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.[25] 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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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.

CHAPTER 8

PRINCIPLES AND USE OF STANDARDS OF QUALITY FOR THE WORK ENVIRONMENT

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INTRODUCTION

Rationale

Total removal of all potentially harmful agents from the work place is the only absolute method of assuring worker safety and health. Since this optimum is not always possible, exposure to potentially toxic substances is unavoidable. Accordingly, it has become necessary to define quantitatively which exposure levels are *not* attended by a risk to the worker's health or well-being.

Basic Underlying Principles

An understanding of the dose-response relationship (see Chapter 7) is a basic determinant of the feasibility of such standards. In brief, all chemical agents cause biological response as a function of the quantity absorbed and the period of time over which such absorption occurs. Thus, there should be a dose (concentration and time dependent) which does not exceed the capability of the organism to metabolize, detoxify or excrete such compounds. This dose is usually referred to as a "no effect" level.

The "no effect" level — is a puristic concept because there is always some biological or chemical alteration when the organism encounters some exogenous material.[1, 2] Whereas in the United States it is clearly understood that such responses are not deleterious *per se*, in the Soviet Union this is not explicitly recognized. Nevertheless, in the United States a "no effect" level is implied to be one which does not produce any deleterious or undesirable effect upon human health and well-being or overload the normal protective mechanisms of the body.[2]

Thus a biological accommodation, e.g., a non-specific alteration in brain waves, a decreased serum catalase (an enzyme normally present in the body far beyond stress demands), is seen as probably not having immediate or long-term effect on health. Such changes are not deleterious in and of themselves. By contrast, although exposure to H_2S at concentrations of 30-50 ppm produces no changes other than self-limited eye irritation. such concentrations are, in normal circumstances, unacceptable. This is in keeping with the WHO* definition of health which considers any encroachment upon human well-being as being ill health and, therefore, undesirable.

Problems in Definition of "No Effect Level"

It can be seen that there may be profound differences of opinion as to what constitutes a "no effect" level. The preponderant opinion in the United States holds that slight deviations within homeostatic limits of biological change are not deleterious.[2]. All necessary life processes required by living organisms are associated with perturbations of a steady state. Thus the basic processes of digestion and absorption are associated with considerable fluxes of, e.g., electrolytes, lipids, proteins, etc., at concentrations which deviate from those found between meals. With each eyelid flicker there are attendant electrical discharges along multiple nerve pathways that previously were essentially quiescent. Therefore, it should be apparent that for all bodily functions there are constant deviations from a "steady state"; such represent necessary accommodative change to environmental alteration in its broadest sense.

While such generalizations are useful, the problem becomes more difficult when one attempts to define the actual limits beyond which change becomes deleterious. Though practically *any* change is considered as being potentially detrimental by the U.S.S.R., it becomes difficult to reconcile this position with the concept of a normal range associated with homeostasis. On the other hand, the question might well be asked whether the accumulated energy expenditures required by accommodation over a lifetime do not contribute to the long-term depletion of life forces which might accelerate the process of aging.

In the strictest sense a "no effect" level does not exist; however, for operational purposes the range of biological response which exceeds homeostatic limits must be ascertained. The problems of defining the effect such stresses (within homeostatic limits) may have over a long-term should be appreciated.

Other Variables Influencing the Use of Workroom Air Quality Standards

Work-rest cycle. All quality standards make certain assumptions regarding the work-rest cycle. Basically, most standards currently utilized in the United States imply an 8-hour day within a 40-hour week.[3] Thus, each work period is followed usually by a 16-hour non-exposed period, during which restituting processes (e.g., detoxification, excretion) occur. Where more prolonged work exposure periods occur, the possibility of a greater total dose being absorbed as well as less time being available for restitution make application of the usual quality standards inappropriate. With deviations from the usual work-rest cycles (e.g., as with continuous exposure in submarines or space capsules), other environmental quality status standards must be applied.

*World Health Organization

Worker Health Status. The standards utilized depend upon an essentially healthy work force. This stems from the fact that persons with a compromised function or pathological condition may not be capable of dealing with absorbed chemicals in the expected manner. Accordingly, such individuals may not be able to completely excrete each day's burden of an absorbed agent; this can lead to a progressive accumulation of such materials.

Adverse Climate Conditions. Since adverse climate conditions place an accommodative burden upon an individual, the additional work involved in accommodating to occupational stressors may be excessive. Accordingly, in such circumstances quality standards may require modifications reflecting such additional physiologic loadings.

Special Genetic and Biological Susceptibility. Because of genetic and biological factors (e.g., glucose-6-phosphate dehydrogenase or serum antitrypsin deficiencies) specific to some few (i.e., 5-10%) individual workers, these workers may possess an undue susceptibility to agents found in the work environment. It is necessary to detect the presence of such unusual persons at special risk prior to work exposure, since quality standards are designed for the normal person and do not apply to special risk workers.[4]

Implications of the Premises Underlying Quality Standards

It becomes immediately apparent that quality standards cannot be utilized without a full understanding of the foregoing premises concerning 1) the work-rest cycle, 2) worker health status, 3) climatic conditions and 4) special susceptibilities. In addition, their use requires concomitant use of adequate environmental monitoring and medical surveillance. The former stems from the need to document the fact that these limits are not being exceeded; the latter requirement, to determine that persons with pathologic or biologic deviations are not exposed (see Chapter 17).

PRINCIPLES FOR DEVELOPING WORKROOM AIR QUALITY STANDARDS

Extrapolation by Chemical Analogy

A. *Principle*. When dealing with a new chemical, animal or human toxicity data are usually unavailable. Therefore, the prevailing principle is that the quality of response of a chemical may be assumed to be analogous to that produced by similar substances. Chemicals that are structurally similar should produce a similar biological response. Thus, as a first approximation, some *estimate* of toxic potential can be obtained. Obviously, the use of such assessments, since they are not absolute predictors of qualitative effects, may be dubious for prediction of quantitative response. Nevertheless, as of 1968, 24% of all Threshold Limit Values published by the American Conference of Governmental Industrial Hygienists were based upon analogy.[5]

B. *Limitations*.

(1) Inconsistency of qualitative effect: Not infrequently one compound in a chemical family of compounds will respond in a totally atypical manner when compared with others of that family. Accordingly, some risk may be attached to predictions of safety or toxicity based upon chemical analogy.

(2) Inconsistency of quantitative effect: as fraught with risk as is prediction of qualitative risk on the basis of chemical analogy, estimating quantitative effect is even more hazardous.

Animal Experimentation

Principles and Purposes. Before workers are exposed to any chemical agents in the workplace, it is advisable to know the toxic effect such materials possess. On this basis one can design the protective measures to protect workers and deal with medical problems caused by such materials. However, in the case of new chemicals, there is often little or no information upon which to act. Accordingly, an important method of developing such new information utilizes animal experimentation.

In some cases clinical experience does exist, but it is often fragmentary, and rarely provides the detailed information needed concerning the metabolites produced following chemical absorption. Data on metabolites is useful in estimating the degree of absorption of substances. Experimentation with an animal host which responds to substances in a manner similar to man can provide such information.

The design of animal experiments should reflect the conditions of industrial usage of the substance in question. Since agents encountered in the workplace may act systemically or locally following skin or mucous membrane exposure, skin testing for possible absorption and systemic toxicity, primary irritation or sensitization is indicated. Exposure of animals to vapors, mists, aerosols or gases for determination of pulmonary effects and uptake or systemic toxicity is extremely relevant to the industrial milieu. By contrast, experiments utilizing gastro-intestinal or subcutaneous absorption are less frequently used except for range-finding toxicity purposes.

Difficult questions revolve about the problems of extrapolation of animal information to man. As a rule, it is desirable to seek toxicological information derived from more than one animal species wherever possible. Quite frequently various species respond in differing fashions qualitatively and quantitatively. Since no one species consistently reacts as does man, one can never predict which species is most like man. Accordingly, it is an operating principle, until otherwise demonstrated, that man should be considered as responding as does the most sensitive animal species; design of control programs should be developed from that point of departure.

Another important factor concerns the number of animals of any one species which are put to test. Here again, because even within any one group of animals, biological individuality will operate, enough animals must be tested. Thus, one attempts to ensure, within a reasonable degree of probability, that even the most sensitive of the group will be tested. In this regard, statistical techniques can be utilized with a view toward determining which confidence limits attend upon animal population size choice.

One last consideration relates to dose ranges used in such experiments. Obviously, a wide range of doses is useful for different purposes. The large doses help force the question, "toxic or non-toxic?" while also providing clearcut answers as to the specific organs susceptible to damage. Likewise, a lower range of doses must be used to give a clearer estimate of thresholds of response.

Criteria of Response — Organ Change. While gross changes in structure clearly delineate the bodily organ at risk of damage, such data are of limited usefulness. This follows since all control measures must be designed so as to prevent any serious, irreversible damage. Thus, while such bodily changes delineate serious responses, satisfactory control is achieved only when exposure prevents even a minimal alteration beyond the homeostatic range. Accordingly, more important data derive from functional changes rather than pathological organ alteration.

Functional Response — Biochemical Changes. Detection of altered organ function occurring prior to structural change provides the organism with greater probability of avoiding permanent damage. Such functional changes are frequently expressed when organs of detoxification produce some metabolic alteration of the absorbed chemical agent. Insofar as such organ of detoxification is not presented with an amount of chemical which does not exceed its detoxification rate, it can continue to cope with such chemical exposures. Experimentation should be designed to define such rate limits in terms of what represents both excess loadings as well as those burdens with which the organism can successfully deal. Especially important is definition of the "break point" in detoxification rates. Such experiments help define the safe "dose"; in addition, quantitative biochemical indicators of over-exposure may also be delineated. As an example of this, one can assay how much absorption of an organo phosphorous pesticide is safe in terms of depression of red cell acetylcholine esterase, or how much lead exposure has occurred by estimation of urinary coproporphyrin or delta aminolevulinic acid. Likewise, measurement of the metabolites of trichloroethylene, e.g., trichloracetic acid, provides useful indicators of the existence and degree of absorption of that solvent.

Neurophysiologic Response. Recently, changes in nervous system function have been studied extensively as a parameter of toxic or subtoxic exposure. Largely as a result of Russian studies, investigation of neurofunctional response has been considered as possibly indicating early change. Where changes in neurologic function impair higher functions, e.g., alertness, cognition, such alterations have obvious industrial implications as regards safety and performance adequacy. However, the relation of certain measurements, e.g., nerve chronaxie, to occupational exposure is problematic. Nevertheless, such studies of higher nervous function increasingly have been undertaken to delineate man's response to his occupational environment.

Other types of response:

(1) Carcinogenesis: Obviously, given the serious implications of occupationally induced cancer, studies designed to detect such a change are of the utmost importance.

Here, the problems of dose-response relationships become extremely complex, since definition of a threshold of response is problematic. Accordingly, testing here is directed largely toward defining whether such a hazard exists; the use of animal experiments for establishing operational control is directed mainly toward defining the necessity for total isolation or substitution. In the present absence of truly effective therapy, once the malignant alteration has been induced, the value of such preclinical indicators is limited.

(2) Mutagenesis and teratogenesis: Mutagenesis is the process wherein normal cells are converted into genetically abnormal cells. The result of such alteration, particularly since it involves the genetic processes which determine normal cell growth and division, are changes in structure and function. This process may result in malignant or other aberrations. Teratogenesis refers to the process whereby abnormalities of the off-spring are generated. Such usually results from damage to embryonal structures in the first trimester of pregnancy, or because of alteration of germinal elements, i.e., ovarian cells or spermatozoan.

While these responses are extremely important — especially where women may be at a risk, the danger of mutagenesis could theoretically also affect male generative tissue. While little such testing has been undertaken with a view toward protection of working populations, serious consideration should be given to such studies in the future.

Application of Animal Data

Principles of Application:

(1) Use of the most sensitive species: because the detoxification represents in essence a genetically controlled metabolic degradation process, it follows that various animal species will respond differently to toxic chemical exposure. Unfortunately, just how any species — including man — will respond is not predictable. Accordingly, when the human quantitative response to a chemical agent is unknown, prudence would dictate that the design of environmental quality standards assume that man responds as does the most sensitive species.

(2) Application of the dose-response curve to setting standards: primarily, environmental quality standards are intended to quantitatively indicate the amount of contaminant which may be present in the workplace without causing harm to man. Obviously, experiments should be directed toward determining the concentra-

tion at which "no effect" is produced, i.e., one which is safe.

Experiments which permit the development of a dose-response curve indicate the several ranges of response. In this manner, the doses producing "no response," a minimal response and the more severe response are defined. In most circumstances, a linear relationship between these doses emerges with the use of logarithmic plots. While a dose-response curve can be estimated without data points being available in the "no response" or safe range, downward extrapolation to this area holds some risk. Problems will occur when a break occurs in such a linear response curve; this is seen particularly in the low dose range.

(3) Safety margins and their bases: because of problems inherent in interpretation of toxicological data (see above), it is desirable to have a margin of safety between the lowest effective dose and a proposed TLV. Expressed mathematically, TLV = lowest effective dose/safety factor. The safety factor depends upon the nature of the response* produced by such lowest effective dose. Where such responses consist of reversible irritation of skin or mucous membranes, safety factors between the dose producing these phenomena and the recommended TLV tend to be low. By contrast, minimal dose-related responses characterized by toxicity usually possess a greater safety margin or factor. The range of safety factors associated with A.C.G.I.H. TLV's has been estimated to extend between 0.2 and 10.[8]

A safety factor of 0.2 denotes that the Threshold Limit Value is 0.2 fold (or 20%) higher than the dose which produces a response; a factor of 10 states that the TLV is 10 fold (or 1000%) higher than the dose producing a threshold response.

While the use of safety margins as an extrapolation process for estimation of the "no response" area is useful, their limitations should be recognized. For one thing, departures from the linearity of the dose-response curve are apt to occur in such estimates of lower ranges. Furthermore, given a steep dose-response line, in the biologically reactive range, the "no effect" level tends to be estimated with a high degree of error. Finally, when dealing with agents that appear to be active at extremely low levels, i.e., 5-10 ppm, departures from linearity appear quite common; this introduces even more chance of an unrealistic standard being set if a 5- or 10-fold safety margin is applied.[7]

It is for such reasons that data in the "no effect" range are preferred by those setting work environmental quality standards.

*What constitutes evidence of a "response" varies. In the United States biochemical, physiologic or even reversible changes in organ morphology may constitute the "minimal" response. In the U.S.S.R. more credence is placed upon subtle neurophysiologic change as evidence of a deleterious alteration (see section on Functional Response).

Problems in the Use of Animal Data for the Establishment of Environmental Quality Standards

In the absence of data based upon human experience, extrapolation from animal experiments must be used in establishing environmental quality standards. But because our concerns are directed toward prevention of human harm, the limitations inherent in animal-derived data should be recognized. Whether man will respond as the most reactive or least reactive species tested frequently cannot be predicted. Further, the question as to whether the most sensitive species has been tested is frequently unanswered. Finally, whether the animal response has any parallel to human responsiveness cannot be answered. (This has occurred in the case of induction of bladder tumors by aromatic amines; unless the dog is tested — a relatively uncommon test animal — such chemicals do not ordinarily produce bladder tumors in the animals usually used in the laboratory.) For these reasons, human exposure data assume considerable importance in quality standard development, though animal-derived information may be commonly the only type in existence.

Sensitization. This type of response, sensitization, is produced with difficulty in animals. Accordingly, if animal testing is relied upon, the potential for such responses may be undetected.

Genetic Defects Peculiar to Man. A number of genetic defects found in various human "strains" have no parallel in animals. Such defects occur commonly in human populations and can deleteriously affect the mode of response to certain environmental chemicals (e.g., glucose-6-phosphate dehydrogenase defects will impede the detoxification process among persons having this aberration who are exposed to various aromatic amines). Accordingly, animal testing alone will not predict whether a chemical might cause untoward reactions in such susceptible populations.

HUMAN DATA AND INDUSTRIAL EXPERIENCE AS A BASIS FOR STANDARD DEVELOPMENT

The Necessity for Human Data

It should be readily apparent from the foregoing that animal data form a problematic basis for the development of occupational environment quality standards. While such data are highly useful in developing a broader understanding of biological response (e.g., metabolism, full range of effects), such information in itself has obvious shortcomings in setting quality standards. It is for this reason that experience based upon human exposure to the substance in question is of ultimate importance in determining standards of safety.

Such data can result from inadvertent or intentional experimental exposure. Concerning the latter, the availability of animal experiments becomes critical; only after thorough exposition of toxicity by this method is human experimentation justified.

Specific Needs Fulfilled by Human Toxicity Data

1. Irritation and nausea: since the less severe degree of irritation can only be detected by subjective means, it is obvious that animal experimentation may not provide such information in this response range.
2. Allergic response: since animals rarely demonstrate this type of response, human experience is necessary if such effect is to be detected.
3. Odor evaluation: since no quantitative measures of odor are presently practicable, this response can only be evaluated by questioning the experimental subject. Obviously, animal experiments are useless in this regard.
4. Higher nervous function effects: an important consideration in occupational safety and health revolves about environmental effects upon human performance. While animal experimentation increasingly involves measurement of neurophysiologic response, extrapolation of such test procedures for the assessment of, e.g., visual performance, manipulation of various devices leads to obvious inadequacies. Thus human testing, particularly where relevant work tasks are performed, meets a unique need in occupational safety evaluation.
5. Human metabolic pathways: while much of such information can be derived from animal experiments, ultimately application of such data for hazard assessment and control design represents an extrapolatory exercise. Thus human exposures will provide the ultimate quantitative and qualitative information regarding human metabolism of the substance in question.

The Use of Data Derived from Occupational Experience

Validity requirements:

1. Environmental sampling adequacy: in order to relate human safety or damage to environmental agents, it is necessary to have some quantitative measurement of its presence. Usually this means extensive sampling of the work environment over time and space, but especially as related to worker absorption opportunities. That is, good industrial hygiene sampling practice (see Chapter 10) is necessary to adequately assess quantitative exposure.
   In brief, in the cases of gases, vapors or dusts, samples should be taken at breathing zones. In addition, in the case of dusts, quantitative characterization of the particulates of respirable size are especially pertinent. Obviously, care should be exercised that sufficient numbers of samples are taken to represent adequately the full range as well as average of concentrations.
2. Human surveillance adequacy: for data based on human experience to be valid, the human portion of the agent-host interaction also must be characterized. Indeed, if no untoward effect is claimed, detailed medical evaluation of those exposed is required. In addition, it is possible to evaluate environmental concentrations by measurement of metabolites or of the agents themselves in biological media. Although such correlations between concentrations in biological material and the work environment may be constructed from occupational exposure situations, usually insufficient data or range of exposures mitigate against development of such a regression line. However, such measurements taken under experimental exposure conditions have been extremely useful (see below, Human Experimentation).

Problems Encountered in the Use of Occupational Exposure Data

1. Irregularity of exposure: most occupational exposures are of a fluctuating character, both in terms of duration and concentrations. Thus the need for having sufficient samples representative of the "peaks," "valleys" and mean concentrations encountered becomes essential.
2. Mixed exposures: occupational exposures to a single agent are rather uncommon. Thus, while the material in question might be specifically measured in the environment, it becomes problematic whether the human response results from exposure to that particular agent *per se*. Furthermore, the biological response can rarely be rationally apportioned as a function of the relative concentration of multiple agents. Whether such agents are acting additively, synergistically or antagonistically can markedly alter responses. Hence, since occupational exposures are mixed, this limitation on their use for occupational environmental quality standard development must be recognized. For a more detailed discussion of evaluation of mixtures, see reference (3).
   As regards the agents in such a mixed exposure, the question of the specificity of the measurement technique for the material of interest becomes significant. This is especially pertinent where mixtures of chemically similar substances are encountered; interferences may also make such measurements of the components of such mixtures non-specific.
3. Absence of long-term data: while measurements of human response over the short-term experience are readily observed, the long-term effects of such exposures are infrequently available. While drastic effects of long-term exposure may be detected — and then with difficulty, e.g., bladder tumors, subtle effects are infrequently reported or investigated.

4. Special susceptibility: unless sufficiently large populations of exposed workers are studied, the few persons who may be at special risk because of genetically determined special susceptibility will not be encountered. Such persons may be at special risk either for reasons that are well-defined, e.g., defects in metabolism, or because of poorly understood reasons (allergic sensitivity). Indeed, while such persons may constitute a small proportion of a potential population at risk, this does not constitute a reason for such effects being ignored if they could potentially be prevented.

Human Experimentation

Ethical Considerations. While it has long been recognized that each man has a moral duty to act charitably toward others, e.g., make blood or skin graft donations, some subtle and gross abuses of human experimentation have made reassessment of that practice necessary. Accordingly, a number of moral codes have been drawn up to protect the person of such subjects (Nuremberg Tribunal Code, the World Medical Association's 1964 Declaration of Helsinki, American Medical Association, etc.).

Minimally, at least four requirements should be met before experiments are considered:

1. Safety should have been extensively established in animal species;
2. Volunteers must be free of any coercion whatsoever and be fully and completely informed of all possible effects in a clearly understood fashion;
3. There must be no possibility of permanent damage, and the subject must be completely free to terminate the experiment at any time;
4. A written agreement of the volunteer to participate in the experiment which is fully described should be obtained.

Practically, it is mandatory that there be sufficient insurance coverage for each subject to compensate him voluntarily in the event of injury.

Design Requirements

1. In testing with airborne narcosis producing materials, assuming sufficiently large chambers and modalities for testing behavioral and other functional parameters, exposures are made in 3 ranges, i.e., "no effect," at borderline levels and at levels producing measureable, though minimal, narcosis in most subjects. In this manner, 3- to 4-hour exposures can aid in estimating the safety factor for human exposure, the safe limit and the rates of uptake and elimination of the agent. The latter two are determined by plotting blood concentrations against atmospheric concentrations as a function of time; such data are extremely valuable in estimating the extent of previously unknown exposure given a blood concentration at any given time after exposure.[4]
2. In testing with airborne irritants, utilizing the aid of an otolaryngologist, examinations are performed both before and after exposure in a dynamic chamber. Because of the possibility of the development of accommodation, exposures should last at least 15 minutes; such exposures should be repeated 10 times in order to establish whether — and to what degree — accommodation occurs. A repetition of these exposures after 10 to 14 days will help establish whether sensitization occurs. Further, repetition has another urgency, since experience has shown that single exposure tests usually lead to unnecessarily low limits.[5]
3. Testing cutaneous irritation and sensitization (see Chapter 34).

Measurement of Response. Since a major reason for permitting the use of human volunteers is the eliciting of data indicative of minor functional change, the criteria of response should accordingly reflect this need. Thus, functional measurement of biochemical (e.g., enzymatic, immunochemical), neurophysiologic (e.g., EEG, conditioned and unconditioned reflexes) organ activity (EKG, liver or kidney function tests) and other parameters (comfort, esthetic) should be measured at the most sensitive and systematically higher levels. While functional change may represent normal and reasonable homeostatic adaptation mechanisms rather than being deleterious, each such change must be carefully elucidated and individually evaluated for its broadest implication as regards potential human harm.

STANDARDS OF QUALITY FOR THE WORKPLACE IN COMMON USE

Quality Standards Used in the United States

United States Historical Development. In 1941 the American Conference of Governmental Industrial Hygienists (A.C.G.I.H.) established a committee of industrial hygienists for the purpose of establishing the maximal allowable concentrations (MAC) for atmospheric contaminants in the workplace. Five years later such a list of recommended MAC values was suggested for use in industry. However, certain difficulties attended this designation, MAC. For one, these values were based upon time-weighted averages (see below) and did not represent a *maximal* ceiling value inherent in the name. For another, inherent in the title was an implication that such concentrations were "allowable," and thus a certain approbation was attached to concentrations below *and up to* such concentrations. At other times and places, this latter problem was associated with the use of the designation, Maximal Permissible Concentrations, or MPC.

In order to obviate these problems, in the 1960's the term Threshold Limit Value (TLV) was substituted for MAC. This new term, TLV, did not suffer these problems; without the implications associated with "allowable," more emphasis could be given to the practice of attempting to keep ambient concentrations below any designated value to the most practicable extent.

The A.C.G.I.H. Threshold Limit Values (TLV)

Nature of the TLV of air for occupational environments — TLV values refer to airborne

concentrations of substances and represent conditions under which it is believed that nearly all workers may be exposed eight hours a day for a forty-hour week over a working lifetime without adverse effect. Because of wide variation in individual susceptibility, exposure of an occasional individual at, or even below, the Threshold Limit may not prevent discomfort, aggravation of a pre-existing condition or occupational illness.

The TLV's represent eight-hour, time-weighted averages, i.e., airborne concentrations averaged with regard to their duration, occurring over an eight-hour period.

Certain chemical agents are associated with a "c" or ceiling designation; exposure to concentrations in excess of this value should not be permitted regardless of duration. Such designations stem from the fact that such agents may provide irritation, sensitization or acute poisoning immediately, or after a short latent period, upon even short exposures. Examples of such compounds among the respiratory irritants are chlorine, formaldehyde, vinyl chloride; narcotic agents such as methyl chloride; sensitizers such as toluene-2,4-diisocyanate; or those compounds which rapidly accumulate, such as benzene.

For those substances not given a "c" designation, excursions above the TLV are permitted. These agents produce their principal effects by cumulative, repeated exposure; thus, short excursions will not necessarily produce deleterious effects. The TLV's for such substances should be considered as average values integrated in relation to time. In general, the permissible range of fluctuations depends upon: the nature of the poison in general, the intensity of concentration required to produce acute effects, the frequency with which the average maximum tolerable concentration is exceeded, the duration of such excesses, and the cumulative effects of the exposure. For such a complex of reasons, it should be apparent that expert opinion should shape the use and interpretation of the TLV's. However, the A.C.G.I.H. gives some guidance for determining how great an excess above the TLV is permissible. For substances not having a "c" designation, the following guides apply:

TLV Range ppm* or mg/M³*	Excursion TLV Factor
0 to 1	3
>1 to 10	2
>10 to 100	1.5
>100 to 1000	1.25

*Whichever unit is applicable

Thus, a substance having a TLV of 5 ppm may fluctuate above the TLV, reaching a value of 10 ppm for periods of up to 15 minutes. However, the time-weighted average for an eight-hour day should not exceed 5 ppm. It is noted that the "Excursion TLV Factor" decreases as the magnitude of the TLV increases. Not to decrease this factor and increasing TLV magnitude would permit exposure to large absolute quantities, a condition that is minimized at low TLV's. Moreover, larger factors at the lower TLV's are consistent with the difficulties in analyzing and controlling trace quantities.[3]

Where the TLV's previously were given in terms of a volume per volume basis, i.e., parts per million, the trend appears to be for statement of TLV's on the basis of mass per volume, e.g., milligrams per cubic meter (mg/M^3) in addition to "ppm." Most toxic dusts are listed in terms of million particles per cubic foot and in mg/M^3 of respirable dust.

Procedure for Establishment of Values. Experts in industrial hygiene and toxicology annually review a list of over 400 substances. On the basis of literature data and personal information known to committee members, TLV's are recommended. Opportunities are afforded for comment by interested persons or organizations. In the case of a new substance being added or a change in the TLV of a material on the list, such new value is listed for two years as a "tentative" value, so that such parties may submit any additional information for the committee's consideration. In addition, periodically the committee publishes a "Documentation of TLVs;" this provides a detailed review for each substance and the bases utilized in assigning the TLV's.[9]

American National Standards Institute (formerly, American Standards Association) Z-37 Committee Standards (ANSI)

Nature of ANSI, Z-37 workplace quality standards, maximal acceptable concentrations:

Time-weighted average: This Standard is essentially the same as the time-weighted eight-hour average of the A.C.G.I.H. Threshold Limit Value (TLV).

Acceptable Ceiling Concentration. The Standard establishes the maximum level allowable concentration during the period of exposure, assuming that the time-weighted eight-hour *average* concentration is not exceeded. However, excursions above this ceiling *may* be permitted under certain conditions, as in:

Maximum Acceptable Peak Concentrations. These constitute the exceptions to the ceiling level noted above. The peak concentrations noted are specified as to their concentration, the duration of such excursion(s), and the number of time(s) such peaks may occur in one eight-hour day.

Formulation Procedure. The Z-37 committee of ANSI is composed of governmental, industrial, professional society and university-based experts in industrial toxicology, hygiene and medicine. Assignments for standard development are given to committee members or others having experience with the material in question. The committee votes upon the standard which is then sent forward for other Institute approval and ultimate publication as a Standard. Maximal *acceptable* concentrations are published for a number of materials as individual documents which give the basis for such judgments. In addition, analytical and sampling methods are recommended; the Standard publication also describes the toxicity of

the material as well as its physical and chemical properties.

Federal Standards

Under the Occupational Safety and Health Act of 1970, the National Institute for Occupational Safety and Health (NIOSH) has the responsibility for developing criteria and recommended standards and the Department of Labor has the responsibility for promulgating standards.

The initial compilation of health and safety standards promulgated by the Department of Labor's OSHA was derived from national consensus standards and recognized Federal Standards. In addition to these sources there have been, and are being developed, documents by NIOSH from formulations which are reviewed by NIOSH and its consultants. Inputs from selected professional societies, other Federal agencies and such interested parties as organized labor and trade associations are also obtained. Finally, the criteria document with the recommended standard is forwarded to the Secretary of Labor. His considerations benefit from any additional review he deems appropriate.

The Secretary of Labor has the responsibility for promulgating standards. In some cases he may refer for study and review a recommended standard to an advisory committee in accordance with provisions of the Act. However, regardless of whether this step is taken, if this is a 6 b regulation, he must publish it as a proposed regulation and standard so that objections and comments can be heard before such a standard is effective.

Note: Standards promulgated under authority of Section 6 a of the Act and emergency standards under Section 6 c of the Act can be promulgated without going through the "proposed" stage.)

In addition, under the Federal Coal Mine Health and Safety Act of 1969 (P.L. 91-173) NIOSH has the responsibility for transmitting to the Secretary of Interior recommended health standards. After a similar review and hearing process such standards are promulgated by the Department of the Interior.

State Regulations and Standards

While most states have lists of in-plant Air Quality Standards, the majority have essentially adopted those of the ACGIH TLV's. Accordingly, these are all eight-hour time-weighted averages, although Pennsylvania has also developed a series of short-term limits. These latter differ from the ACGIH values in that specific exposure durations for such excursions are stated in the Pennsylvania regulations.

WORKPLACE QUALITY FORMULATIONS IN USE OUTSIDE THE UNITED STATES

U.S.S.R.

Philosophy. Standards are absolute limits that may not be exceeded during any part of the working day, regardless of lower concentration that may have existed during that day. These Standards are legally binding.

The major scientific bases utilized in setting MAC's in the U.S.S.R. derive from reactions of the higher nervous system and physiological alteration. Feasibility does not seem to be considered in the standard setting process, although there is some question as to whether such standards represent goals or working realities. Thus, because such minimal physiological or neurofunctional changes (= adaptive responses?) are considered as designating the borderline between harm and safety, and since a safety margin is then applied, the Soviet Standards tend to be lower than those found in the United States. However, close examination of these differences reveals that in actuality only relatively few cases of gross differences (more than 4-fold) exist.[10]

Formulation Procedures. Much of the work involved in establishing standards is performed by the Academy of Medical Sciences, and The Institute of Industrial Hygiene and Occupational Diseases in Moscow, as well as other institutes. The data are then evaluated by the Permanent Committee for the setting of MAC's. Ultimately, standards are promulgated as Soviet Standard 245-63 by the U.S.S.R. Ministry of Health.

West Germany

Maximum allowable concentrations (MAK-Werte) are developed by an expert commission of the German Research Association (Deutschen Forschungsgemeinschaft) and are adopted in total by the Ministry of Labor & Welfare. In essence, they reflect the values adopted by the A.C.G.I.H. with some variations. The values adopted represent legal standards. A documentation is presently in preparation.

United Kingdom

The Factory Inspection Service of the Department of Employment utilizes a list of standards which act as benchmarks for the inspectorate. The values used are essentially those of the A.C.G.I.H.

France

Although French legal codes are extremely detailed regarding precautionary measures (e.g., medical, technical) for the protection of workers exposed to toxic substances, only a very few, specific materials are given numerical values in French codes. This stems from recognition of the reality that such values *do not* represent inflexible, absolute dividing lines between safety and hazard.

Others

Eastern Bloc Nations. Legal standards specifically stated in terms of numerical values are the rule. These are then promulgated by the Ministries of Health or those relating to production and are legally binding. It is of interest to note that most frequently (except for Bulgaria) the values cited are not identical with those adopted in the U.S.S.R.

Asiatic. Several of these recommend tests of standards of air quality in workplaces. The most notable of these is Japan; the numbers recommended by the Japanese Association of Occupational Health largely reflect those published by the A.C.G.I.H.

UTILIZATION OF STANDARDS OF QUALITY FOR THE OCCUPATIONAL ENVIRONMENT

The Philosophic Basis of Their Use

Consideration of the foregoing should clearly indicate that the formulation of quality standards

has no *absolute* informational basis. The variability of biological response, the judgmental elements which enter into evaluation of environmental and biological data, the imprecise nature of the biological response — all of these imply that after such evidence is weighed, a less than absolute decision must be reached. While a numerical value is ultimately decided upon, the non-absolute nature of the data upon which it is based should suggest that such value must not be taken to represent an *absolute* boundary between the positively safe and the positively unsafe. Thus, for example, if the "safe" value is 50, this cannot be taken to mean that 49 is *always* safe or that 51 represents an unsafe area. At best, such values represent *benchmarks,* or *guides* for protective action. Within this context, if a time-weighted average of 49 is attained, this should not be understood to mean that a lower value should not be pursued. Conversely, a value of 51 does not mean that damage to the individual so exposed will necessarily ensue. Within the context of legal codes such values do indicate the boundary between "safe" and "unsafe." Application of TLV's must take into account the multiple biological considerations discussed in this chapter and elsewhere and the elements of professional judgment inherent in the formulation of such standards (see section on Principles for Developing Workroom Air Quality Standards).

Obviously, repeated excursions above an air quality standard should not be tolerated. Where "c" or ceiling values are listed (see above), such excursions may lead to health or functional impairment, e.g., for liposoluble volatile solvents with narcotic properties as trichloroethylene or carbon disulfide. With substances not having such ceiling designations, excursions above such TLV's may only be permitted consistent with the recommended level (see above discussion of A.C.G.I.H. values).

In the event that a survey indicates excursions above TLV's, the competent authority is responsible for more definitive evaluation of such situations. Thus, repeated samples of the work environment representative of temporal and spatial variations in worker exposure should be obtained, consistent with good sampling procedures (see Chapter 10).

In addition, medical biological evaluation of the workers at possible risk is indicated. The appropriate medical examinations should delineate whether health damage, actual or potential, is occurring. Samples of biological media (blood, urine, expired air, tissues such as hair) should be analyzed to determine whether undue body burdens are being taken up.

If such more definitive evaluations indicate the presence of an occupational risk to worker health and safety, appropriate control action is necessitated.

That such values represent indicators for further evaluation and control action must be clearly understood. Such values can only be properly utilized by those possessing knowledge regarding these facts as well as an understanding of health implications of the specific environmental agent concerned. Thus a considerable element of judgmental evaluation is required; *there should be no automatic, unthinking application of such values for the protection of worker safety and health.*

Appropriate Application of Standards

Health and Medical Control. Possibly the most important use of quality standards relates to their use for medical control. Since medical and clinical laboratory testing imply certain costs, judicious planning for their deployment requires some guidelines to determine the frequency and extent of medical surveillance *consistent with worker safety and health.* Thus, if threshold limit values are repeatedly exceeded, more frequent and extensive medical surveillance is indicated while and after control measures are being accomplished. Certainly, as such quality standards are exceeded, the nature of medical testing becomes quite different than if these standards are never approached. It should be clearly indicated that even if such quality standards are *not* exceeded, medical surveillance *cannot* be neglected or omitted. However, their stringency should reflect the degree to which standards are approached or exceeded. It should be emphasized that medical action becomes useless as regards prevention unless coordinated with appropriate engineering action for amelioration of workplace contamination.

Design of Engineering Controls and Practices. Given such numerical values, it becomes possible for the design engineer to ascertain that engineering control of the process is required. With a knowledge of the physical properties of the material in question, the amounts used and the possible loss from the process, one can then formulate the ventilation or enclosure requirements necessary which will capture the contaminant in question and prevent its escape to the work environment.

Good engineering practice should never permit the workplace concentration to reach the quantitative level prescribed by the standard. It should be recognized that the economic cost of controls may mount geometrically as lower levels of workplace contamination are sought. Consequently, there is decreasingly less merit in attempting to attain absolute levels of capture, nevertheless, while the lowest level feasible should be sought, it can be seen that quality standards do provide benchmarks against which performance can be measured, consistent with economic considerations.

Surveillance of Adequacy of Control and Maintenance Practices. Once such control equipment is installed, its performance should be monitored. Given accumulation of material in ducts or fans. wear and aging of equipment, the performance of such equipment will tend to deteriorate. The point at which maintenance or replacement is required — with its attendant economic cost — can be determined by monitoring the work area. Since such decisions and the attendant depreciation costs may be considerable, the benchmarks for environmental quality become useful in rational planning of maintenance and replacement.

Use for Development of Analytical Techniques. In the realm of environmental monitoring, the design of analytical methodologies requires that some specific range of sensitivity should be sought if the method is to have practical use. Thus, the analyst

can use such quality standards in ascertaining how such analysis need be carried out. For example, while wet chemical methods may be quite adequate for the measurement at the 100 ppm level, at one-thousandth of this level other techniques may be called for, e.g., gas chromatography. Thus, knowing what concentration range must be measured is of obvious value; quality standards clearly indicate such ranges.

Basis for Communication and Interaction Among the Various Specialty Disciplines in the Occupational Health Team

Misuse of Standards — Comparison of Standards with Single Environmental Determinations. Generally speaking, to properly evaluate environmental quality in the workplace, the obtaining of a short-period single determination has little or no value. Likewise, to compare such short-period sample with an 8-hour environmental quality standard represents a misuse of such standards. Since most standards represent time-weighted averages (see above), one sample probably cannot provide such an evaluation, unless it is an eight-hour sample or can be reliably related to the full-shift exposure. Even where ceiling values (see above) are exceeded, a single sample may be invalid unless it is clearly related to the worker, e.g., in relation to his breathing zone. Obviously, quality standards have meaning only when adequate industrial hygiene sampling techniques are utilized (see Chapter 10).

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CHAPTER 9

THE SIGNIFICANCE AND USES OF GUIDES, CODES, REGULATIONS, AND STANDARDS FOR CHEMICAL AND PHYSICAL AGENTS

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INTRODUCTION

The passage of the Social Security Act (1935), assured the eventual acceptance in the United States of the philosophy that the worker had the right to earn a living without endangering his health. During the period since 1935 a number of states[1,2,3,4] adopted codes and regulations governing conditions of work to prevent injury to health and in many instances established threshold limit values which limited levels of exposures in the working environment.

The adoption of state codes and regulations governing the control of the working environment led to greatly accelerated research to obtain data both for the establishment of rational threshold limit values and for their extension to cover as many agents as possible. This research, in turn, led to new procedures for studying the effects of environmental agents on worker health.[5] Significantly, this research revealed that many agents which gave rise to acute responses from high exposure levels over a relatively short period of time elicited a different response to lower levels of exposure to the same agents over a prolonged period of time.

Through data obtained both from epidemiologic and animal research, a body of knowledge has been acquired which permits establishing the rationale for threshold limit values. This rationale is succinctly stated by Hatch:[6] "1) There exists a systemic dose-response relationship between the magnitude of exposure to the hazardous agent and the degree of response in the exposed individual, and 2) there is a graded decrease in the risk of injury as the level of the exposure goes down, which risk becomes negligible when exposure falls below a certain tolerable level. Thus, in the face of recognized potential dangers associated with certain physical and chemical agents, these principles say that such agents can be dealt with safely at some acceptable level of contact above zero and, therefore, that they do not have to be eliminated altogether from industry in order to protect the workers' health."

PROMULGATION OF GUIDES, CODES, REGULATIONS AND STANDARDS

Two general procedures are used in the establishment of occupational safety and health laws. The first is through statutes promulgated by legislative action. The second procedure is through codes, regulations and standards promulgated by agencies with rule-making authority. The latter procedure is, by far, the most common one and is more readily responsive to need for changes. Promulgations through either course of action have the same force and effect of law.

A code is a body of law established either by legislative or by administrative agencies with rule-making authority. It is designed to regulate completely, so far as a statute may, the subject to which it relates. "New York State Industrial Code Rule No. 12 Relating to Control of Air Contaminants in Factories" is an example of such a code.[7]

A regulation is an authoritative rule dealing with details of procedure; or, a rule or order having the force of law, issued by an executive authority of government. The State of Michigan "Regulation Governing the Use of Radioisotopes, X Radiation and All Other Forms of Ionizing Radiation" is an example.[8]

A standard is any rule, principle or measure established by authority. The term "occupational safety and health standard" under the Occupational Safety and Health Act of 1970 means "a standard which requires conditions, or the adoption or use of one or more practices, means, methods, operations, or processes, reasonably necessary or appropriate to provide safe or healthful employment and places of employment."[9]

A guide is an instrument that provides directive or guiding information. Examples of guides are the "American Industrial Hygiene Association Guides"[10] and the "Threshold Limit Values of Airborne Contaminants and Physical Agents" adopted by the American Conference of Governmental Industrial Hygienists.[11] Although such guides, per se, do not have the force of law, their values may be incorporated into codes, regulations and standards that do have the force of law.

SOURCES OF DATA FOR EXPOSURE LIMIT VALUES

Exposure limit values are based on data arising out of experimental animal and human studies and from data on industrial experience obtained through clinical and epidemiologic studies of workers. Interrelated data from the three sources give the most rational data upon which to base exposure limits. Animal and human experimental data are most suitable for deriving biologic re-

sponse data on single substances or specific combinations of substances. Workers, however, are seldom exposed to such limited combinations of substances in their work environment. Also, the personal habits of workers, such as cigarette smoking, consumption of alcoholic beverages, and use of drugs may alone have a profound influence on the health profile of workers, or they may have an additive or synergistic action on exposures in the work environment. The health of the worker represents the influence of his twenty-four hour a day environment over a lifetime. Thus procedures and data are needed which will distinguish between health patterns from on and off-the-job stresses. Well designed epidemiologic studies can delineate the influence of multiple on and off-the-job stresses in the environment and have the advantage of being able to study workers over a lifetime.

Research to obtain biologic response data upon which to base exposure limit values is very costly and time consuming. The resources for such studies come mainly from government, industry and foundations. The research may be carried out at facilities operated by the government, educational institutions, foundations, consultants and industry. The Occupational Safety and Health Act of 1970 will stimulate research at all these levels for obtaining data upon which to base exposure limit values.

NATURE AND SOURCES OF EXPOSURE LIMIT VALUES

As stated previously, occupational health codes, regulations and standards may be both general and specific in their coverage depending on their objectives and the procedures intended for their implementation. Any one act may cover a single or several elements to accomplish the stipulated requirements including such areas as threshold limit values, methods and procedures for monitoring the environment, methods of control, use of respiratory protective equipment and protective clothing, and handling of waste.

The establishment and use of exposure limit values are so fundamentally a part of occupational health, codes, regulations and standards that special attention is devoted to their development, significance and use.

The American Conference of Governmental Industrial Hygienists publishes annually a list of "Threshold Limit Values of Airborne Contaminants and Physical Agents."[11] The lists are reviewed annually and values are updated as relative data becomes available. Intended changes are published as a part of the annual list and comments supported with data are requested. The threshold limit values of the American Conference of Governmental Industrial Hygienists are airborne concentrations of substances and levels of physical agents below which values it is believed that nearly all workers may be exposed repeatedly eight hours per day, forty hours per week, without adverse effect. In the use of these values, medical surveillance is recommended to detect workers who are hypersusceptible to specific chemicals or physical agents, so that they can be removed from the exposure or given special protection. Ceiling values in connection with threshold limit values represent exposure values which should not be exceeded and relate to substances which are fast acting and whose threshold limits are more appropriately based on a particular biologic response. In instances where the cutaneous route is an important source of absorption, substances are marked with the notation "skin" to stress this property since the threshold limit value refers only to inhalation as the source of entry of the agents into the body.

The American National Standards Institute, Inc., publishes consensus standards of acceptable concentrations for chemical and physical agents.[12] The standards are useful in establishing engineering procedures for the prevention of objectionable levels of chemical and physical agents in the work environment. Acceptable concentration values are presented in terms of a time-weighted eight-hour workday, acceptable ceiling concentrations within an eight-hour workday, and acceptable maximum peak concentrations for short specified durations. American National Standard acceptable concentrations are values below which ill effects are unlikely. The values are not to be used as the basis for establishing the presence of occupational disease.

The Commonwealth of Pennsylvania Department of Health has established a list of short-term limits as a part of the "Regulations Establishing Threshold Limit Values in Places of Employment."[13] The short-term limit is the upper limit of exposure for which a workman may be exposed to a contaminant for a specified short period. Short-term episodes are included in the daily average concentrations for compliance with the established threshold limit values for contaminants to which workers may be exposed for an eight-hour workday.

The Committee on Toxicology of the National Research Council (operating arm of the National Academy of Sciences and National Academy of Engineering) publishes a list of recommended emergency exposure limits.[14] These recommended emergency exposure limits are not intended to be used as guides in the maintenance of healthful working environments but rather as guidance in advance planning for the management of emergencies.

The American Industrial Hygiene Association publishes a Hygienic Guide Series[10] covering an extensive list of chemicals. A hygienic guide for a given material contains the following information: Significant Physical Properties: Hygienic Standards (limits) for eight-hour, time-weighted exposures, short exposure tolerance, and atmospheric concentrations immediately hazardous to life; Toxic Properties, including exposure via inhalation, ingestion, skin contact and eye contact; Industrial Hygiene Practice, including industrial uses, evaluation of exposures, hazards and their recommended controls; and Medical Information, including emergency treatment and special medical procedures.

The National Institute for Occupational Safety and Health, Public Health Service, Department of Health, Education, and Welfare has a responsi-

bility for developing and publishing criteria dealing with toxic materials and harmful physical agents which will describe safe levels of exposure for various periods of employment.[9] The Institute also is responsible for conducting and publishing research, including industry-wide studies, which will lead to the development of criteria documents.

A number of official agencies and organizations publish recommended exposure limits for specific agents. Examples include: National Bureau of Standards Handbook No. 59 "Permissible Dose for Ionizing Radiation"[15] and Handbook No. 93 "Safety Standards for Non-medical X Ray and Sealed Gamma Ray Sources;"[16] "Intersociety Guidelines for Noise Exposure Control"[17] developed by an Inter-society Committee representing the American Industrial Hygiene Association, American Conference of Governmental Industrial Hygienists, Industrial Medical Association, and the American Academy of Ophthalmology and Otolaryngology.

A number of organizations have programs for developing threshold limits for biologic materials, i.e., urine and blood. The National Institute for Occupational Safety and Health, Office of Research and Standards Development,[18] has developed a procedure whereby consultants are appointed to a committee for the purpose of establishing biologic threshold limits for specific substances. The Permanent Commission and International Association on Occupational Health[19] has established a committee for developing international standards for levels of contaminants and their metabolites in biologic materials. The American Industrial Hygiene Association established a Committee on Biochemical Assays to study and recommend procedures for determining levels of specific contaminants and their metabolites in biologic materials, and recommend levels indicative of excessive exposure.

The International Labour Office,[20] Geneva, Switzerland, publishes model codes, codes of practice, guides and manuals in the areas of occupational safety and health. The publications cover both chemical and physical exposures and treat the subject in depth.

SIGNIFICANCE AND USE OF EXPOSURE LIMIT VALUES

Exposure limit values are the crux of most occupational health codes, regulations and standards. If there is no exposure to a harmful agent it follows that the presence of this agent does not create a health problem. Also the toxicity of a material per se, though extremely important, is not the sole criterion of whether or not a health problem is present where the material is encountered. The terms "toxicity" and "hazard" are not synonymous. Many factors, in addition to the toxic nature of a material, are important in evaluating a hazard potential. These include the chemical and physical properties of the toxic substances, the ability of the toxic substances to interact with surrounding materials, and the influence of surrounding conditions such as temperature and humidity on the toxic substances, as well as the concentration, stability, and conditions of use of the toxic substances and the conditions under which they are encountered.

The toxicity of a substance expressed in terms of a threshold limit value, however, is an important criterion and concept in evaluating the presence of a health hazard. As stated in the introduction, threshold limit values are based on the concept of a dose-response relation between the agent and its health effects on the worker, that this is of a graded nature, and that consequently there is a lower level of exposure at which level the substance will exert no deleterious effect on the worker. The application of this knowledge to assure that workers are not exposed to concentrations above these threshold values is an important concept in the prevention of occupational diseases. Due to individual variations in susceptibility and the many unknown factors in the working environment and their effects on a given toxic material, the threshold limit value of a material is not a fine distinction between a safe and dangerous condition. Though levels of exposure may be kept within a designated threshold limit value, this is no assurance that an individual worker may not show some deleterious effects if he has unusual susceptibility. The importance of ceiling levels, skin absorption, etc. must also be considered especially if they are contained as an integral part of the threshold limit value.

Biologic standards, i.e., the concentration of a specific agent in the urine or blood, represents the body burden of that agent and may be used as a monitor of the exposure of a worker to a specific substance. Thus biologic levels of a material represent the integrated relation of a combination of the complex chemical and physical characteristics of an exposure on the worker and can be used to indicate where excessive exposures have occurred, when removal from further exposure is indicated, etc. As with threshold limit values, biologic standards do not represent a fine line of distinction between safe and dangerous conditions and alone are not definitive of a state of disease. It must also be stressed that the body burden of an agent represents all sources and routes of exposure and is not limited to industrial exposures. Habits, hobbies, etc. that may involve factors which influence the absorption and retention of a substance may be important.

The application of exposure limit values in the evaluation of the work environment requires a knowledge of the limit values, of their application and meaning, and of acceptable methods and procedures for measuring exposure levels. The latter is discussed separately under the heading "Selection of Methods and Procedures for Measuring Exposure Levels."

Threshold limit values are expressed as time-weighted averages for an eight-hour workday and forty-hour workweek. The time-weighted averages for specific substances, unless designated by special categories or ceiling limits, permit limited excursions above the threshold limit value provided they are compensated by offsetting excursions below the value.[11]

In the application of threshold limit values to mixtures of toxic substances, in the absence of

other information, their effects are considered additive. Thus their additive factor should not exceed unity in terms of their individual exposure concentrations over the threshold limit values.

Threshold limit values are becoming increasingly significant since they are used in most occupational health codes, regulations, and standards as the yardstick for measuring compliance. Exceeding the values can bring on severe penalties. It is extremely important that the employer have worker exposure monitoring data assuring compliance with relevant standards. These monitoring data should include time-weighted averages, extent of excursions above time-weighted averages, ceiling levels, and short-term exposure levels as relevant.

In addition to data monitoring exposure levels, data on levels of exposure in the general room area and at contaminant disseminating sites are useful in assuring the ability of the control system to adequately contain the contaminant and of its continuing satisfactory performance.

SELECTION OF METHODS AND PROCEDURES FOR MEASURING EXPOSURE CONCENTRATIONS

The measurement of exposure concentrations in the working environment assume utmost importance since compliance to standards are based upon comparison of existing levels of exposure with values stipulated in the standards. In the adoption of exposure limit values into standards, it must be assumed that there are valid, tested and reproducible procedures for the collection and analysis of the agent involved. Seemingly small errors or departures from accepted practices may have a considerable impact, on the one hand on the health protection afforded the workers through application of the standard should inadvertently low values be obtained, and on the other hand on the economic loss involved for compliance should inadvertently high values be obtained in measuring exposure levels.

In some standards acceptable methods and procedures are listed for measuring exposure levels for compliance. Where this is not done, reliance must be placed upon the experience and competence of the persons involved. The decisions include not only methods and procedures to be used but also the assurance of representative samples, the proper calibration of equipment, the use of internal controls, and a sampling regimen that will satisfy compliance requirements. For these reasons, laboratories engaged in measuring worker exposure levels, either through the collection of airborne samples or biologic fluids, should be accredited for this purpose.[21]

ENACTMENT OF OCCUPATIONAL HEALTH GUIDES, CODES, REGULATIONS, AND STANDARDS

A number of official agencies have rule-making authority for the enactment of occupational health legislation for the protection of the worker.

The most recent and comprehensive legislation of this nature, Public Law 91-596 enacted by the 91st Congress,[9] "establishes authority in the Secretary of Labor for the adoption and enforcement of standards for safe and healthful working conditions of working men and women employed in any business affecting commerce." The safety and health standards promulgated under the Walsh-Healey Act, as well as other established federal standards relating to construction work, ship repairing, shipbuilding, shipbreaking and longshoring operations were adopted as safety and health standards under the Federal Occupational Safety and Health Act, and are subject to revision under that Act. Exceptions to this primarily relate to the Atomic Energy Act of 1954, and the Federal Coal Mine Health and Safety Act of 1969 since the Occupational Safety and Health Act of 1970 does not apply where other federal agencies regulate under applicable federal law.

The Occupational Safety and Health Act established a National Institute for Occupational Safety and Health within the Department of Health, Education, and Welfare to conduct research and training, develop criteria, publish a list of toxic substances, and make inspections relative to these responsibilities. The Act also provides for the participation of state official agencies in carrying out the provisions of the Act.

The Federal Metal and Nonmetallic Mine Safety Act[22] vests authority in the Secretary of the Interior for promulgating and carrying out health and safety standards "for the purpose of the protection of life, the promotion of health and safety, and the prevention of accidents in Metal and Nonmetallic Mines."

The Federal Coal Mine Health and Safety Act of 1969[23] vests authority in the Secretary of the Interior to promulgate and enforce standards for the protection of life and the prevention of injuries in a coal mine. The Act directs the Secretary of Interior to develop and promulgate, as may be appropriate, improved mandatory safety standards and to promulgate mandatory health standards transmitted to him by the Secretary of Health, Education, and Welfare. The Act also provides cooperation and assistance to states in the development and enforcement of effective state coal mine health and safety programs.

The Bureau of Mines, Department of Interior, also has responsibility for the approval of respiratory devices for protection against the inhalation of gaseous and particulate substances.[24]

The Atomic Energy Commission has authority for establishing radiation standards in a number of areas. Examples include "Standards for Protection Against Radiation"[25] and "Licenses for Radiography and Radiation Safety Requirements for Radiographic Operators."[26] The former sets forth a very detailed set of standards which have the effect of law. The latter specialized standard was published because of the large number of isotope sources used for radiography and the fact that many overexposures had occurred during radiographic procedures.

Several state agencies have responsibilities for establishing and enforcing standards for protecting the health of workers coming within their jurisdictions. The enactment of the Occupational Safety and Health Act of 1970, however, had a

profound influence on the Federal-State relationship in this area since the latter covers all workers engaged in activities related to commerce. Designated state agencies with standards and programs approved by the Department of Labor can by agreement undertake the enforcement of the Federal Act within their boundaries.

SIGNIFICANCE AND IMPACT OF OCCUPATIONAL SAFETY AND HEALTH ACT OF 1970

The Occupational Safety and Health Act of 1970 has brought important, new dimensions in safeguarding the health of workers and in the practice of industrial hygiene. Although the impact of many of these newer dimensions is immediate, new interpretations and applications of the Act are made by the courts as the need arises. Thus it will be many years before the full impact of the Act is fully realized.

The coverage of the Act is comprehensive and has brought into its jurisdiction numerous workers heretofore excluded from such benefits. Generally, the Act applies to all workers employed in places of work, engaged in a business affecting commerce, except for government employees.

To appreciate the impact of the Occupational Safety and Health Act it is necessary to review briefly the coverage by regulations and the practices prior to its enactment.

Prior to 1936 the only regulations and guides relating to occupational health were administered by state and local governmental agencies. In most instances the guides and regulations were very general, difficult of enforcement, and relied on professional judgment with respect to compliance. Most of the states had no programs relating to occupational health, and those that existed were far too minimal in staffs and funds to carry out effective programs.

The Walsh-Healey Act of 1936 (41 U.S.C. 35; 49 Stat. 2036) which enabled the Federal Government to establish standards for safety and health in work places engaged in activities relating to Federal contracts, was the forerunner in establishing today's concepts of occupational health regulations. The 1936 Act stimulated research into the cause, recognition, and control of occupational disease and led to the development of occupational health programs by official organizations, insurance companies, foundations, managements and unions. Subsequently other Federal legislation had further impact on the promulgation of Federal safety and health standards. These include the Service Contract Act of 1965 (41 U.S.C. 351; 79 Stat. 1034), Public Law 85-742, Act of 1958 (33 U.S.C. 941; 72 Stat. 835), Public Law 91-54, Act of 1969 (40 U.S.C. 333; 83 Stat. 96), and the National Foundation of Arts and Humanities Acts (79 Stat. 845). The interim period between 1936-1970 also saw a number of states issuing occupational safety and health regulations to cover workers in their jurisdictions. None of the occupational health programs in official agencies during this period, however, were adequate in scope, staff, or funds to carry out their responsibilities.

The lack of uniformity within the various regulations established by Federal, state and local official agencies led to great confusion in industries that operated interstate. Programs by industry for compliance with regulations had to vary from state to state and could not be established on a uniform corporate-wide basis.

The Occupational Safety and Health Act of 1970 has brought a restructuring of programs and activities relating to safeguarding the health of the worker. Uniform occupational health regulations now apply to all businesses engaged in commerce, regardless of their locations within the jurisdiction. Threshold limit values have been incorporated into the regulations and now have the effect of law.

In the earlier years, the establishment of threshold limit values, whether with the effect of law or used as guides, was done more on the basis of professional opinion and judgment than on the basis of facts. Data were minimal on the health effects of exposures to most materials encountered in industry. Uniformity of procedures and methods for the collection and analysis of airborne contaminants was generally lacking. The interpretation of compliance with a regulation or threshold limit value was often that of professional judgment. Information on investigations and inspections relative to violations and compliance of standards was usually restricted to the official agency and management concerned. Likewise, medical data obtained through the examination of workers in many instances were not available to the medical department of the industry.

The Occupational Safety and Health Act of 1970 has more clearly defined procedures for establishing regulations, the conduct of investigations for compliance, and the handling and availability of exposure data on workers, the keeping of records, etc.

The Act provides for a greatly accelerated program by the National Institute for Occupational Safety and Health (NIOSH) to conduct research on the health effects of exposures in the work environment, to develop criteria for dealing with toxic materials and harmful agents, including safe levels of exposure, to train professional personnel for carrying out various responsibilities prescribed by the Act, and in general, to conduct research and assistance programs for protecting and maintaining worker health.

The first standard promulgated on the basis of a criteria document developed by NIOSH was "Standard for Exposure to Asbestos Dust" (*Federal Register* Vol. 37, No. 110 — Wednesday, June 7, 1972). This standard is especially significant because as the first of such permanent standards for a number of target hazardous materials, it is anticipated that it will serve as the basic model for other standards to come.

The asbestos standard includes sections on definitions; permissible exposures; methods of compliance; work practices; personal protective equipment; method of measurement; monitoring, both personal and environmental; caution signs and labels; housekeeping; recordkeeping, including

employee notification; medical examinations; and medical records.

This standard differs from prior standards in OSHA regulations, which specified only the permissible concentrations of airborne contaminants or permissible levels at physical exposures (Occupational Safety and Health Standards, Paragraphs 1910.93, 1910.95, 1910.96 and 1910.97 of the *Federal Register*, Vol. 36; No. 105, May 29, 1971). The far reaching provisions of the new standard include the specification of methods of compliance, which include engineering controls such as ventilation and wet methods; personal protective equipment such as respirators, and including shift rotation of employees to reduce exposure; caution signs and labels, not only for the work place in which asbestos is handled but also for products containing asbestos fibers; recordkeeping, including a requirement that employees exposed to airborne concentrations of asbestos fibers in excess of the limits shall be notified in writing of the exposure as soon as practicable but not later than five days of the finding; and medical examinations, including preplacement, annual and termination of employment examinations and specifying the minimum requisite examination procedures and tests which shall be included.

The interpretation of the general duty clause requirements for providing a safe and healthful working environment and the publication of the permanent asbestos standards add new dimensions to the protection of employee health. Both emphasize that final responsibility for compliance with the provisions of the Occupational Safety and Health Act remains with the employer.

The Act prescribes procedures for use by the Secretary of Labor in promulgating regulations. It is of special interest that threshold limit values for exposures to toxic materials and harmful agents are contained in the regulations, and have the effect of law. Since procedures are given for measuring exposure levels to specific materials and agents in the standards promulgated by the Department of Labor, the use of professional judgment as required in the past for such activities is largely obviated, as is also the interpretation of the values obtained. The employee or his representative now has the right to observe monitoring procedures and have access to data on exposure levels. Disagreements on the validity of monitoring data and its meaning are now relegated to the courts for settlement. Professional skills and judgments are still required, however, in applying the intent of the many aspects of the Act in safeguarding workers' health.

The Act has had a similar impact on the medical and nursing programs in industry.[27] Many medical programs in industry had already seen the transformation from the earlier emphasis on the treatment of traumatic injuries to the modern concept of the prevention of occupational diseases and injuries. This trend, however, has not been universal and the fact remains that a vast number of workers still do not have immediate access to medical and nursing services.

Among the changes in industrial medical programs brought on by the Act is the maintenance of medical records on employees and the access to data contained in them. All practicing physicians representing employers are now required to keep records of the occupational injuries and illnesses of their employees. Standards for specific materials and agents prescribe the nature of medical examinations to be given the employees, the length of time the employer must maintain the records, and who may have access to these records data. Specifically, both the Assistant Secretary of Labor for Occupational Safety and Health and the Director, National Institute for Occupational Safety and Health, and authorized physicians and medical consultants may have access to these data. Also, medical data from examinations required by the regulation shall be given the employer, and upon request by the employee, must be given to the employee's physician.

The industrial physician, with the knowledge that the employee has information on both his exposure levels to toxic materials and harmful agents and on his health status, must now maintain a preventive program for follow-up of situations where excessive exposures have occurred or where biochemical or medical tests indicate early or impending changes in employee health patterns. Since the health profile of a worker represents the effect of his twenty-four hours a day environment, the industrial physician is finding it prudent to obtain information on workers' off-the-job activities and habits, such as hobbies, smoking, use of drugs, that either may directly affect their health or may have an additive influence to on-the-job stresses.

There has been a similar change in the practices of industrial nursing over the past decades.[28,29,30] The Occupational Safety and Health Act of 1970 will provide a major impetus not only in increasing the number of industrial nurses available for medical services to workers, but also in using their fullest capability both in carrying out preventive medical programs and in maintaining and promoting the optimal health of the worker. In the early practice of industrial nursing, activities were largely centered around the emergency treating of traumatic injuries and were prescribed in written orders of a physician. Advancing industrial technology along with modern concepts of preventive medical services soon assured that the industrial nurse could no longer accept such a limited role. The industrial nurse, in addition to giving specific medical services, is now called upon to give broad health counseling to the worker in his overall environment. The Act will increasingly propel the industrial nurse to give a more comprehensive service in promoting worker health. This will necessitate a close working relationship with both the industrial hygienist and the safety officer, and will require a knowledge of the toxic materials and harmful agents in the in-plant environment.

A number of sources are available for keeping informed on enforcement aspects relating to the Act as well as citations and their review by the Occupational Safety and Health Review Commission where appeal has been made by the employer.[31,32,33] The following citations issued by the Occupational Safety and Health Administration

and their review, where appealed, by the Review Commission, show the impact which the Act will have on occupational health and the practice of industrial hygiene and of the importance of keeping informed on these decisions.

A landmark ruling defining the employer's responsibilities with respect to providing a safe and healthful working environment is contained in Case 10 before a Hearing Examiner of the Occupational Safety and Health Review Commission, U.S. Department of Labor. The case involves the Omaha, Nebraska plant of the American Smelting and Refining Company (ASARCO) and a citation dated July 7, 1971. The citation alleged that ASARCO, at a plant in Omaha, Nebraska, was in violation of Section 5 (a) (1) of the Act, which provides that "Each employer shall furnish to each of his employees employment and a place of employment which are free from recognized hazards that are causing or likely to cause death or serious physical harm to his employees."

The following description of the alleged violation is set forth in this citation:

"Airborne concentrations of lead significantly exceeding levels generally accepted to be safe working levels, have been allowed to exist in the breathing zones of employees working in the lead-melting area, the retort area, and other work places. Employees have been, and are being exposed to such concentrations. This condition constitutes a recognized hazard that is causing or likely to cause death or serious physical harm to employees."

ASARCO contended that the levels of airborne lead found in its Omaha plant during an OSHA inspection, in excess of the threshold limit value (TLV) of 0.2 milligram per cubic meter of air (0.2 mg Pb/M³) did not constitute a recognized hazard causing or likely to cause death or serious physical harm to its employees in view of the protective safety measures in effect. These included the use of respirators, transferring employees from high exposure jobs and its biological sampling program.

The Act, however, places the responsibility upon employers to provide safe and healthful working conditions for its employees, as far as possible. It does not allow employers to provide unsafe, unhealthful or hazardous working conditions for its employees even though the adverse effects of such working conditions are attempted to be minimized. ASARCO's first responsibility, as set forth by the Hearing Examiner, was to provide safe and healthful working conditions, by reducing the levels of airborne concentrations of lead to the generally recognized safe level of 0.2 mg Pb/M³, or as close to that figure as possible.

ASARCO argued that no hazard likely to cause death or serious physical harm to employees existed at its Omaha plant because no evidence was presented that any of its employees suffered from lead intoxication or had been in any way injured by the airborne concentrations of lead found to exist at its plant. It should be stated here that ASARCO also collected air samples and the results of analyses generally confirmed the findings of the OSHA representative. The Hearing Examiner, however, found that proof of a violation of Section 5 (a) (1). of the Act does not depend upon proof that a hazard has produced injury. All that is required is a showing that the hazard is likely to cause serious physical harm or death.

During the hearing, it was found that ASARCO's preventive program, consisting of blood lead determinations, transferring of employees from job to job and the availability of approved respirators in work places having high concentrations of lead "simply has not worked."

The Hearing Examiner, after review of all evidence, found that the levels of airborne concentrations of lead significantly in excess of the threshold limit value (TLV) of 0.2 mg Pb/M³ constituted a violation of Section 5 (a) (1) of the Act, upheld the original citation and affirmed the proposed penalty of $600.00. This finding, that concentrations of an airborne material above the threshold limit value alone constitutes a violation of the Act, is a profound interpretation of the employer's responsibilities with respect to providing a safe and healthful working environment.

On May 28, 1971, the Occupational Safety and Health Administration issued a citation for serious violation for exposure to mercury.[34] Excessive concentrations of mercury vapor in the work environment were found by investigators from the National Institute for Ocupational Safety and Health. Visible pools of mercury were found in many areas. In response to the citation, the management claimed that the pools of mercury resulted from pipeline leakage when the mercury cell operation was shut down for scheduled maintenance and equipment installation. The management stated that the condition had been corrected and that steps had been taken to tighten up maintenance and housekeeping procedures.

A citation for serious violation of section 5 (a) (1) of the Act was issued by the Occupational Safety and Health Administration following an accident in which three employees were killed and two seriously injured from exposure to hydrogen sulfide gas.[35] The quantity of hydrogen sulfide gas evolved at an operation from the slurry, when partially decomposed fish were treated with a mild solution of sulfuric acid, could not have been sufficient to cause serious injury or death. A further investigation revealed that deadly quantities of hydrogen sulfide gas could have been evolved through another operation. Another worker cut a hole for ventilation through a metal floor-ceiling resulting in the reaction of the iron with the sulfur in phenothiozene thus forming iron sulfide, which reacted with the sulfuric acid. Judge William J. Bronz, Occupational Safety and Review Commission (Docket No. 31), dismissed the citation and proposed penalty. He ruled that past experience did not indicate the need for protection when working with the slurry. The employer could not have reasonably foreseen the probability of serious injury or death to employees arising out of such an episode.

A citation was issued relative to workers being subjected to noise levels in excess of those permitted under 2 9 C F R 1910.95 (b) (1).[36] The

employer contended that he had complied with the regulation by providing employees with protective equipment. Judge James A. Cronin, Jr., Occupational Safety and Health Review Commission (Docket No. 158), ruled that the citation and penalty were appropriate. He stated that the employer was aware that the employees were not wearing the ear muffs provided for protection from noise, and had taken no affirmative action, even though an inspector from the Occupational Safety and Health Administration had indicated the violation. He further brought out that the Senate Report on the Act did not intend for 5 (b) relating to the employees' duty under the Act to diminish the employer's responsibility.

A citation was issued for the failure of a company to provide protective gloves to employees working with a solvent in violation of 2 9 C F R 1910.132(a).[27] Three employees were working with "Stoddard Solvent" five days a week, 8 hours a day. The "Stoddard Solvent" was a petroleum distillate containing paraffins, napthenes, and aromatics. Evidence indicated that the solvent could cause irritation upon prolonged exposure. The citation was affirmed by Judge Harold A. Kennedy, Ocupational Safety and Health Review Commission (Docket No. 79). It was brought out that although the solvent was not classified hazardous under the context of the consideration by any known agency, this did not mean that it was not a hazard within the meaning of the standard. The fact that employees who had used the solvent intermittently for years had received no injuries did not reduce the inherent risk or the duty to provide protective equipment.

A citation was issued for alleged violation of 2 9 C F R 1910.252 (f) (2) (i) relative to lack of adequate ventilation at a welding and cutting site.[28] The employer asserted that there was no violation of the regulation and that the compliance officer had incorrectly calculated the volume of the welding bays and had failed to establish substantial evidence of lack of mechanical ventilation. Judge Joseph L. Chalk, Occupational Safety and Health Review Commission (Docket No. 262), ruled in favor of the employer. It was noted that the volumes of the welding bays, divided by fiberized glass curtains, could not be calculated to imaginary lines at the ends of the bays and should include all space reasonably open to the welding area.

A citation was issued for serious violation of 2 9 C F R 1918.93 (a) (1) (i) and (ii).[29] Fifty-four employees were working in a ship's hold in concentrations of carbon monoxide between 100 and 200 ppm. The citation was affirmed and the penalty deemed appropriate by Judge John J. Larkin, Occupational Safety and Health Review Commission (Docket 296). The Captain's claim of lack of knowledge of the fact was not mitigating since the current standard under the longshoring law had been in effect for a number of years. The Captain had not examined the testing equipment, nor required that records of measurements be kept as specified by the standard. Following measurements for carbon monoxide by the compliance officer, employees were removed from the hold of the ship. The employees were returned to the hold before a second measurement for carbon monoxide was made by the compliance officer, which showed no decrease in the carbon monoxide concentration.

SUMMARY

The significance of and guidance from guides, codes, and regulations has changed with advances in the art and science of industrial hygiene and in the enactment of recent laws. The implications, interpretations of, and application of the Occupational Safety and Health Act of 1970 will continue to be developed as standards are promulgated by the Secretary of Labor and as they are interpreted by the administrative and judicial processes specified by the Act.

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