hazards of hundreds of new chemicals each year, most injuries from chemicals are due to those which have been familiar for a generation or more. It is important for the perspective of the toxicologist that he keep this fact well to the forefront of his mind. He must not neglect talking about the hazards of the old standbys, lead, benzene and chlorinated hydrocarbons just because this week he discovered the horrifying action of something brand new. Part of his responsibility is a continuing program of communication aimed at informing everyone of the means required to handle safely any chemical whatsoever."

DISCIPLINES INVOLVED IN INDUSTRIAL TOXICOLOGY

In order to assess the potential hazard of a substance to the health of workers industrial toxicology draws perforce on the expertise of many disciplines.

Chemistry: The chemical properties of a compound can often be one of the main factors in its toxicity. The vapor pressure indicates whether or not a given substance has the potential to pose a hazard from inhalation. The solubility of a substance in aqueous and lipid media is a guiding factor in determining the rate of uptake and excretion of inhaled substances. The toxicologist needs to determine the concentration of toxic agents in air and in body organs and fluids. It is important to know if a substance is, for example, taken up by the liver, stored in the bones, or rapidly excreted. For this, analytical methods are needed which are both sensitive and specific.

Biochemistry: The toxicologist needs knowledge of the pathways of metabolism of foreign compounds in the body. Such information can serve as the basis for monitoring the exposure of workmen, as for example the assessment of benzene exposure by the analysis of phenol in the urine. Differences in metabolic pathways among animal species form one basis for selective toxicity. Such knowledge is useful, for example, in developing compounds that will be maximally toxic to insects and minimally so to other species. Such knowledge can also serve as a guide in the choice of a species of experimental animal with a metabolic pathway similar to that of man for studies which will be extrapolated to predict safe levels for human exposure. Rational therapy for injury from

toxic chemicals has as its basis an understanding of the biochemical lesion they produce. One outstanding example is the development of B.A.L. (British Anti-Lewisite, 1,2-dimercaptopropanol) which arose from studies of the inhibition of sulfhydryl enzymes and the manner of binding of arsenic to these enzymes. This led to the use of B.A.L. in therapy for industrial poisons (such as mercury) which interfere with sulfhydryl enzymes. Studies of the nature of the reaction of organic phosphorus esters with the enzyme acetylcholine esterase led to the development of 2-PAM (2-pyridine aldoxime methiodide) which reverses the inhibition of the enzyme. In conjunction with atropine, 2-PAM provides rational therapy for treatment of poisoning by these compounds. In the important area of joint toxic action, understanding comes from elucidation of biochemical action. If, for example, Compound A induces enzymes which serve to detoxify Compound B, the response to the combination may be less than additive. On the other hand, if Compound A should act to inhibit the enzyme that serves to detoxify Compound B then the response may be more than additive.

Physiology: The toxicologist obviously needs to know something of the normal functioning of organ systems. Modern toxicology is moving more and more towards the search for means to detect reversible physiological changes produced by concentrations of toxic substances too low to produce irreversible histological damage or death in experimental animals. Measurement of increases in pulmonary flow-resistance has proved a sensitive tool for assessing the response to irritant gases and aerosols. Tests of pulmonary function can be used to assess response of workmen to industrial environments. Renal clearance and other kidney function tests can serve to detect renal damage. The effects of exercise or nonspecific stress on the degree of response to toxic chemicals is another important research area in modern toxicology.

Pathology: The toxicologist is concerned with gross and histological damage caused by toxic substances. Most toxicological studies include a thorough pathological examination which may include examination of subcellular structure by electron microscopy.

Immunology and Immunochemistry: It is recognized that immunology and immunochemistry constitute an important area for investigation in industrial toxicology. The response to many chemicals, especially inhaled products of biologic origin, has as its basis the immune reaction.

Physics and Engineering: The toxicologist who is concerned with inhalation as the route of exposure needs some knowledge of physics and engineering in order to establish controlled concentrations of the substances he studies. If the toxic materials are to be administered as airborne particles, knowledge is needed of methods of generation of aerosols and methods of sampling and sizing appropriate to the material studied. Without careful attention to these factors, toxicological studies are of limited value. An understanding of the factors governing penetration, deposition, retention and clearance of particulate material from the respiratory tract requires knowledge of both the physical laws governing aerosol behavior and the anatomy and physiology of the respiratory tract. The growing interest in prolonged exposure to closed atmospheres encountered in manned space travel or deep sea exploration has led to experimental studies involving round-the-clock exposures of experimental animals for long periods. Such studies raise additional engineering problems above and beyond those of maintaining the more conventional exposure chambers.

Statistics: Statistics are used in the analysis of data and in the establishing of an experimental design that will yield the maximum of desired information with the minimum of wasted effort. The toxicologist relies heavily on statistics, as the calculation of the LD_{50} (Lethal Dose — 50% probable) is a statistical calculation. Experimental studies of joint toxicity are planned in accord with established statistical designs.

Communication: The ultimate aim of the toxicologist is (or should be) the prevention of damage to man and the environment by toxic agents. One important function is the distribution of information in such terms that the people in need of the information will understand it. The toxicologist's responsibility does not end with the publication of his research results in a scientific journal for the erudition of his peers. He is called upon to make value judgments in extrapolation of his findings in order to advise governmental agencies and others faced with the problem of setting safe levels, be they air pollution standards or Threshold Limit Values for industrial exposure or tolerance levels of pesticide residues in food. In addition to this, when he makes such value judgments, he should above all be honest with himself and with those he advises, that they are value judgments and as such should be subject to frequent review as new knowledge and experience accumulate.

DOSE-RESPONSE RELATIONSHIPS

Experimental toxicology is in essence biological assay with the concept of a dose-response relationship as its unifying theme. The potential toxicity (harmful action) inherent in a substance is manifest only when that substance comes in contact with a living biological system. A chemical normally thought of as "harmless" will evoke a toxic response if added to a biological system in sufficient amount. For example, the inadvertent inclusion of large amounts of sodium chloride in feeding formulae in a hospital nursery led to infant mortality. Conversely, for a chemical normally thought of as "toxic" there is a minimal concentration which will produce no toxic effect if added to a biological system. The toxic potency of a chemical is thus ultimately defined by the relationship between the dose (the amount) of the chemical and the response that is produced in a biological system.

In preliminary toxicity testing, death of the animals is the response most commonly chosen. Given a compound with no known toxicity data,

the initial step is one of range finding. A dose is administered and, depending on the outcome, is increased or decreased until a critical range is found over which, at the upper end, all animals die and, at the lower end, all animals survive. Between these extremes is the range in which the toxicologist accumulates data which enable him to prepare a dose-response curve relating percent mortality to dose administered.

From the dose-response curve, the dose that will produce death in 50 percent of the animals may be calculated. This value is commonly abbreviated as LD_{50}. It is a statistically obtained value representing the best estimation that can be made from the experimental data at hand. The LD_{50} value should always be accompanied by a statement of the error of the estimated value, such as the probability range or confidence limits. The dose is expressed as amount per unit of body weight. The value should be accompanied by an indication of the species of experimental animal used, the route of administration of the compound, the vehicle used to dissolve or suspend the material if applicable, and the time period over which the animals were observed. For example, a publication might state "For rats, the 24 hr. ip LD_{50} for "X" in corn oil was 66 mg/kg (95% confidence limits 59-74)." This would indicate to the reader that the material was given to rats as an intraperitoneal injection of compound X dissolved or suspended in corn oil and that the investigator had limited his mortality count to 24 hours after administering the compound. If the experiment has involved inhalation as the route of exposure, the dose to the animals is expressed as parts per million, mg/m^3, or some other appropriate expression of concentration of the material in the air of the exposure chamber, and the length of exposure time is specified. In this case the term LC_{50} is used to designate the concentration in air that may be expected to kill 50 percent of the animals exposed for the specified length of time. Various procedures have been recommended for the estimation of the LD_{50} or LC_{50}. For information on the more commonly used techniques, papers such as those of Bliss,[2] Miller and Tainter,[3] Litchfield and Wilcoxon[4] or Weil[5] may be consulted.

The simple determination of the LD_{50} for an unknown compound provides an initial comparative index for the location of the compound in the overall spectrum of toxic potency. Table 7-1 shows an attempt at utilizing LD_{50} and LC_{50} values to set up an approximate classification of toxic substances which was suggested by Hodge and Sterner.[6]

Over and above the specific LD_{50} value, the slope of the dose-response curve provides useful information. It suggests an index of the margin of safety, that is the magnitude of the range of doses involved in going from a non-effective dose to a lethal dose. It is obvious that if the dose-response curve is very steep, this margin of safety is slight. Another situation may arise in which one compound would be rated as "more toxic" than a second compound if the LD_{50} values alone were compared but the reverse assessment of relative toxicity would be reached if the comparison was made of the LD_5 values for the two compounds because the dose-response curve for the second compound had a more gradual slope. It should thus be apparent that the slope of the dose-response curves may be of considerable significance with respect to establishing relative toxicities of compounds. For an excellent non-mathematical discussion of the underlying concepts of dose-response relationships, Chapter 2 of Loomis[7] is well worth reading.

TABLE 7-1
Toxicity Classes

Toxicity Rating	Descriptive Term	LD_{50}-Wt/kg Single oral dose Rats	4 hr Inhalation LC_{50} — PPM Rats
1	Extremely toxic	1 mg or less	<10
2	Highly toxic	1-50 mg	10-100
3	Moderately toxic	50-500 mg	100-1,000
4	Slightly toxic	0.5-5 g	1,000-10,000
5	Practically non-toxic	5-15 g	10,000-100,000
6	Relatively harmless	15 g or more	>100,000

By similar experiments dose-response curves may be obtained using a criterion other than mortality as the response and an ED_{50} value is obtained. This is the dose which produced the chosen response in 50 percent of the treated animals. When the study of a toxic substance progresses to the point at which its action on the organism may be studied as graded response in groups of animals, dose-response curves of a slightly different sort are generally used. One might see for example, a dose-response curve relating the degree of depression of brain choline esterase to the dose of an organic phosphorus ester or a dose-response curve relating the increase in pulmonary flow-resistance to the concentration of sulfur dioxide inhaled.

ROUTES OF EXPOSURE

Toxic chemicals can enter the body by various routes. The most important route of exposure in industry is inhalation. Next in importance is contact with skin and eyes. The response to a given dose of toxic agent may vary markedly depending on the route of entry. A cardinal principle to remember is that *the intensity of toxic action is a function of the concentration of the toxic agent which reaches the site of action.* The route of exposure can obviously have an influence upon the concentration reaching the site of action.

Parenteral: Aside from the obvious use in administration of drugs, injection is considered mainly as a route of exposure of experimental animals. In the case of injection, the dose administered is known with accuracy. Intravenous (iv) injection introduces the material directly into the circulation, hence comparison of the degree of response to iv injection with the response to the dose administered by another route can provide information on the rate of uptake of the material by the alternate route. When a material is administered

by injection, the highest concentration of the toxic material in the body occurs at the time of entrance. The organism receives the initial impact at the maximal concentration without opportunity for a gradual reaction, whereas if the concentration is built up more gradually by some other route of exposure, the organism may have time to develop some resistance or physiological adjustment which could produce a modified response. In experimental studies intraperitoneal (ip) injection of the material into the abdominal fluid is a frequently used technique. The major venous blood circulation from the abdominal contents proceeds via the portal circulation to the liver. A material administered by ip injection is subject to the special metabolic transformation mechanisms of the liver, as well as the possibility of excretion via the bile before it reaches the general circulation. If the LD_{50} of a compound given by ip injection was much higher (i.e., the toxicity is lower) than the LD_{50} by iv injection, this fact would suggest that the material was being detoxified by the liver or that the bile was a major route of excretion of the material. If the values for LD_{50} were very similar for ip and iv injection, it would suggest that neither of these factors played a major role in the handling of that particular compound by that particular species of animal.

Oral: Ingestion occurs as a route of exposure of workmen through eating or smoking with contaminated hands or in contaminated work areas. Ingestion of inhaled material also occurs. One mechanism for the clearance of particles from the respiratory tract is the carrying up of the particles by the action of the ciliated lining of the respiratory tract. These particles are then swallowed and absorption of the material may occur from the gastro-intestinal tract. This situation is most likely to occur with larger size particles (2μ and up)although smaller particles deposited in the alveoli may be carried by phagocytes to the upward moving mucous carpet and eventually be swallowed.

In experimental work, compounds may be administered orally as either a single or multiple dose given by stomach tube or the material may be incorporated in the diet or drinking water for periods varying from several weeks or months up to several years or the lifetime of the animals. In either case, the dose the animals actually receive may be ascertained with considerable accuracy. Except in the case of a substance which has a corrosive action or in some way damages the lining of the gastro-intestinal tract, the response to a substance administered orally will depend upon how readily it is absorbed from the gut. Uranium, for example, is capable of producing kidney damage, but is poorly absorbed from the gut and so oral administration produces only low concentrations at the site of action. On the other hand, ethyl alcohol, which has as a target organ the central nervous system, is very rapidly absorbed and within an hour 90 percent of an ingested dose has been absorbed.

The epithelium of the gastro-intestinal tract is poorly permeable to the ionized form of organic compounds. Absorption of such materials generally occurs by diffusion of the lipid-soluble non-ionized form. Weak acids which are predominately nonionized in the high acidity (pH 1.4) of gastric juice are absorbed from the stomach. The surface of the intestinal mucosa has a pH of 5.3. At this higher pH weak bases are less ionized and more readily absorbed. The pK of a compound (see Chapter 5) thus becomes an important factor in predicting absorption from the gastro-intestinal tract.

Inhalation: Inhalation exposures are of prime importance to the industrial toxicologist. The dose actually received and retained by the animals is not known with the same accuracy as when a compound is given by the routes previously discussed. This depends upon the ventilation rate of the individual. In the case of a gas, it is influenced by solubility and in the case of an aerosol by particle size. The factors that influence the dose of a substance retained in an inhalation exposure will be discussed later. For the moment, suffice it to say that the concentration and time of exposure can be measured accurately and this gives a working estimate of the exposure. Two techniques are sometimes utilized in an attempt to determine the dose with precision and still administer the compound via the lung. One is intratracheal injection which may be used in some experiments in which it is desirable to deliver a known amount of particulate material into the lung. The other is so called "precision gassing." In this technique the animal or experimental subject breathes through a valve system and the volume of exhaled air and the concentration of toxic material in it are determined. A comparison of these data with the concentration in the atmosphere of the exposure chamber gives an indication of the dose retained.

Cutaneous: Cutaneous exposure ranks first in the production of occupational disease, but not necessarily first in severity. The skin and its associated film of lipids and sweat may act as an effective barrier. The chemical may react with the skin surface and cause primary irritation. The agent may penetrate the skin and cause sensitization to repeated exposure. The material may penetrate the skin in an amount sufficient to cause systemic poisoning. In assessing the toxicity of a compound by skin application, a known amount of the material to be studied is placed on the clipped skin of the animal and held in place with a rubber cuff. Some materials such as acids, alkalis and many organic solvents are primary skin irritants and produce skin damage on initial contact. Other materials are sensitizing agents. The initial contact produces no irritant response, but may render the individual sensitive and dermatitis results from future contact. Ethyleneamines and the catechols in the well known members of the Rhus family (poison ivy and poison oak) are examples of such agents. Chapter 34 is devoted to the damaging effects of industrial chemicals on the skin. The physiochemical properties of a material are the main determinant of whether or not a material will be absorbed through the skin. Among the important factors are pH, extent of ionization,

water and lipid solubility and molecular size. Some compounds such as phenol and phenolic derivatives can readily penetrate the skin in amounts sufficient to produce systemic intoxication. If the skin is damaged, the normal protective barrier to absorption of chemicals is lessened and penetration may occur. An example of this is a description of cases of mild lead intoxication that occurred in an operation which involved an inorganic lead salt and also a cutting oil. Inorganic lead salts would not be absorbed through intact skin, but the dermatitis produced by the cutting oil permitted increased absorption.

Ocular: The assessment of possible damage resulting from the exposure of the eyes to toxic chemicals should also be considered. The effects of accidental contamination of the eye can vary from minor irritation to complete loss of vision. In addition to the accidental splashing of substances into the eyes, some mists, vapors and gases produce varying degrees of eye irritation, either acute or chronic. In some instances a chemical which does no damage to the eye can be absorbed in sufficient amount to cause systemic poisoning. The extreme toxicity of fluoroacetate was discovered accidentally in this manner by a group of Polish chemists who tested it for lachrymatory action in a rabbit. They had hoped that fluoroacetate would be as irritating to the eyes as iodoacetic acid. The latter had proved unsuitable for warfare purposes because of the purple cloud of iodine vapor that betrayed its presence when it was exploded in a bomb. Their rabbit showed no signs of eye irritation, but alerted their interest when it had convulsions and died. An excellent reference on ocular effects of toxic chemicals is "Toxicology of the Eye" by Grant.[8]

CRITERIA OF RESPONSE

After the toxic material has been administered by one of the routes of exposure discussed above, there are various criteria the toxicologist uses to evaluate the response. In modern toxicological research, these criteria are oriented whenever possible towards elucidating the mechanisms of action of the material.

Mortality: As has been indicated, the LD_{50} of a substance serves as an initial test to place the compound appropriately in the spectrum of toxic agents. Mortality is also a criterion of response in long term chronic studies. In such studies, the investigator must be certain that the mortality observed was due to the chronic low level of the material he is studying; hence an adequate control group of untreated animals subject to otherwise identical conditions is maintained for the duration of the experiment.

Pathology: By examination of both gross and microscopic pathology of the organs of animals exposed, it is possible to get an idea of the site of action of the toxic agent, the mode of action and the cause of death. Pathological changes are usually observed at dose levels which are below those needed to produce the death of animals. The liver and the kidney are organs particularly sensitive to the action of a variety of toxic agents. In some instances the pathological lesion is typical of the specific toxic agents, for example, the silicotic nodules in the lungs produced by inhalation of free silica or the pattern of liver damage resulting from exposure to carbon tetrachloride and some other hepatotoxins. In other cases the damage may be more diffuse and less specific in nature.

Growth: In chronic studies the effect of the toxic agent on the growth rate of the animals is another criterion of response. Levels of the compound which do not produce death or overt pathology may result in a diminished rate of growth. A record is also made of the food intake. This will indicate whether diminished growth results from lessened food intake or from less efficient use of food ingested. It sometimes happens that when an agent is administered by incorporation into the diet, especially at high levels, the food is unpalatable to the animals and they simply refuse to eat it.

Organ Weight: The weight of various organs, or more specifically the ratio of organ weight to body weight may be used as a criterion of response. In some instances such alterations are specific and explicable, as for example the increase of lung weight to body weight ratio as a measure of the edema produced by irritants such as ozone or oxides of nitrogen. In other instances the increase is a less specific general hypertrophy of the organ, especially of the liver and kidney. In a summary of data from two major industrial toxicology laboratories where a wide variety of compounds had been screened for toxicity,[9] it was pointed out that in using body growth, liver weight and kidney weight as criteria of response, a change in one or more of these was observed at the lowest dose at which any effect was seen in 80 percent of 364 studies. If liver and kidney pathology were included in the list, then a change in one or more criteria was observed at the lowest dose at which any effect was seen in 96 percent of these studies. The other 4 percent included materials with very specific action such as the organophosphorus insecticides which will produce alterations in acetylcholine esterase at very low levels. Such nonspecific increases in organ weight are difficult to interpret and may not of necessity represent a harmful change, but they lower the threshold at which a dose may be termed "no effect."

Physiological Function Tests: Physiological function tests are useful criteria of response both in experimental studies and in assessing the response of exposed workmen. They can be especially useful in chronic studies in that they do not necessitate the killing of the animal and can, if desired, be done at regular intervals throughout the period of study. Tests in common clinical use such as bromsulphalein retention, thymol turbidity, or serum alkaline phosphatase may be used to assess the effect of an agent on liver function. The examination of the renal clearance of various substances helps give an indication of localization of kidney damage. The ability of the kidney (especially in the rat) to produce a concentrated urine may be measured by the osmolality of the urine produced. This has been suggested for the evaluation of alterations in kidney function.[10] Alterations may be detected following inhalation of materials such as chlorotrifluoroethylene at levels of reversi-

ble response. In some instances measurement of blood pressure has proved a sensitive means of evaluating response.[11] Various tests of pulmonary function have been used to evaluate the response of both experimental animals and exposed workmen. These tests include relatively simple tests which are suitable for use in field surveys as well as more complex methods possible only under laboratory conditions. Simple tests include such measurements as peak expiratory flowrate (PEFR), forced vital capacity (FVC), and 1-second forced expiratory volume ($FEV_{1.0}$). More complex procedures include the measurement of pulmonary mechanics (flow-resistance and compliance) and their application in epidemiologic surveys. Information on the effects of various agents on the lungs is discussed in Chapter 33.

Biochemical Studies: The study of biochemical response to toxic agents leads in many instances to an understanding of the mechanism of action. Tests of toxicity developed in animals should be oriented to determination of early response from exposures that are applicable to the industrial scene. Many toxic agents act by inhibiting the action of specific enzymes. This action may be studied *in vitro* and *in vivo*. In the first case, the toxic agent is added to tissue slices or tissue homogenate from normal animals and the degree of inhibition of enzymatic activity is measured by an appropriate technique. In the second case, the toxic agent is administered to the animals; after the desired interval the animals are killed and the degree of enzyme inhibition is measured in the appropriate tissues. A judicious combination of *in vivo* and *in vitro* studies is especially useful when biotransformation to a toxic compound is involved. The classic example of this is the work of Peters [12] on the toxicity of fluoroacetate. This material, which was extremely toxic when administered to animals of various species, did not inhibit any known enzymes *in vitro*. Peters' work demonstrated that fluoroacetate entered the carboxylic acid cycle of metabolism as if it were acetic acid. The product formed was fluorocitrate which was a potent inhibitor of the enzyme aconitase. Biological conversion in the living animal had resulted in the formation of a highly toxic compound. He coined the term "lethal synthesis" to describe such a transformation. An elegant paper by Cremer[13] on the ethyl lead compounds is worth discussing as an example of research techniques in this area. She injected rats with tetra-, tri-, and di-ethyl lead and with lead acetate. Symptoms of excitability, tremors and convulsions were observed in the animals injected with the tetraethyl and triethyl lead but not in the animals injected with diethyl lead or the inorganic lead. The triethyl lead was more potent than the tetraethyl lead, which suggested that perhaps the toxic response resulted from biologically formed triethyl lead. By analytic methods, she was able to demonstrate the presence of triethyl lead in the tissues of animals poisoned with tetraethyl lead. She found *in vitro* that liver preparations were capable of converting tetraethyl lead to triethyl lead. She measured the metabolism of brain slices from animals treated *in vivo* and found that the oxygen consumption was lowered in animals receiving tetraethyl or triethyl lead but not in animals treated with diethyl lead or lead acetate. Turning again to *in vitro* experiments, she measured the oxygen consumption of brain cortex slices from normal animals to which the ethyl lead compounds were added. These experiments showed that tetraethyl lead is without effect and that triethyl lead is the active component.

The fundamentals of the metabolism of toxic compounds are discussed in Chapter 5. The classic reference in the field is *Detoxification Mechanisms* by Williams.[14] The term "biotransformation" is in many ways preferable to "detoxication" for in many instances the toxic moiety may be the metabolic product rather than the compound administered. There are some instances, of course, such as the conversion of cyanide to thiocyanate, which are truly "detoxication" in the strict sense.

Tests for the level of metabolites of toxic agents in the urine have found wide use in industrial toxicology as a means of evaluating exposure of workmen. These are commonly referred to as biologic threshold limits which serve as biologic counterparts to the TLV's. The presence of the metabolic product does not of necessity imply poisoning; indeed the opposite is more commonly the case. Normal values have been established and an increase above these levels indicates that exposure has occurred and thus provides a valuable screening mechanism for the prevention of injury from continued or excessive exposure. Table 7-2 lists some of these metabolic products which have been used to evaluate exposure as well as the agents for which they may be used.

TABLE 7-2
Metabolic Products Useful As Indices Of Exposure

Product in Urine	Toxic Agents
Organic Sulfate	Benzene Phenol Aniline
Hippuric Acid	Toluene Ethyl benzene
Thiocyanate	Cyanate Nitriles
Glucuronates	Phenol Benzene Terpenes
Formic Acid	Methyl alcohol
2, 6, dinitro-4-amino toluene	TNT
p-nitrophenol	Parathion
p-aminophenol	Aniline

There are other instances in which a biochemical alteration produced by the toxic agent is useful as a criterion of evaluating exposure. Lead, for example, interferes in porphyrin metabolism and increased levels of delta-aminolevulinic acid may be detected in the urine following lead exposure. Levels of plasma choline esterase may be used to evaluate exposure to organic phosphorus insecticides. Levels of carboxyhemoglobin provide a means of assessing exposure to carbon monoxide. Levels of methemoglobin can be used to evaluate exposure to nitrobenzene or aniline. Hemolysis

of red cells is observed in exposure to arsine. Analysis of blood, urine, hair, or nails for various metals is also used to evaluate exposure, though whether these would be termed "biochemical tests" depends somewhat on whether you are speaking with an engineer or a biochemist.

The use of biologic threshold limit values provides a valuable adjunct to the TLV's which are based on air analysis. The analysis of blood, urine, hair, or exhaled air for a toxic material *per se* (e.g., Pb, As) or for a metabolite of the toxic agent (e.g., thiocyanate, phenol) gives an indication of the exposure of an individual worker. These tests represent a very practical application of data from experimental toxicology. Research in industrial toxicology is often oriented towards the search for a test suitable for use as a biologic threshold which will indicate exposure at a level below which damage occurs.

Behavioral Studies: When any toxic agent is administered to experimental animals, the experienced investigator is alert for any signs of abnormal behavior. Such things as altered gait, bizarre positions, aggressive behavior, increased or decreased activity, tremors or convulsions can suggest possible sites of action or mechanisms of action. The ability of an animal to maintain its balance on a rolling bar is a frequently used test of coordination. The loss of learned conditioned reflexes has also been used and by judicious combination of these tests it is possible to determine, for example, that the neurological response to methyl cellosolve differs from the response to ethyl alcohol.[15] Ability to solve problems or make perceptual distinctions has been used on human subjects, especially in an effort to determine the possible effects of low levels of carbon monoxide and other agents which might be expected to interfere with efficient performance of necessary tasks, thus creating a subtle hazard. Effects on neurological variables such as dark adaptation of the eye are much used by Russian investigators in determining threshold limit values.

Reproductive Effects: It is possible that a level of a toxic material can have an effect on either male or female animals which will result in decreased fertility. In fertility studies the chemical is given to males and females in daily doses for the full cycle of oogenesis and spermatogenesis prior to mating. If gestation is established, the fetuses are removed by caesarean section one day prior to delivery. The litter size and viability are compared with untreated groups. The young are then studied to determine possible effects on survival, growth rate and maturation. The tests may be repeated through a second and third litter of the treated animals. If it is considered necessary the test may be extended through the second and third generation.

Teratogenic Effects: Chemicals administered to the pregnant animal may, under certain conditions, produce malformations of the fetus without inducing damage to the mother or killing the fetus. The experience with the birth of many infants with limb anomalies resulting from the use of thalidomide by the mothers during pregnancy alerted the toxicologists to the need for more rigid testing in this difficult area. Another example of human experience in recent times was the teratogenic effect of methyl mercury as demonstrated in the incidents of poisoning in Minamata Bay, Japan. The study of the teratogenic potential poses a very complex toxicological problem. The susceptibility of various species of animal varies greatly in the area of teratogenic effects. The timing of the dose is very critical as a chemical may produce severe malformations of one sort if it reaches the embryo at one period of development and either no malformations or malformations of a completely different character if it is administered at a later or earlier period of embryogenesis. For a discussion of a recommended method of teratogenic testing and a summary of the literature in this area, the paper by Cahen[16] may be consulted.

Carcinogenicity: The study of the carcinogenic effects of a toxic chemical is a complex experimental problem. Such testing involves the use of sizeable groups of animals observed over a period of two years in rats or four to five years in dogs because of the long latent period required for the development of cancer. Efforts to shorten the time lag have led to the use of aging animals. This may reduce the lag period one third to one fourth. Various strains of inbred mice or hamsters are frequently used in such experiments. Quite frequently materials are screened by painting on the skin of experimental animals, especially mice. Industrial experience down through the years has made plain the hazard of cancer from exposure to various chemicals. Among these are many of the polynuclear hydrocarbons, beta-naphylamine which produces bladder cancer, chromates and nickel carbonyl which produce lung cancer. An excellent summary of recent experimental work in the area of the production of lung cancer in experimental animals is given by Kuschner.[17]

The FDA Advisory Committee on Protocols for Safety Evaluation Panel on Carcinogenesis has recently published in the literature their *Report on Cancer Testing in the Safety Evaluation of Food Additives and Pesticides*.[18] The particular emphasis is on testing materials which would come into contact with man principally through the diet, either as food additives or as contaminating residues on food products as in the case of pesticides; however, many fundamental points pertinent to the overall area of experimental testing for carcinogenesis by the toxicologist are raised and thoughtfully discussed. This reference is highly recommended reading. For ubiquitous substances air quality standards must consider contributions from all sources, food and beverages, water, ambient air, and smoking, as well as those from the industrial environment, e.g., asbestos and lead.

FACTORS INFLUENCING INTENSITY OF TOXIC ACTION

Rate of Entry and Route of Exposure: The degree to which a biological system responds to the action of a toxic agent is in many cases markedly influenced by the rate and route of exposure. It has already been indicated that when a substance is administered as an iv injection, the material has maximum opportunity to be carried by the blood

stream throughout the body, whereas other routes of exposure interpose a barrier to distribution of the material. The effectiveness of this barrier will govern the intensity of toxic action of a given amount of toxic agent administered by various routes. Lead, for example, is toxic both by ingestion and by inhalation. An equivalent dose, however, is more readily absorbed from the respiratory tract than from the gastro-intestinal tract and hence produces a greater response.

There is frequently a difference in intensity of response and sometimes a difference even in the nature of the response between the acute and chronic toxicity of a material. If a material is taken into the body at a rate sufficiently slow that the rate of excretion and/or detoxification keeps pace with the intake, it is possible that no toxic response will result even though the same total amount of material taken in at a faster rate would result in a concentration of the agent at the site of action sufficient to produce a toxic response. Information of this sort enters into the concept of a threshold limit for safe exposure. Hydrogen sulfide is a good example of a substance which is rapidly lethal at high concentrations as evidenced by the many accidental deaths it has caused. It has an acute action on the nervous system with rapid production of respiratory paralysis unless the victim is promptly removed to fresh air and revived with appropriate artificial respiration. On the other hand, hydrogen sulfide is rapidly oxidized in the plasma to non-toxic substances and many times the lethal dose produces relatively little effect if administered slowly. Benzene is a good example of a material which differs in the nature of response depending on whether the exposure is an acute one to a high concentration or a chronic exposure to a lower level. If one used as criteria the 4 hr LC_{50} for rats of 16,000 ppm which has been reported for benzene, one would conclude (from Table 7-1) that this material would be "practically non-toxic" which, of course, is contrary to fact. The mechanism of acute death is narcosis. Chronic exposure to low levels of benzene on the other hand produces damage to the blood-forming tissue of the bone marrow and chronic benzene intoxication may appear even many years after the actual exposure to benzene has ceased.

Age: It is well known that, in general, infants and the newborn are more sensitive to many toxic agents than are adults of the same species, but this has relatively little bearing on a discussion of industrial toxicology. Older persons or older animals are also often more sensitive to toxic action than are younger adults. With aging comes a diminished reserve capacity in the face of toxic stress. This reserve capacity may be either functional or anatomical. The excess mortality in the older age groups during and immediately following the well known acute air pollution incidents is a case in point. There is experimental evidence from electron microscope studies that younger animals exposed to pollutants have a capacity to repair lung damage which was lost in older animals.[19]

State of Health: Pre-existing disease can result in greater sensitivity to toxic agents. In the case of specific diseases which would contraindicate exposure to specific toxic agents, pre-placement medical examination can prevent possible hazardous exposure. For example, an individual with some degree of pre-existing methemoglobinemia would not be placed in a work situation involving exposure to nitrobenzene. Since it is known that the uptake of manganese parallels the uptake of iron, it would be unwise to employ a person with known iron deficiency anemia as a manganese miner. It has been shown that viral agents will increase the sensitivity of animals to exposure to oxidizing type air pollutants. Nutritional status also affects response to toxic agents.

Previous Exposure: Previous exposure to a toxic agent can lead to either tolerance, increased sensitivity or make no difference in the degree of response. Some toxic agents function by sensitization and the initial exposures produce no observable response, but subsequent exposures will do so. In these cases the individuals who are thus sensitized must be removed from exposure. In other instances if an individual is re-exposed to a substance before complete reversal of the change produced by a previous exposure, the effect may be more dangerous. A case in point would be an exposure to an organophosphorus insecticide which would lower the level of acetylcholine esterase. Given time, the level will be restored to normal. If another exposure occurs prior to this, the enzyme activity may be further reduced to dangerous levels. Previous exposure to low levels of a substance may in some cases protect against subsequent exposure to levels of a toxic agent which would be damaging if given initially. This may come about through the induction of enzymes which detoxify the compound or by other mechanisms often not completely understood. It has been shown, for example, that exposure of mice to low levels of ozone will prevent death from pulmonary edema in subsequent high exposures.[20] There is also a considerable "cross tolerance" among the oxidizing irritants such as ozone and hydrogen peroxide, an exposure to low levels of the one protecting against high levels of the other.

Environmental Factors: Physical factors can also affect the response to toxic agents. In industries such as smelting or steel making, high temperatures are encountered. Pressures different than normal ambient atmospheric pressure can be encountered in caissons or tunnel construction.

Host Factors: For many toxic agents the response varies with the species of animal. There are often differences in the response of males and females to the same agent. Hereditary factors also can be of importance. Genetic defects in metabolism may render certain individuals more sensitive to a given toxic agent.

CLASSIFICATION OF TOXIC MATERIALS

Within the scope of this chapter it is not possible to discuss the specific toxic action of a variety of materials, although where possible specific information has been used to illustrate the principles discussed. It might, however, be useful to consider several ways in which toxic agents may be

classified. No one of these is of itself completely satisfactory. A toxic agent may have its action on the organ with which it comes into first contact. Let us assume for the moment that the agent is inhaled. Materials such as irritant gases or acid mists produce a more or less rapid response from the respiratory tract when present in sufficient concentration. Other agents, such as silica or asbestos, also damage the lungs but the response is seen only after lengthy exposure. Other toxic agents may have no effect upon the organ through which they enter the body, but exert what is called systemic toxic action when they have been absorbed and translocated to the site of biological action. Examples of such agents would be mercury vapor, manganese, lead, chlorinated hydrocarbons and many others which are readily absorbed through the lungs, but produce typical toxic symptoms only in other organ systems.

Physical Classifications: This type of classification is an attempt to base the discussion of toxic agents on the form in which they are present in the air. These are discussed as gases and vapors or as aerosols.

Gases and Vapors: In common industrial hygiene usage the term "gas" is usually applied to a substance which is in the gaseous state at room temperature and pressure and the term "vapor" is applied to the gaseous phase of a material which is ordinarily a solid or a liquid at room temperature and pressure. In considering the toxicity of a gas or vapor, the solubility of the material is of the utmost importance. If the material is an irritant gas, solubility in aqueous media will determine the amount of material that reaches the lung and hence its site of action. A highly soluble gas, such as ammonia, is taken up readily by the mucous membranes of the nose and upper respiratory tract. Sensory response to irritation in these areas provides the individual with warning of the presence of an irritant gas. On the other hand, a relatively insoluble gas such as nitrogen dioxide is not scrubbed out by the upper respiratory tract, but penetrates readily to the lung. Amounts sufficient to lead to pulmonary edema and death may be inhaled by an individual who is not at the time aware of the hazard. The solubility coefficient of a gas or vapor in blood is one of the factors determining rate of uptake and saturation of the body. With a very soluble gas, saturation of the body is slow, is largely dependent upon ventilation of the lungs and is only slightly influenced by changes in circulation. In the case of a slightly soluble gas, saturation is rapid, depends chiefly on the rate of circulation and is little influenced by the rate of breathing. If the vapor has a high fat solubility, it tends to accumulate in the fatty tissues which it reaches carried in the blood. Since fatty tissue often has a meager blood supply, complete saturation of the fatty tissue may take a longer period. It is also of importance whether the vapor or gas is one which is readily metabolized. Conversion to a metabolite would tend to lower the concentration in the blood and shift the equilibrium towards increased uptake. It is also of importance whether such metabolic products are toxic. For a discussion of the interplay of factors relating to the uptake of gases and vapors, Chapter 5 of Henderson and Haggard[21] or Chapter 6 of Patty[22] should be consulted.

Aerosols: An aerosol is composed of solid or liquid particles of microscopic size dispersed in a gaseous medium (for our purposes, air). Special terms are used for indicating certain types of particles. Some of these are: "dust", a dispersion of solid particles usually resulting from the fracture of larger masses of material such as in drilling, crushing or grinding operations; "mist", a dispersion of liquid particles, many of which are visible; "fog", visible aerosols of a liquid formed by condensation; "fume", an aerosol of solid particles formed by condensation of vaporized materials; "smoke", aerosols resulting from incomplete combustion which consist mainly of carbon and other combustible materials. The toxic response to an aerosol depends obviously on the nature of the material, which may have as a target organ the respiratory system or may be a systemic toxic agent acting elsewhere in the body. In either case, the toxic potential of a given material dispersed as an aerosol is only partially described by a statement of the concentration of the material in terms of weight per unit volume or number of particles per unit volume. For a proper assessment of the toxic hazard, it is necessary to have information also on the particle size distribution of the material. Understanding of this fact has led to the development of instruments which sample only particles in the respirable size range. Chapters 13 and 14 discuss analytical methods for obtaining the needed data. The particle size of an aerosol is the key factor in determining its site of deposition in the respiratory tract and, as a sequel to this, the clearance mechanisms which will be available for its subsequent removal. The deposition of an aerosol in the respiratory tract depends upon the physical forces of impaction, settling, and diffusion or Brownian movement which apply to the removal of any aerosol from the atmosphere, as well as upon anatomical and physiological factors such as the geometry of the lungs and the air-flow rates and patterns occurring during the respiratory cycle. The interrelationship of these factors has been examined both theoretically and experimentally. The monograph by Hatch and Gross, "Pulmonary Deposition and Retention of Inhaled Aerosols"[23] gives an excellent discussion of the subject and should be required reading for anyone entering the field of environmental toxicology. The most recent theoretical treatment is that of the Task Force on Lung Dynamics[24] which also gives an excellent summary of past work.

In the limited space available only one point will be emphasized here, namely, the toxicological importance of particles below 1 μm in size. Aerosols in the range of 0.2-0.4 μm tend to be fairly stable in the atmosphere. This comes about because they are too small to be effectively removed by forces of settling or impaction and too big to be effectively removed by diffusion. Since these are the forces that lead to deposition in the respiratory tract, it has been predicted theoretically and confirmed experimentally that a lesser *percentage* of these particles is deposited in the respiratory tract.

On the other hand, since they are stable in the atmosphere, there are large numbers of them present to be inhaled, and to dismiss this size range as of minimal importance is an error in toxicological thinking which should be corrected whenever it is encountered. Aerosols in the size range below 0.1μm are also of major toxicological importance. The percentage deposition of these extremely small particles is as great as for 1μm particles and this deposition is alveolar. This fact was predicted theoretically by Findeisen as far back as 1935[25] and has been confirmed experimentally.[26] Particles in the sub-micron range also appear to have greater potential for interaction with irritant gases, a fact which is of importance in air pollution toxicology.

Chemical Classification: Toxic compounds may be classified according to their chemical nature. Volume II of Patty[22] is so structured and is an excellent practical reference. *Industrial Toxicology* by Hamilton and Hardy[27] is also arranged more or less according to the chemical classification. Since both of the authors were distinguished as industrial physicians (the late Dr. Alice Hamilton being one of the pioneers in that area), the book is more oriented to medical signs and symptoms than towards experimental toxicology. Several more specialized works deal with certain types of chemical compounds. Among these may be included Browning's *Toxicity of Industrial Metals*[28] and *Toxicity and Metabolism of Industrial Solvents*[29] and Gerarde's *Toxicology and Biochemistry of Aromatic Hydrocarbons*.[30]

Physiological Classification: Such classification attempts to frame the discussion of toxic materials according to their biological action. Most such systems (including the present one) have as their basis the now classic scheme proposed by Henderson and Haggard.[21]

Irritants: The basis of classifying these materials is their ability to cause inflammation of mucous membranes with which they come in contact. While many irritants are strong acids or alkalis familiar as corrosive to non-living things such as lab coats or bench tops, bear in mind that inflammation is the reaction of a living tissue and is distinct from chemical corrosion. The inflammation of tissue results from concentrations far below those needed to produce corrosion. As was indicated earlier in discussing gases and vapors, solubility is an important factor in determining the site of irritant action in the respiratory tract. Highly soluble materials such as ammonia, alkaline dusts and mists, hydrogen chloride and hydrogen fluoride affect mainly the upper respiratory tract. Other materials of intermediate solubility such as the halogens, ozone, diethyl or dimethyl sulfate and phosphorus chlorides affect both the upper respiratory tract and the pulmonary tissue. Insoluble materials such as nitrogen dioxide, arsenic trichloride, or phosgene affect primarily the lung. There are exceptions to the statement that solubility serves to indicate site of action. One such is ethyl ether and other insoluble compounds that are readily absorbed unaltered from the alveoli and hence do not accumulate in that area. In the upper respiratory passages and bronchi where the material is not readily absorbed, it can accumulate in concentrations sufficient to produce irritation. Another exception is in materials such as bromobenzyl cyanide which is a vapor from a liquid boiling well above room temperature. It is taken up by the eyes and skin as a mist. In initial action, then, it is a powerful lachrymator and upper respiratory irritant, rather than producing a primarily alveolar reaction as would be predicted from its low solubility.

Irritants can also cause changes in the mechanics of respiration such as increased pulmonary flow-resistance or decreased compliance (a measure of elastic behavior of the lungs). One group of irritants among which are sulfur dioxide, acetic acid, formaldehyde, formic acid, sulfuric acid, acrolein and iodine produce a pattern in which the flow-resistance is increased, the compliance is decreased only slightly and at higher concentrations the frequency of breathing is decreased. Another group among which are ozone and oxides of nitrogen have little effect on resistance, produce a decrease in compliance and an increase in respiratory rate. There is evidence that in the case of irritant aerosol, the irritant potency of a given material tends to increase with decreasing particle size[31] as assessed by the increase in flow-resistance. Following respiratory mechanics measurements in cats exposed to irritant aerosols, the histologic sections prepared after rapid freezing of the lungs showed the anatomical sites of constriction.[32] Long term chronic lung impairment may be caused by irritants either as sequelae to a single very severe exposure or as the result of chronic exposure to low concentrations of the irritant. There is evidence in experimental animals that long term exposure to respiratory irritants can lead to increased mucous secretion and a condition resembling the pathology of human chronic bronchitis without the intermediary of infection.[33, 34] The epidemiological assessment of this factor in the health of residents of polluted urban atmospheres is currently a vital area of research.

Irritants are usually further subdivided into primary and secondary irritants. A primary irritant is a material which for all practical purposes exerts no systemic toxic action either because the products formed on the tissues of the respiratory tract are nontoxic or because the irritant action is far in excess of any systemic toxic action. Examples of the first type would be hydrochloric acid or sulfuric acid. Examples of the second type would be materials such as Lewisite or mustard gas, which would be quite toxic on absorption but death from the irritation would result before sufficient amounts to produce systemic poisoning would be absorbed. Secondary irritants are materials which do produce irritant action on mucous membranes, but this effect is overshadowed by systemic effects resulting from absorption. Examples of materials in this category are hydrogen sulfide and many of the aromatic hydrocarbons and other organic compounds. The direct contact of liquid aromatic hydrocarbons with the lung can cause chemical pneumonitis with pulmonary edema, hemorrhage and tissue necrosis. It is for

this reason that in the case of accidental ingestion of these materials the induction of vomiting is contraindicated because of possible aspiration of the hydrocarbon into the lungs.

Asphyxiants: The basis of classifying these materials is their ability to deprive the tissue of oxygen. In the case of severe pulmonary edema caused by an irritant such as nitrogen dioxide or laryngeal spasm caused by a sudden severe exposure to sulfuric acid mist, the death is from asphyxia, but this results from the primary irritant action. The materials we classify here as asphyxiants do not damage the lung. Simple asphyxiants are physiologically inert gases which act when they are present in the atmosphere in sufficient quantity to exclude an adequate oxygen supply. Among these are such substances as nitrogen, nitrous oxide, carbon dioxide, hydrogen, helium and the aliphatic hydrocarbons such as methane and ethane. All of these gases are not chemically unreactive and among them are many materials which pose a major hazard of fire and explosion. Chemical asphyxiants are materials which have as their specific toxic action rendering the body incapable of utilizing an adequate oxygen supply. They are thus active in concentrations far below the level needed for damage from the simple asphyxiants. The two classic examples of chemical asphyxiants are carbon monoxide and cyanides. Carbon monoxide interferes with the transport of oxygen to the tissues by its affinity for hemoglobin. The carboxy-hemoglobin thus formed is unavailable for the transport of oxygen. All aspects of current research on carbon monoxide were the subject of a recent conference of the New York Academy of Sciences and the monograph resulting from this meeting is an excellent reference.[35] Over and above the familiar lethal effects, there is concern about how low level exposures will affect performance of such tasks as automobile driving, etc. In the case of cyanide, there is no interference with the transport of oxygen to the tissues. Cyanide transported to the tissues forms a stable complex with the ferric iron of ferric cytochrome oxidase resulting in inhibition of enzyme action. Since aerobic metabolism is dependent upon this enzyme system, the tissues are unable to utilize the supply of oxygen, and tissue "hypoxia" results. Therapy is directed towards the formation of an inactive complex before the cyanide has a chance to react with the cytochrome. Cyanide will complex with methemoglobin so nitrite is injected to promote the formation of methemoglobin. Thiosulfate is also given as this provides the sulfate needed to promote the enzymatic conversion of cyanide to the less toxic thiocyanate.

Primary Anesthetics: The main toxic action of these materials is their depressant effect upon the central nervous system, particularly the brain. The degree of anesthetic effect depends upon the effective concentration in the brain as well as upon the specific pharmacologic action. Thus, the effectiveness is a balance between solubility (which decreases) and pharmacological potency (which increases) as one moves up a homologous series of compounds of increasing chain length. The anesthetic potency of the simple alcohols also rises with increasing number of carbon atoms through amyl alcohol which is the most powerful of the series. The presence of multiple hydroxyl groups diminishes potency. The presence of carboxyl groups tends to prevent anesthetic activity which is slightly restored in the case of an ester. Thus acetic acid is not anesthetic, ethyl acetate is mildly so. The substitution of a halogen for a hydrogen of the fatty hydrocarbons greatly increases the anesthetic action, but confers toxicity to other organ systems which outweighs the anesthetic action.

Hepatotoxic Agents: These are materials which have as their main toxic action the production of liver damage. Carbon tetrachloride produces severe diffuse central necrosis of the liver. Tetrachloroethane is probably the most toxic of the chlorinated hydrocarbons and produces acute yellow atrophy of the liver. Nitrosamines are capable of producing severe liver damage. There are many compounds of plant origin such as some of the toxic components of the mushroom Amanita phalloides, alkaloids from Senecio, and aflatoxins which are capable of producing severe liver damage and in some instances are powerful hepatocarcinogens.

Nephrotoxic Agents: These are materials which have as their main toxic action the production of kidney damage. Some of the halogenated hydrocarbons produce damage to the kidney as well as to the liver. Uranium produces kidney damage, mostly limited to the distal third of the proximal convoluted tubule.

Neurotoxic Agents: These are materials which in one way or another produce their main toxic symptoms on the nervous system. Among them are metals such as manganese, mercury and thallium. The central nervous system seems particularly sensitive to organometallic compounds, and neurological damage results from such materials as methylmercury and tetraethyl lead. Trialkyl tin compounds may cause edema of the central nervous system. Carbon disulfide acts mainly on the nervous system. The organic phosphorus insecticides lead to an accumulation of acetyl choline because of the inhibition of the enzyme which would normally remove it and hence cause their main symptoms in the nervous system.

Agents which act on the blood or hematopoietic system: Some toxic agents such as nitrites, aniline and toluidine convert hemoglobin to methemoglobin. Nitrobenzene forms methemoglobin and also lowers the blood pressure. Arsine produces hemolysis of the red blood cells. Benzene damages the hematopoietic cells of the bone marrow.

Agents which damage the lung: In this category are materials which produce damage of the pulmonary tissue but not by immediate irritant action. Fibrotic changes are produced by materials such as free silica which produces the typical silicotic nodule. Asbestos also produces a typical damage to lung tissue and there is newly aroused interest in this subject from the point of view of possible effects of low level exposure of individuals who are not asbestos workers. Asbestosis was the subject of a recent conference of the New York Academy of Sciences and the papers in the re-

sulting monograph present the various aspects of current research in the area.[36] Other dusts, such as coal dust, can produce pneumoconiosis which, with or without tuberculosis super-imposed, has been of long concern in mining. Drinker and Hatch[37] is a classic reference in this area and Hunter[38] discusses at length occupational exposures to dusts. Many dusts of organic origin such as those arising in the processing of cotton or wood can cause pathology of the lungs and/or alterations in lung function. The proteolytic enzymes added to laundry products are an occupational hazard of current interest. Toluenediisocyanate (TDI) is another material which can cause impaired lung function at very low concentrations and there is evidence of chronic as well as acute effects.[39] Chapter 33 discusses materials in this category.

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A.M.A. Archives of Environmental Health; American Industrial Hygiene Association Journal and The British Journal of Industrial Medicine have many articles on industrial toxicology.

Journals: (Foreign)

Medicina del Lavoro — Italian

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Pracovni lekarstvi (Czechoslovakian)

Japanese Journal of Labor Science

Abstracts:

Chemical Abstracts

Exerpta Medica Abstracts in Occupational Health and Industrial Medicine

Bulletin of Hygiene (British)

Scientific Reports on Industrial Hygiene and Occupational Diseases in Czechoslovakia (Published Annually by Inst. of Indust. Hyg. & Occ. Diseases in Prague. In English)

Hygienic Guides:

A series of useful pamphlets published by Am. Industrial Hygiene Association, 210 Haddon Ave., Westmont, N.J. 08108.