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Toxicology Principles for the Industrial Hygienist

Second Edition

AIHA's most comprehensive toxicology reference, is written by industry experts specifically for the industrial hygienist.

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Chapter 1 . . .

The Role of Toxicology in Industrial Hygiene

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Introduction

In order for the practitioner of industrial hygiene to fulfill the responsibility to "anticipate, recognize, evaluate, control, and manage"[1,2] potential exposures to harmful materials, they must be able to apply the principles, methodologies and data from many disciplines within the biological, chemical, physical and social sciences. Toxicology is among the chief disciplines used to address the full-spectrum of potential impacts on worker health. Indeed, the history of toxicology and industrial hygiene/occupational health is intertwined. Their futures will continue to be interdependent as many of the incentives for new directions in toxicology research are a consequence of the addition of new materials and methods in commerce and the workplace.

Challenges remain throughout the world, especially among the poorest countries where the understanding of toxicology and industrial hygiene practice is rudimentary if not altogether missing, while the most developed countries see scientific advances in areas like nanotechnology expand the research boundaries for toxicology. Additionally, the rapid globalization of trade brings with it some promising new opportunities as multilateral programs such as Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) and Globally Harmonized System of Classification and Labelling of Chemicals (GHS) serve as an impetus to increase the knowledge and communication of toxic properties of materials shipped and used around the world. Also, it is now recognized that exposures outside of the workplace (ingestion of contaminants in foods, chemical use in hobbies, environmental contamination resulting from industrial discharges and terrorist activities) can have a profound impact on worker health and susceptibility to further adverse outcomes.

Humans, who have always used natural products from animals and plants, have experienced the toxic effects of animal venoms and plant compounds. Consequently, the use and study of poisons for a variety of purposes has been undertaken since the earliest times. Indigenous peoples have and continue to use naturally occurring toxins to obtain food, in religious rites and against enemies.[4,6-8] Naturally occurring toxins have been implicated in incidents that have affected communities and nations.[4,6-8]

The science of toxicology was formally described by Paracelsus (1493–1541), who articulated the key principle of toxicology: "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy."[3,4] Whether this axiom is applied in basic acute lethality studies, or is extended to the applied science of chemical risk assessment, Paracelsus' maxim forms a bulwark for all aspects of toxicology. A Renaissance man, Paracelsus formulated other views that remain an integral component of modern toxicology. He promoted the idea that experimentation is essential in understanding the effects of exposure to chemicals and emphasized the distinction between therapeutic and toxic properties of chemicals.

The science of toxicology has changed dramatically since Paracelsus' time. Toxicity testing now provides data on endpoints ranging from acute lethality to organ-specific toxicity to carcinogenicity. Test data are also generated to better understand the chemical and metabolite pathways and rates of movement through the body and to determine the specific mechanisms by which adverse health outcomes occur. Animal testing, the norm for decades, is now being partially replaced by more extensive use of *in vitro* studies. Most recent is the enhanced application of computers to use *in vitro* and *in vivo* data as the framework for rapid toxicity screening and predictive modeling. Computational toxicology approaches are also being used to prioritize research by modeling the effects or potency of chemicals based on their similarity in molecular structure to those with known toxicity. Despite the advent of alternatives, many regulatory agencies still require the use of at least one animal model in safety evaluation studies of chemicals intended for human use.[5] An in-depth historical account of the entire evolution of toxicology can be found in Casarett & Doull's *Toxicology – The Basic Science of Poisons, 8th edition*.[4]

The popular definition of toxicology is "the study of poisons." However, the scientific definition is much more descriptive: toxicology is the study of adverse effects of agents on living organisms and a toxicologist studies the nature of those effects and the probability of their occurrence. The study of toxicology falls into primarily three categories: mechanistic, descriptive and regulatory. When military services and law enforcement and first responders activities are included, a fourth category can possibly be added, that of deployment toxicology. Mechanistic toxicology concerns itself with the identification and characterization of cellular, biochemical, and molecular mechanisms that are utilized by chemicals to exert toxic effects on living organisms. Descriptive toxicology addresses primarily toxicity testing, while regulatory toxicology addresses those areas for decision making that become law or impinge on the safety of humans via the environment from both consumable and non-consumable products. Deployment toxicology, which might be more accurately termed "Deployment Environmental Health", involves both material solutions (hardware/software/information) and the science knowledge to protect U.S. armed forces and law enforcement and responders against threats or vulnerabilities caused by environmental contaminants, as coordinated with the Nuclear, Biological, Chemical and Radiological (NBCR) community.[9,10] These primary categories can be further broken down into sub-categories, including environmental, forensic, clinical and ecotoxicology specialties.

Toxicants can be classified by system interaction. The most common classifications are:

- *Hepatotoxicants* – cause damage to the liver (Acetaminophen, Ethyl alcohol)
- *Nephrotoxicants* – damage to kidneys (Cadmium, Mercury)
- *Neurotoxicants* – damage to the nervous system (Lead)
- *Immunotoxicants* – damage to the immune system (Toluene)
- *Hematoxicants* – damage to the blood forming tissues (Benzene)
- *Dermatoxicants* – damage to the skin (Magnesium chromate)
- *Pulmonotoxicants* – damage to the lungs (Asbestos)
- *Carcinogens* – agents that increase cancer risk (Hexavalent chromium)

The "toxicity" of a material is its inherent ability to cause damage to living organisms or tissues. The "hazard" of a material takes into account the probability of biologic organisms being exposed to the toxic material. Terms such as "highly toxic", "moderately toxic", and "nontoxic" are of little value to the worker unless they are used in relation to common experience. Chapter 34, Risk Assessment Process for Industrial Hygienists, presents Table 34.1 addressing a common scheme for classification of materials as related to their oral toxicity in humans where the LD_{50} is the concentration of the test material at which 50% of the exposed organisms died. Caution must be exercised in the interpretation of data such as those presented in Table 34.1. Though a compound may be "highly toxic," it may not present a significant hazard if the probability of exposure is remote (enclosed process), the exposure is small (low concentration, short duration), or if the route of exposure poses no risk. In contrast, material of low toxicity may present a significant hazard under the proper exposure conditions. For example, a small amount of ingested water is not toxic, but water in the lung can cause severe problems.

Table 1.1 — Some Representative Chemical Agents with Various Toxicities[5, modified].

Agent	LD_{50} (mg/kg in Test Animals)	Toxicity Rating
Ethyl alcohol	10,000	Slightly Toxic
Sodium chloride (Table Salt)	4,000	Moderately Toxic
Ferrous sulfate (Iron Tablets)	1,500	Moderately Toxic
Morphine sulfate	900	Moderately Toxic
Phenobarbital sodium	150	Very Toxic
Picrotoxin	5	Extremely Toxic
Strychnine sulfate	2	Supertoxic
Nicotine	1	Supertoxic
Tetrodotoxin	0.1	Supertoxic
Dioxin	0.001	Supertoxic
Botulinum	0.00001	Supertoxic

Some examples of materials in these toxicity categories are given in Table 1.1.

Toxicity information provided on the Safety Data Sheet (SDS), or other source, should include the test species and conditions under which the data were collected. For example, using the Department of Defense's Hazardous Materials Information System (HMIS)[7], the definition of "Highly Toxic" is:

1. A chemical that has a median lethal dose (LD_{50}) of 50 milligrams or less per kilogram of body weight when administered orally to albino rats weighing between 200 and 300 grams.
2. A chemical that has a median lethal dose (LD_{50}) of 200 milligrams or less per kilogram of body weight when administered by continuous contact for 24 hours (or less, if death occurs within 24 hours) with the bare skin of albino rabbits weighing between 2 and 3 kilograms each.
3. A chemical that has a median lethal concentration (LC_{50}) of gas or vapor in air of 200 parts per million (ppm) or less by volume, or 2 milligrams per liter or less of mist, fume, or dust, when administered by continuous inhalation for 1 hour (or less, if death occurs within 1 hour) to albino rats weighing between 200 and 300 grams each, provided such concentration or condition, or both, are likely to be encountered by man when the chemical is used in any reasonably foreseeable manner.
4. A chemical that is a liquid having a saturated vapor concentration (ppm) at 68.5°F (20.5°C) equal to or greater than ten times its LC_{50} (ppm), if the LC_{50} value is 1000 ppm or less when administered by continuous inhalation for 1 hour to albino rats weighing between 200 and 300 grams each, provided such concentration, or condition, or both, are likely to be encountered by man when the chemical is used in any reasonably foreseeable manner.

The first three definitions are also used by OSHA (29 CFR 1910.1200, Appendix A) to define a "toxic chemical."

The term "hazardous" is used by federal and state agencies to describe substances that are subject to laws and regulations. The Occupational Safety and Health Administration (OSHA) defines a "hazardous chemical" as any chemical that is a physical hazard or a health hazard according to the OSHA Hazard Communications Standard criteria. The Department of Transportation (DOT) describes a "hazardous material" as a substance or material that has been determined by the Secretary of Transportation to be capable of posing an unreasonable risk to health, safety, and property when transported in commerce, and which is so designated. Under DOT a material, including its mixtures and solutions, that (1) is listed in the Appendix to the DOT hazardous materials table; (2) is in a quantity, in one package, which equals or exceeds the reportable quantity (RQ) listed in the appendix to the hazardous materials table; and (3) when in mixture or solution, in a concentration by weight which equals or exceeds the concentration corresponding to the RQ of the material, is hazardous.

Other terms used in common sources relate to the cancer causing potential of a material. The American Conference of Governmental Industrial Hygienists (ACGIH®) provides definitions of terms in its publication entitled "TLVs® and BEls® Based on the Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices."[11] TLVs® are Threshold Limit Values and BEls® are Biological Exposure Indices. A chemical is listed as "A1-Confirmed Human Carcinogen" when there is "weight of evidence from epidemiologic studies of, or convincing clinical evidence in, exposed humans". The designation of "A2-Suspected Human Carcinogen" is applied when "the agent is carcinogenic in experimental animals at dose levels, by route(s) of administration, at site(s), of histologic type(s), or by mechanism(s) that are considered relevant to worker exposure. Available epidemiologic studies are conflicting or insufficient to confirm an increased risk of cancer in exposed humans." The term "A3-Confirmed Animal Carcinogen with unknown relevance to humans" is applied when animal studies at high doses resulted in cancers; available epidemiologic data do not reveal increased cancers among exposed individuals; and available evidence suggests that cancer probably will not occur in humans except under "uncommon or unlikely routes of exposure." "A4-Not Classifiable as a Human Carcinogen" means that for a particular agent there is insufficient data to adequately address the issue. "A5-Not Suspected as a Human Carcinogen" means that based on adequate epidemiologic studies there is no evidence that the material will cause cancer in humans. It must be remembered that for substances where no data have been collected, there are no designations.

Uses of Toxicology Principles

One of the most fundamental principles of toxicology is the dose-response curve. This curve or relationship illustrates the fact that a high dose of a compound has a greater effect than a low dose. The magnitude of the exposure can be expressed as a dose, concentration, duration of exposure, or some other expression of exposure, and it is depicted along the x axis. The magnitude of the effect can be expressed as the degree of response, number of animals with a certain outcome, or some other expression of effect, and is depicted along the y axis as a cumulative percent response. Most dose-response curves are a sigmoid shape (s-shaped). In the first part of the curve, the flat portion, an increase in dose produces no effect. This is the sub-threshold phase. The lowest dose that produces an observable or measurable effect is the threshold. When possible, distinctions are also made between the no observable adverse effect (NOAEL) and the lowest observable adverse effect level (LOAEL). Subjects may have some natural defenses against the insult such that despite exposure, the biological effects are indistinguishable from the control population; this is the NOAEL. Beyond the threshold point, the curve rises steeply and enters a linear phase where the increase in response is proportional to the increase in dose. The slope of this linear phase should be of great interest to the industrial hygienist, because if the slope is steep, a small increase in exposure could result in a sudden increase in response. In the last part of the curve, the curve flattens out (parallel to the axis) showing a maximal response. At this point, all the exposed individuals or all the susceptible individuals have shown the effect.[12] The relationship between dose and response is discussed throughout this book but it is presented in detail in Chapter 3, Principles of Toxicology, as well as in Chapter 42, Toxicology Test Data.

Another fundamental principle of toxicology involves exposure considerations. The route and site of exposure as well as the duration and frequency of the exposure must be elicited. Routes of entry include primarily pulmonary, dermal, and the gastrointestinal systems. Another route of entry can include injection. As a result of exposure to a chemical, absorption, distribution, metabolism and excretion (ADME) can occur, as illustrated in Figure 1.1. Chapters 4, Mechanisms of Toxicity, and 5, Disposition of Toxicants, discusses these concepts.

The amount of a substance needed to cause an adverse effect varies widely among different materials. For example, botulism toxin can cause death with just a few micrograms being ingested, whereas many other chemicals are essentially harmless following doses in grams. The intrinsic toxicity of a substance is important, but it is the associated degree of risk caused by the exposure circumstances that can be critical in determining if workers become exposed. A very toxic chemical when carefully handled may be less hazardous than a relatively nontoxic substance that is improperly handled. A key element in assessing the degree of risk for any chemical is the exposure that can potentially occur.

Toxic effects of a chemical are produced only if the chemical or its metabolites reach the appropriate receptors in the body at a concentration and for a length of time sufficient to cause the toxic effects. Exposure considerations such as route of exposure, the dose, and the duration and frequency of exposure will all determine if toxic effects actually occur.[13] Exposure circumstances need further study when any of the following

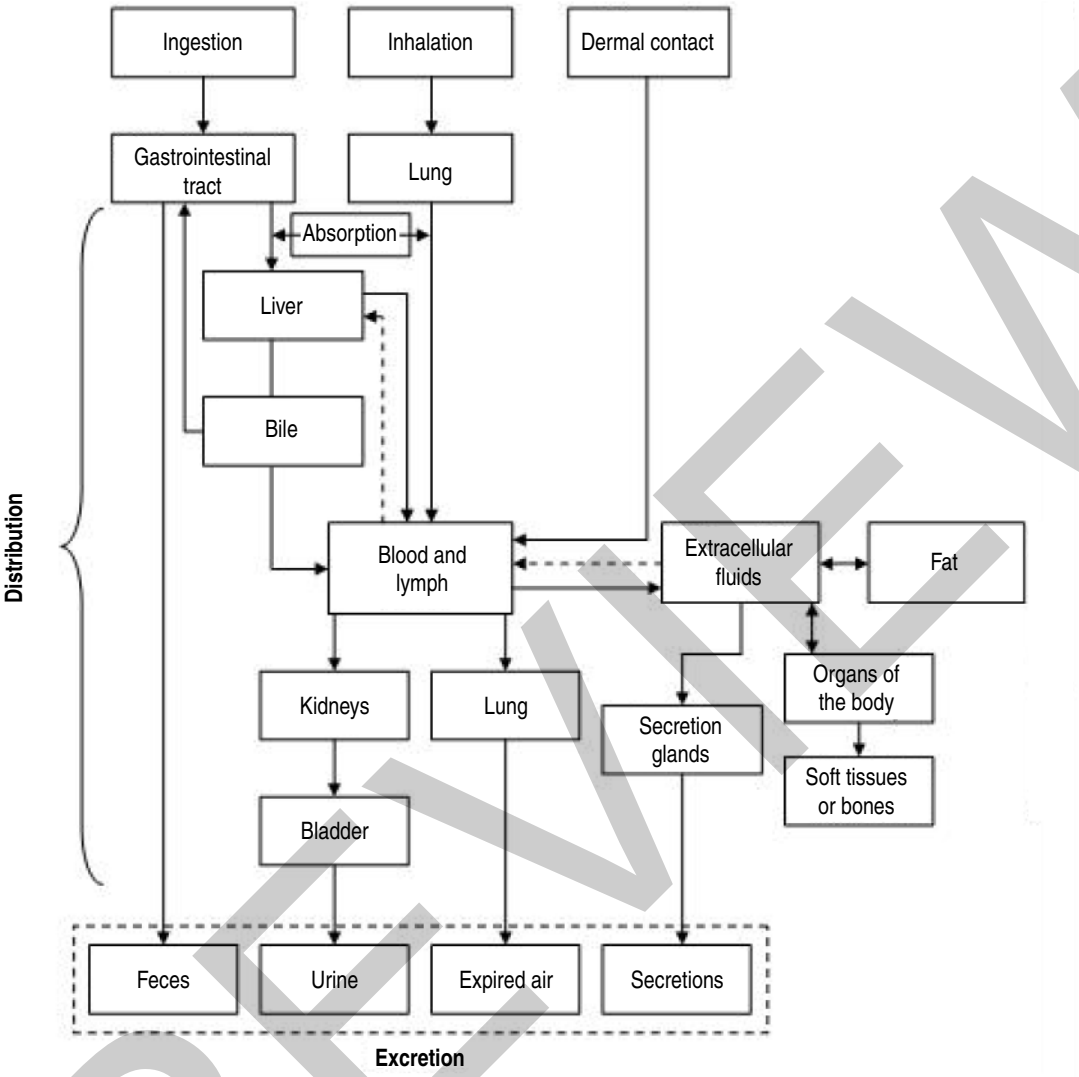

Figure 1.1 — Routes and modes of entry. (Source: C.D. Klaassen, *Cassarett and Doull's Toxicology*, 8th edition (New York: McGraw-Hill, 2001); reprinted with permission).

conditions exist: (1) uptake routes include both the lung and skin; (2) acute toxicity data from animal studies show extreme toxicity due to very low LD_{50} values; (3) chronic toxicity data shows lethality, carcinogenicity, or embryotoxicity; (4) warning properties of the substance, such as odor or irritation threshold, are at levels substantially higher than typical exposure levels; (5) the substance is a gas, respirable aerosol, or a highly volatile liquid; (6) very large quantities are used over periods of time; (7) there is a large number of workers potentially exposed to the substance (>125); or (8) if any of the following conditions exist: open process, manually operated, frequent intervention in the process during service or maintenance, regular leaks and spills, the absence of adequate ventilation.[14] Exposure considerations are discussed throughout this book but in detail in Chapter 3, Principles of Toxicology; Chapter 31, Exposure Assessment; Chapter 33, Exposure Reconstruction; Chapter 34, Risk Assessment Process for Industrial Hygienists; and Chapter 38, Derivation of Occupational Exposure Limits.

The principles of toxicology are needed to assess the significance of a toxic effect. When does a toxic effect become significant? When does a pathophysiologic change indicate a disease process? Body defense mechanisms, such as mucociliary clearance and inflammation, normally occur in response to environmental stresses. A disease is likely to occur if the body defense mechanisms become overwhelmed by the environmental stressors. However, some changes that occur in response to chemical exposures do not cause disease. In these cases, the significance is not completely known. For example, is hyperplasia or hypertrophy in animals considered a normal physiologic adaptation to a stress or should it be considered a pathologic process that could lead to cancer? Often a worker can be exposed to a toxin and show no sign of illness. Does normal biologic adaptation

cause an unacceptable effect on the body? Is there a limit to which the body can compensate for toxic effects? Looking at it from another point of view, is there a certain amount of stress that is beneficial to the body? In other words, can a low-level exposure to a substance ever cause a beneficial effect? Hormesis is an area of study that reports beneficial effects of low-level exposures to a substance, while higher exposures cause disease. Currently, there are no clear cut answers to these questions.[12] In this book, sites of action of chemicals and their effects are discussed in detail in the second section that includes Chapters 6 through 16 that deal with the various tissues and organ systems in the body. Also, Chapter 34, Risk Assessment Process for Industrial Hygienists, discusses issues dealing with the significance of toxic effect.

Various particulate materials have taken on a newer and more detailed consideration. In view of this increased interest in particulates a dedicated section of the book addresses several areas of current concern: Chapter 23 provides an overview of the toxicology of particulate matter, Chapter 24 looks at the toxicology of nano- and ultrafine particles, Chapter 25 addresses atmospheric particulate matter (PM 1/PM 2.5), Chapter 26 discusses Silica which is becoming an area of increased research and OSHA re-evaluation, Chapter 27 addresses asbestos, a material that remains of national and international concern, Chapter 28 discusses coal, a historical particulate entity that remains of concern globally and nationally, Chapter 29 looks at the toxicology of synthetic mineral fibers, and Chapter 30 evaluates diesel exhaust particulate matter. Each of these chapters are of concern to practicing industrial hygienists in industrialized countries and more so in developing countries. Chapter 2 addresses the area of toxicology concerns for industrial hygienists in globally developing countries. Chapters 31 (Exposure Assessment), 32 (Epidemiology), 33 (Exposure Reconstruction) and 34 (Risk Assessment Process for Industrial Hygienist) provide information useful for the development of data to address particulate matter health and safety concerns while Chapter 38 (Derivation of Occupational Exposure Limits) provides sufficient detail to develop OELs for chemicals or particles of unique concern.

Types of Toxicological Tests

Toxicology testing has always been important in determining potential toxicity of a chemical. For example, because of the Toxic Substances Control Act (TSCA), the Environmental Protection Agency may require data on mutagenic, carcinogenic, teratogenic, synergistic, or behavioral effects by using epidemiologic, *in vitro*, or laboratory animal methods whenever an unreasonable risk to health or environment may exist and there are not sufficient data to determine the risk. This law was updated on June 22, 2016, when President Obama signed the Frank R. Lautenberg Chemical Safety for the 21st Century Act, which requires additional chemical data reporting by chemical manufacturers and specific provisions for consideration of worker safety.

The principles of toxicology have contributed to several fundamental assumptions that underlie all toxicity testing. First, the effects observed in laboratory animals are often the same effects observed in humans. First, the degree of adverse effect increases as the dose or exposure increases. Second, as a general principle, if the absorption, distribution, metabolism, and excretion of a material are similar in humans and a particular animal species, test results in that species are generally predictive of the toxicity of the material in humans. However, since there are usually important differences in these characteristics, toxicology studies must be carefully interpreted.[13] The standard toxicology testing methods that are commonly used to assess chemical toxicity are described in Chapter 42, Toxicity Test Data. This section of the book also contains additional information sources: Chapter 43 discusses regulations, standards, and guidelines, Chapter 44 provides information on professional organizations and publications, and Chapter 45 discusses websites and electronic databases.

Uses and Interpretation of Toxicological Data

The results of toxicological tests are often used to assess whether exposures may be of any health significance in the workplace, in an emergency situation, and in litigation. Knowledge of how a substance is absorbed, distributed in the body, metabolized, and excreted will help determine if exposure was significant and if it should be evaluated. This information will also determine if biological monitoring is appropriate in a certain situation. For example, in the case of the solvent trichloroethylene, it is known that it is metabolized into a number of metabolites, including trichloroethanol and trichloroacetic acid, and these are excreted in the urine. If exposure is uncertain (e.g., as a result of both inhalation and dermal exposure), but important, these metabolites can be measured in the urine, giving an indication of the magnitude of exposure. Also, knowing that the half-lives of trichloroethanol and trichloroacetic acid in urine are 10 to 15 hours and 70 to 100 hours, respectively, any biological monitoring a week after exposure would not be very useful.[13] The entire fifth section of this book, Chapters 31 through 41, describes the application of toxicological information. For example, Chapter 34, Risk Assessment Process for Industrial Hygienists, presents the application of toxicology data in human health and environmental risk assessment.

In assessing and interpreting toxicological data, the animal model that was used in the study, the route of exposure, the dose levels used, and the time period over which exposure took place, must be considered. The relevance of the animal study to humans is greatly increased if the route of exposure used in the animal study is the same as the route of exposure in humans. An oral feeding study in animals does not have much significance to humans, if there is very little potential humans will ingest the substance, although in some circumstances results from oral studies can be used to evaluate effects from inhalation. In addition, the methods used in the animal study must be evaluated by asking specific questions. Did the study use an adequate

number of animals? Were control animals used? Was the proper animal model (i.e., the correct type of animal [mouse, pig] used for the endpoint being studied? Was the laboratory qualified to conduct the study? Were the results statistically significant? Were potential confounding variables, such as effects of other agents or laboratory procedures considered (e.g., inhalation studies that are not "nose only")? Have the results been replicated in other studies? Are the results consistent with any epidemiologic studies in which workers were exposed to the substance being studied? Have the limitations of the animal studies been considered? For example, are there wide variations in the susceptibility of individual species and strains of animals?[13]

Chapter 38 provides a detailed description for deriving occupational exposure levels, and biological exposure indices are discussed in Chapter 39.

Providing Impetus for Research

From the industrial hygiene point of view, toxicology is a preventive science. It is to assist us in preventing chemicals from impacting the health of workers and people in the community. In order to accomplish this, a variety of data is needed, including: data about the chemicals being handled; data about the work environment, especially the exposure to the chemicals; and data about the individuals who come into contact with the chemicals.[14] Toxicology helps provide data about the chemicals and data about the individuals who may become exposed to the chemicals. As a result, toxicology provides an impetus for research in these areas. The physico-chemical properties of the chemicals and their toxic properties require research efforts in chemistry, as well as research with experimental animals and *in vitro* studies. Research in regards to understanding the mechanistic linkages between sources, exposure, dose, and response are necessary before risk assessment can be undertaken. Ultimately, studies must be accomplished that determine how a substance behaves within the body—that is, toxicokinetic parameters are explored. Although this book is not focused upon the research aspects of toxicology, the third section of the book addresses the toxicology of chemical groups in Chapters 17 through 22, which discuss the most important research that has allowed us to understand the effects of chemicals most commonly found in the workplace. Throughout this book, areas currently needing additional research are highlighted, such as information needed for updating occupational exposure limits (Chapter 38), computational exposure assessment (Chapter 31), and complex chemical mixtures (Chapter 22).

Summary

For the industrial hygienist, toxicology is primarily concerned with assessing toxicological risk associated with humans and their interaction with potentially harmful substances. Toxicology is an important part of industrial hygiene, contributing to the reduction of serious cases of occupational poisoning involving disease and disability. Now efforts are focused upon insidious types of poisoning, especially in situations where workers are exposed for long periods of time to low concentrations of harmful substances. The approach now is towards health surveillance in conjunction with exposure monitoring, which includes environmental monitoring and integrating exposures to workers by conducting biological monitoring. Based upon that information, actions can be taken to maintain exposures below appropriately established occupational exposure limits. The setting of such limits depends upon toxicology data.

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Chapter 3 . . .

Principles of Toxicology

By Randal J. Keller, PhD, CIH and John Kind, PhD, CIH

What is Toxicology?

Toxicology is the study of the adverse effects of chemical, physical or biological agents on living organisms and the ecosystem, including the prevention and amelioration of such adverse effects.[1] It has also been described as the "science of poisons."[2] **A toxicologist** is an individual trained to assess those adverse effects.[3] Toxicology is very closely related to the field of pharmacology. Many medical schools in the country contain departments consisting of both pharmacology and toxicology. Pharmacology is the study of drug action, and a pharmacologist looks at the possible beneficial effects of chemicals on living systems. A pharmacologist and toxicologist may be researching the same chemical, with the pharmacologist examining the efficacy or beneficial effects and the toxicologist examining the toxic effects. Generally, these effects are differentiated by dose, since as stated by Paracelsus "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy"[3], however other factors, such as timing of the dose and individual differences in susceptibility, are involved as well.

There are many types of toxicologists, but industrial hygienists will primarily use information from descriptive, mechanistic and regulatory toxicologists.[2,3] A **descriptive toxicologist** is mainly involved with assessing the safety of chemicals. Any chemical that is introduced into commerce in the U.S., must undergo a safety assessment outlined by federal regulatory agencies, Similarly, the European Union requires that all chemicals in commerce be evaluated for safety though the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) program.[4] These assessments involve a series of animal testing protocols, such as acute, chronic and reproductive toxicity. Examples of these protocols can be found in the Food and Drug Administration (FDA) Redbook[5] or the Environmental Protection Agency (EPA) Health Effects Test Guidelines.[6] These testing protocols need to be strictly adhered to under Good Laboratory Practices (GLP)[7] before the manufacturer submits testing results to regulatory agencies such as the FDA. Good laboratory practices are a method of requiring laboratories to carefully document all experimental procedures to assure data quality and integrity. A descriptive toxicologist is the individual responsible for overseeing the study and ensuring that the testing is properly performed. A **mechanistic toxicologist** is usually a researcher employed by a university or a private company. Mechanistic toxicologists try to understand the reasons that chemicals' toxicities occur. This information may be useful in devising antidotes to chemical poisonings, understanding the human relevance of animal toxicity studies or establishing acceptable levels of exposures to the chemical. A **regulatory toxicologist** is generally employed by the state or federal government. They use data generated by descriptive and mechanistic toxicologists in the risk assessment process to establish exposure levels for various chemicals, such as the establishment of standards for the amount of chemicals permitted in ambient air, in drinking water or in occupational environments.[2,3]

There are other areas of toxicology that an industrial hygienist might interact with.[2,3] If a worker suffers a chemical poisoning, a **clinical toxicologist**, usually a physician trained in emergency care, would medically manage the poisoned patient. **Forensic toxicologists** are experts in the medical and legal aspects of toxicology, and may work with medical examiners in establishing cause of death in situations involving poisonings. An **environmental toxicologist** will look at a wide range of adverse effects that chemicals have on organisms within an ecosystem. These adverse effects include a variety of endpoints, for example toxicities to nematodes or behavioral effects on wildlife.[3]

Case Study

Jim was recently employed as an industrial hygienist at a small specialty chemical manufacturing facility. As one of his first duties, Jim decides to develop an air monitoring program to ensure that all chemical exposure levels are below any standards or recommendations.

One of the main chemicals they produce at the facility is p-nitroaniline. While developing the air monitoring program, Jim notices that p-nitroaniline has a Permissible Exposure Limit set by the Occupational Safety and Health Administration (OSHA PEL)[8] and a Threshold Limit Value® set by the American Conference of Governmental Industrial Hygienists (ACGIH® TLV®)[9] for inhalation exposure, and both exposure values have an associated skin notation. Jim refers to the TLV® documentation for health effects data and discovers that p-nitroaniline is readily absorbed through the skin and its toxic mechanism of action is the induction of methemoglobin. Dermal exposure from potentially contaminated surfaces is a concern at Jim's facility, and Jim needs to know what surface concentration of p-nitroaniline is safe for his workers. Jim checks all available resources and he cannot find any published surface standards for p-nitroaniline. Jim reaches out to the corporate toxicologist for assistance. Jim provides the toxicologist with information regarding the workers' likely exposure scenario, including details such as the potential surface area of a worker's exposed skin, their work practices, and their frequency of potential exposure. The toxicologist then combines this information with dermal toxicity data from rabbit studies to derive a surface exposure level that he believes to be below a threshold that would induce toxic effects in the workers.

Unfortunately, the above situation is familiar to many industrial hygienists. With approximately 84,000 chemicals listed in the Toxic Substance Control Act (TSCA) inventory[10], and regulations or recommendations available for only a small percentage of those, it sometimes becomes necessary for industrial hygienists to use general principles of toxicology to make educated decisions on a safe exposure level to a chemical. These principles will help the industrial hygienist in determining how likely it is that the usage of the chemical can pose harm to the worker. For example, understanding the route of exposure (i.e. inhalation, dermal, or more rarely ingestion), exposure scenario (i.e. the manner, frequency, and duration by which an individual may come in contact with a chemical), the likely fate in the body (absorption, distribution, metabolism, and elimination), and structural similarity to known hazardous chemicals are all useful in helping an industrial hygienist minimize the risk of harm to a worker from the chemical. A more complete description of this process can be found in Chapter 37 entitled "Derivation of Occupational Exposure Limits."

Toxic Agent Classification

There are several methods available for the classification of toxic agents that industrial hygienists generally need to be familiar with. These systems are listed in Table 3.1, and include classifications of target organ, use, effects, physical state, toxic potency and mechanism of action. Most toxicology textbooks, including this one, have a section devoted to the classification of toxic agents based upon **target organ toxicity**.[2,3] Section 2 of this book examines effects of toxic agents on target organs, and grouping agents by what organs they adversely affect is very common in industrial hygiene. For example, knowing if exposure to this chemical may result in lung damage, liver damage or central nervous system damage may assist in recognizing signs of overexposure. Agents are also commonly classified by use. Pesticides, which are diverse chemicals used to control various pests, whether they are insects, weeds, microorganisms, or rodents, can be classified together. Solvents can as well, although they too represent a diverse combination of chemicals with markedly differing toxicities. Section 3 of this textbook reviews the toxicity of chemicals by groups including pesticides and solvents.

Table 3.1 — Toxic Agent Classification

Toxic Agent Classification	Example
Target Organ	Liver toxicant, lung toxicant
Use	Solvent, pesticide
Effects	Carcinogen, teratogen
Physical State	Aerosol, gas, liquid, solid
Toxic Potency	Highly toxic, virtually nontoxic
Mechanism of Action	Cholinesterase inhibition, P450 Induction

The TLV® booklet[9] includes a column on TLV® Basis – Critical Effects. Effects are another method of toxic agent classification. Some common effects which are listed in the TLV® booklet include irritation, narcosis, cancer, reproductive or genotoxic effects. A relatively high percentage of substances with a TLV® are irritants; and it is important for industrial hygienists to be aware of the critical effects caused by exposure to a certain chemical. When workers are exposed to a mixture of chemicals with the same critical effect, the industrial hygienist should consider whether or not to account for additive effects when assessing worker exposure. For example, the critical effect of both carbon tetrachloride and 1,1,1-trichloroethane is liver toxicity (i.e. hepatotoxicity); if an industrial hygienist were evaluating a worker with a mixed exposure to both of these solvents, one would need to account for the additive effects of these compounds. This is accomplished by summing up the concentration of each chemical divided by its respective occupational exposure level. If the sum exceeds 1.0, then the additive mixture exposure limit has been exceeded.

Other methods of classification include physical state, toxic potency and mechanism of action. The classification by physical state, such as gases, vapors and aerosols, is very important to industrial hygienists because it refers to what they typically measure. Section 4 of this book will further discuss the toxicity of gases and particulate matter.

Toxic potency is a popular method of classification for the layman that addresses the question of how much of a substance can lead to harm. Toxic potency typically uses a range of ex-

posures and a subjective measure of the associated toxicities as listed in Table 3.2. Toxic potency is expressed as the dose necessary to elicit a given effect (i.e. lethality, central nervous system depression, eye irritation, etc…), and is frequently expressed as milligrams of a substance per kilogram body weight for an ingestion exposure, or milligrams per cubic meter of air for an inhalation exposure. For chemicals like botulism toxin where a dose of a few micrograms may lead to death, that chemical might be rated "super toxic." On the other extreme, if a person would only be affected after consuming quarts of a liquid, it might be rated as "practically nontoxic."

Mechanism of action is another method of classification usually used among toxicologists. In this method, agents are classified on what they actually do that results in the adverse effect. Some examples of this include cholinesterase inhibitors and chemicals that covalently bind to nucleic acids and cytochrome-P450 inducers. Mechanisms of toxicity will be discussed further in the next chapter.

Table 3.2 — Toxic Potency

Category	Lethal Dose for a 70 kg Person (154 lbs)	Relative Amount
Supertoxic	< 5 mg/kg or less	A taste (< 7 drops)
Extremely toxic	5–50 mg/kg	7 drops–1 tsp
Highly toxic	50–500 mg/kg	1 tsp–1 ounce
Moderately toxic	0.5–5 g/kg	1 ounce–1 pint
Slightly toxic	5–15 g/kg	1 pint–1 quart
Practically nontoxic	>15 g/kg	> 1 quart

Exposure

An important consideration in assessing the potential toxicity of any toxic agent is to determine the likelihood of exposure to that agent, since as stated in *Casarett & Doull* "Adverse or toxic effects in a biological system are not produced by a chemical agent unless that agent or its biotransformation products reach appropriate sites in the body at a concentration and for a length of time sufficient to produce the toxic manifestation."[3]

The inherent toxicity of the chemical is unique to the chemical itself, but it presents no hazard to workers unless they have the potential to be exposed to it. Industrial hygienists need to be familiar with not only the toxicity of a chemical, but how workers might be exposed to the chemical since these two factors will ultimately determine the danger the chemical poses.[2] A toxic chemical that is not present in a facility poses no danger to the workers. If the chemical is present, it will not result in toxicity unless workers are exposed to it for a sufficient duration at a sufficient concentration to result in a toxic dose.

Basic Toxicological Principles

Toxicology is a complex field and requires years of study prior to beginning professional practice. Although it is not the intent of this chapter of this textbook to train industrial hygienists to become practicing toxicologists, there are a few basic toxicological principles on how chemicals behave in biological systems that are useful for industrial hygienists. These include how chemicals enter the body (routes of entry), acute versus chronic toxicity, the classifications of adverse effects that are caused by chemicals, the dose response relationship, and understanding the concept of risk from chemical exposure.

Exposure and Dose

The concepts of dose and exposure are central to toxicology and are often used synonymously even though they are distinctly different. The term "exposure" refers to the contact of an organism with a chemical or physical agent, whereas the term "dose" refers to the amount of a chemical or physical agent that has actually entered the body and crossed some absorption barrier. Not all exposures lead to an actual dose; however, there can be no dose in the absence of exposure. The probability and severity of adverse health effects is determined by the dose that reaches the target tissue.[11]

Routes of Entry

Most occupational exposures occur by inhalation[2], although other routes of entry, such as ocular, dermal, or ingestion exposure may be important in certain occupational circumstances. All exposure standards and recommendations are set for concentrations of airborne contaminants. This is because most workers will be exposed to gases, vapors and aerosols, and may inhale sufficient quantities to be potentially toxic if proper respiratory protection is not used. Once a chemical reaches the alveolar sacs in the pulmonary regions of the lungs, it can readily cross the thin capillary lining found there and enter the circulation. The capillary linings of the lungs are some of the thinnest membrane barriers in the body, and although their main purpose is to allow gases like carbon dioxide and oxygen to readily cross, other inhaled chemicals can as well. Once a chemical crosses the capillary linings of the lungs, it is in the bloodstream and is capable of causing toxicity to other organs. A further description of the respiratory system will be presented in Chapter 6, "Respiratory Toxicology."

The second most common route of entry for occupational chemicals is by skin exposure. The skin consists of three main layers; the epidermis, the dermis and the subcutaneous layer. Once chemicals cross the epidermis, they have access to the blood vessels found in the dermis and subcutaneous layer. The portion of the epidermis that acts as a barrier is called the stratum corneum. Some chemicals, if lipophilic or soluble in lipids, can readily cross the stratum corneum. If the stratum corneum is not intact, for example, due to an injury or a skin rash, a non-lipophilic chemical can cross into the bloodstream. Although occupational exposure levels are not based on skin exposure, industrial hygienists need to be aware of a chemical's potential to cross the skin. The "TLV® booklet"[9] uses a "Skin" designation to indicate that skin absorption may contribute significantly to the dose of a chemical. This tells the industrial hygienists

to further consider this chemical, because skin exposure may result in a significant dose of the chemical. If the potential for significant skin absorption exists, workers should be advised to wear proper personal protective clothing. NIOSH has developed an extensive evaluation system to provide users a warning on the direct, systemic, and sensitizing effects of exposures of the skin to chemicals.[12] Dermal toxicology will be addressed in detail in Chapter 7.

Occupational exposures due to ingestion should not occur but sometimes are found in the following situations. Workers who eat and drink in contaminated areas, or do not adequately wash their hands may ingest chemicals. Workers who smoke may also ingest contaminants that are on their hands. Occupational exposures via ingestion should be minimal with good hygiene and other practices, but could be appreciable in some situations.

Acute versus Chronic Toxicity

The type of exposure situation can have a great influence on toxicity.[2,3] An acute exposure, which generally occurs in a short time frame of 24 hours or less, may have a markedly different toxicity than a chronic exposure, which may take place over a period of several years. Most cases of chronic toxicity occur because the toxicant accumulates within the body or a particular organ, or because the organ has insufficient time for repair before a subsequent exposure to the toxicant. Chemicals that accumulate, like lead, are generally associated with chronic toxicity. In some cases, acute and chronic exposures to the same chemical have different target organ toxicities. One well known example of this is ethanol. In an acute exposure, which may involve consuming a large amount of ethanol over a short time period, the target organ is the central nervous system, whereas if an individual continues to consume large amounts of ethanol over an extended period of time, the target organ shifts to the liver. The reason for this is that ethanol causes a transient effect called steatosis[2], or fatty liver, in which the liver increases its lipid content and turns yellowish in color. Although fatty liver is a reversible condition, if the liver is repeatedly exposed to ethanol before recovery can occur, a scarring of the liver, or cirrhosis, will occur. Further examples of liver toxicities will be addressed in Chapter 11, "Hepatic Toxicology."

An occupational example of this same principle involves benzene toxicity. Benzene is an agent capable of causing narcosis, and in an acute high-level exposure the central nervous system is affected. If a lower level exposure to benzene occurs over an extended period of time, the target organ shifts to the blood forming tissues, and the result may be anemia or leukemia. The permissible exposure limit of 1 ppm for benzene was established on the basis of the potential for benzene to cause leukemia.[8]

General Classifications of Adverse Effects

Local versus Systemic Effects

There are multiple adverse effects that can occur after exposure to a chemical, and a few examples are discussed in this section. Chemical exposures might result in a local or systemic effect. A local effect takes place at the site of exposure to the chemical. An example of a local effect is an acid spill on the skin; the skin will immediately redden at the site of contact with the acid. Sensory irritation is an important local effect that is often reported in the workplace, and minimizing sensory irritation forms the basis of many occupational exposure levels. Systemic effects occur at places other than the site of exposure. An example of a systemic effect is an allergic reaction, which is a type of immunotoxicity. For an allergic reaction to occur, a person must have prior exposure to the chemical or a structurally similar one at which time antibodies against the chemical are formed. Upon subsequent exposures, the immune system recognizes the chemical as foreign, and causes a sensitization reaction to occur. Immune system toxicities will be covered in the chapter entitled "Immunotoxicology." Most occupational exposures occur by inhalation, yet many systemic effects other than lung toxicity may occur. For example, inhalation of the vapors from many solvents results in narcosis. Chapter 5, "Disposition of Toxicants" will discuss this concept further.

Reversible versus Irreversible Effects

Some exposures to chemicals result in either reversible or irreversible effects. Reversible effects heal or resolve over time. The example listed above for the inhalation of solvents might be a reversible effect. If a worker inhales a sufficiently high concentration of solvent to produce narcosis, and is subsequently removed from further exposure, they will likely make a complete recovery and not suffer a lifetime of central nervous system impairment. Alternatively, inhalation of mercury vapors over extended periods of time might lead to irreversible nervous tissue damage.[2,3] Exposure to agents that are carcinogenic might lead to an irreversible effect. Once a cell has become cancerous, it cannot revert to a non-cancerous cell.

Immediate versus Delayed Effects

Responses to chemicals may also be immediate or delayed. An acid spill on the skin will result in an immediate effect, whereas exposure to a carcinogen may result in the development of cancer decades later. The concepts involved in the carcinogenicity of chemicals will be discussed in Chapters 14–16 on "Mutagenesis, Carcinogenesis, and Teratogenesis."

The Dose Response Relationship

The dose response relationship is of central importance to the study of toxicology, and works under the principle that increasing the dose of a chemical will increase the effect or biological response that the chemical elicits. The plotted relationship between the dose of a chemical or agent and its biological effects is known as a dose-response curve. Dose response curves are typically generated from either the response of an individual organism, or from the study of a population, as depicted in Figures 3.1 and 3.2.

Several types of information can be derived from dose response curves. Figure 3.1 is an example of a lethality study from which a lethal dose (LD), or lethal concentration (LC) of

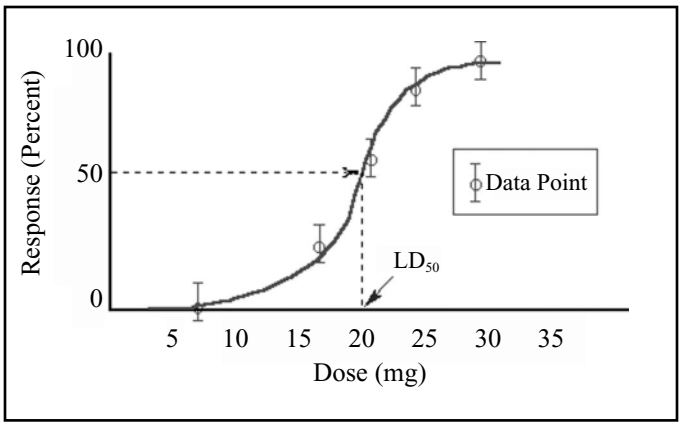

Figure 3.1 — Dose response curve for LD_{50} determination. From Toxicology Tutor I, National Library of Medicine.[13]

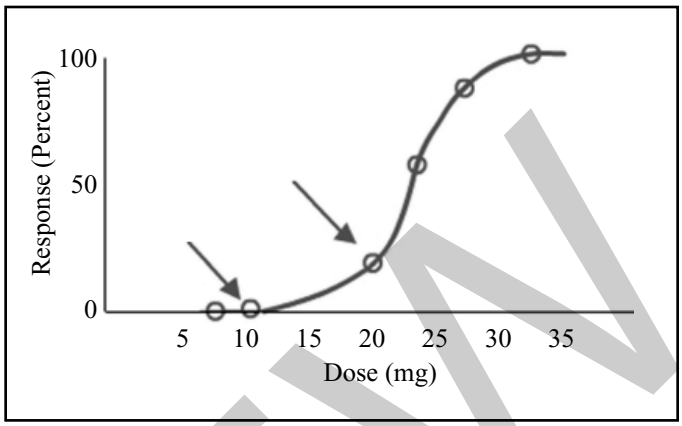

Figure 3.2 — Dose response curve demonstrating NOAEL and LOAEL doses. From Toxicology Tutor I, National Library of Medicine.[13]

the chemical, might be calculated. An LD_{50} is a statistically derived dose that is expected to cause lethality in 50% of the study population.[2,3]

Population dose-response relationships are most commonly used in toxicology (Figure 3.1). In these cases, the response refers to what proportion of the studied population is showing a specific response. Figure 3.1 demonstrates a typical percent mortality curve that shows mortality increasing in the population as the dose of the toxicant increases. Population dose responses usually follow a normal frequency distribution. In a population, there will be some dose below which no effects will be observed; this is known as the threshold dose, which is a key concept for non-carcinogenic health effects, and in establishing health-protective exposure guidelines. Some individuals exposed to low doses of the toxicant will be adversely affected. These individuals are considered sensitive. As the dose of the toxicant increases, the majority of the individuals in the population are affected. Some individuals in a population will be resistant to the effects of the toxicant, and will be only adversely affected when the dose is high. Although this example utilizes percent mortality, other endpoints can also be studied with population dose-response relationships, such as the determining the percentage of individuals in a population who exhibit central nervous system impairment at different exposure concentrations of a solvent.

Individual dose response relationships are useful in industrial hygiene in understanding the effects caused by increasing levels of chemical exposure. For example, if a worker is exposed to a solvent associated with a central nervous system effect like narcosis, as the level of solvent increases, the worker will become increasingly impaired. By measuring some type of impairment (reaction time, etc.) and plotting it against solvent concentration, an individual dose response curve would show increased impairment with increasing solvent exposure.

Information derived from dose response studies may be used to develop occupational exposure levels. The threshold level, or the lowest exposure resulting in a measurable response, is important because exposure levels below the threshold cause no detectable response. The NOAEL, or no observable adverse effect level and the LOAEL, the lowest observable adverse effect level, are also determined from the dose-response relationship.[13] These concepts are depicted in Figure 3.2. The establishment of occupational exposure limits can sometimes utilize the NOAEL or the LOAEL. Since the NOAEL or LOAEL is determined from laboratory animal testing, a regulatory toxicologist would not directly use this number to set an occupational or environmental exposure level without the application of safety factors to account for uncertainty in the data. In a simplistic example, if the NOAEL is determined from laboratory animals to be 100 mg/kg, a toxicologist might apply a safety factor of 10 for extrapolation from laboratory animals to humans, and a safety factor of 10 for variations in toxic responses among humans, establishing the occupational exposure limit of (100 mg/kg)/10/10 or 1 mg/kg, resulting in an exposure value that is believed to be protective of human health. This process will be covered more extensively in Chapter 37, entitled "Derivation of Occupational Exposure Limits."

Although dose response curves are used in helping establish safe levels of chemical exposures, they should be used with caution. Several variables may have an influence on the dose response relationship. Some of these variables include route of exposure (inhalation, dermal, ingestion), timing of the dose, sex, age, nutritional status, disease, past exposures, co-exposures, and genetic differences. All of these variables emphasize the complexities in applying information obtained from dose response relationships and form the basis for the application of uncertainty factors in the derivation of occupational exposure values.

Toxicological Risk

Risk is commonly defined as the probability or likelihood of experiencing an adverse outcome. In toxicology, the risk of experiencing an adverse health effect from a given exposure is a function of the exposure concentration or dose of a chemical and its inherent toxicity that is given in the following equation:

Risk=Toxic Potency x Dose

Although the risk is truly related to the dose at the target organ or tissue, this information is often not available, and exposure concentration is often used as a surrogate for target organ dose. Risk is a key concept in both toxicology and industrial hygiene, and along with the concepts of dose-response and threshold effects, forms the basis for establishing occupational exposure levels.

Summary

This chapter has covered the definition of toxicology, which is the study of the adverse effects of chemicals on living systems. Although toxicologists are specifically trained to study these effects, industrial hygienists need to be able to understand and apply some basic principles of toxicology. Not all chemicals that are present in the work environment have established occupational exposure levels, so an industrial hygienist needs to be able to interpret toxicity information on those chemicals and apply it to their specific situation. Knowing the relationship between exposure and toxicity will assist industrial hygienists in developing strategies in minimizing the development of occupational diseases.

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Chapter 31 . . .

Exposure Assessment

By Coreen A. Robbins, PhD, MHS, CIH, Lonie J. Swenson, CIH, and Susan Arnold, PhD, CIH

Introduction

Exposure assessment (EA) can be defined as "identification and evaluation of the human population exposed to a toxic agent, describing its composition and size, as well as the type, magnitude, frequency, route and duration of exposure."[1] Exposure is defined as the occurrence of a 'receptor' in the presence of an 'agent' of interest, with direct contact of the outer boundary or the receptor (e.g., skin) by the agent in some manner.[2] That is, exposure occurs when the receptor is in contact with an environmental media (air, water, etc.) containing the agent.

Exposure can be illustrated mathematically as:

$$E = \int_{t_1}^{t_2} C(t)dt \qquad (1)$$

where E is exposure, C(t) is a concentration that varies with time, integrated from the start to the end of exposure. Exposure has dimension of mass times time, divided by volume. For example, min.mg/m^3, could represent a 60-minute exposure to a chemical vapor in air. Exposure can be related to the potential dose by multiplying exposure by the contact rate, such as breathing rate, food intake rate, etc.

Exposure is distinct from *dose*. Dose in the realm of toxicology usually refers to the amount of the agent absorbed by the person or animal, receptor, or receptor target tissue or organ. It is possible for an agent to be *present* in the environment with no exposure occurring because the receptor and agent are not in contact (e.g., liquid chemicals stored in a sealed container). *Assessment* is generally the evaluation and measurement of the potential for, or actual exposure. Exposure assessments are also used to estimate dose by extrapolation from environmental measurements; and conversely, measures of receptor dose (e.g., via biological exposure indices) are sometimes used to estimate exposure.

Exposure assessment is at the heart of industrial hygiene (IH) and is critical to the recognition, evaluation and control of hazardous exposures in the workplace, but is also applicable to exposures in the general environment, including homes and outdoors.[3,4] Recognizing hazards is a first approximation of exposure assessment. Evaluating hazards is the act of quantifying and qualifying potential exposures now recognized. Control of hazards is impossible without some assessment of exposure. A discussion of EA is appropriate in a toxicology text for industrial hygienists because the two are inextricably linked: "Understanding the underlying toxicological relationships — such as between workplace exposure and internal dose, target-organ dose, pre-clinical effects and clinical effects — is fundamental to exposure assessment."[5] In practice, this means that the industrial hygienist must appreciate the potential for adverse health effects for likely exposure scenarios in order to know when and if they should monitor or measure exposures or take some other action.

Exposure assessment is considered by some to be a profession in its own right, with its origin credited to industrial hygiene.[6] Expanding from its use by industrial hygienists in the occupational setting, it is now used to examine human contact with toxicants found in the personal or community environments. Although the science to conduct EAs is within the continuum that follows the movement of a toxicant from its source through to ultimate health effects, industrial hygiene takes this a step further to devise and implement reduction or elimination of exposure.

Exposure assessments are also used in the fields of risk assessment (RA), epidemiology, and toxicology.[4] The activities and goals of EA vary in these different disciplines. In the field of risk assessment, EA may include estimates of exposures from sources in all environments, home, work and school. The main objective of EA in a risk assessment is to determine the source, type, magnitude, and duration of contact with the agent of interest.[7] In occupational epidemiology, the goal of the EA is typically to define exposures for jobs, tasks, or job categories in order to compare effects among workers experiencing different levels of exposures. Toxicologists use EA data to estimate doses, and to elucidate the relationship between exposures and

health effects. Exposure assessment in industrial hygiene encompasses many activities, but the measurement of exposure is often the central activity. Industrial hygienists use EA data typically for RA and management in the occupational environment. The ultimate purpose of IH exposure assessment is to prevent or stop exposures that could result in adverse health effects.

Occupational Exposure Assessment and Toxicology

Occupational exposure assessment (OEA) is a process which includes identifying and characterizing workplace exposures; evaluating their significance; and developing exposure estimates for individuals or groups of workers.[5] The assessment process is based on measurement and evaluation of characteristics of the work environment and may involve hypothesis testing. Occupational exposure is "the act or the condition of being subjected (as a result of work) to a chemical, physical, or biological agent, or to a specific process, practice, behavior, or work organization."[5]

Occupational exposure assessment is defined as: "the application of a body of knowledge to determine the relevant characteristics of one or more environmental factors that pose health and safety risks to workers."[5] Although safety-related factors are often important aspects of EAs for IHs, since this chapter is within a toxicology context, safety-related factors will not be addressed. Radiation and physical agents such as heat stress, noise, and ergonomics, for which EA are within the scope of IH activities, will not be addressed here.

Fundamental to OEA is an understanding of the underlying toxicological relationships between workplace exposure and internal dose, and target-organ dose, pre-clinical and clinical effects.[5] Exposure assessment data for substances must be combined with toxicity information to determine the potential for health risk. This is because health risks from exposure are directly related to the exposure level and the toxicity of the substance. For example, exposure to high concentrations of a substance of low inherent toxicity may not pose any risk; conversely, exposure to low concentrations of a substance of high toxicity may pose a risk of adverse health effects.

In the context of human toxicology, the EA is a measurement of the potential dose to the human body. While the toxicologist ideally desires a measurement of how much of substance "A" reaches the target organ, the industrial hygienist most often measures the amount of substance "A" only in the environment. The toxicologist must then extrapolate that measurement to an estimate of delivered dose. Industrial hygiene related biological exposure indices (BEIs) are available for some compounds, whereby the dose is estimated from toxicants or byproducts found in exhaled air or bodily fluids or tissues. In many cases, the exposure concentration is inferred from the BEI measurement. However, BEIs are less common than environmental measures and are less useful to the IH in preventing exposure and determining the environmental source and means to control it because BEIs generally do not provide information about the source(s) of exposure.

For environmental monitoring to represent human exposure, methods must be employed that measure substances in a way that mimics human exposure, e.g., air samples are collected to evaluate inhalation exposures and surface samples are collected to evaluate dermal exposure. Exposures measured this way are not a measure of dose, but they can sometimes be used to estimate the dose received. The dose calculation takes into account exposure level and duration, and includes factors such as breathing rate and fraction retained for inhalation exposure, or absorption rate and skin area exposed for dermal exposure.

Time Course of Exposure

The time course of an exposure can have a large impact on the potential for adverse health effects, and this depends on whether the agent's mode of action is acute or chronic and how the agent is metabolized if at all. For example, a full day of exposure to a low concentration of carbon monoxide (CO) may have no adverse health effect, whereas a brief but high concentration exposure to CO can have significant toxicity or cause unconsciousness resulting in falls or incoordination leading to injury. For other agents, such as those that accumulate in the body, the reverse may be found: brief and high intensity (acute) exposure concentrations result in minimal dose and cause little or no adverse health outcome, but chronic low concentration exposures cause adverse health effects. Asbestos fibers are an example of this. For the same total exposure (C x T) a brief but intense exposure to airborne asbestos fibers may result in a minor or no dose and no adverse health effect since little can be absorbed by the body in a short time interval, whereas for the same total (C x T) but from a long and low intensity exposure (over weeks or months) the result can be a larger dose and potential adverse health effects because a longer exposure interval can allow more fibers to be deposited in the lungs.

Exposure assessment methods need to account for the time course of exposure as changes in the magnitude of the agent present (concentration in air, etc.) occurs. Exposure can be continuous or intermittent, and can occur in an infinite number of combinations of the two. Examples are shown below in Figure 31.1. This is reflected in exposure limits and guidelines that are specified as short-term exposure limits (STELs), ceiling limits, (CLs), or 8-hr TWAs.

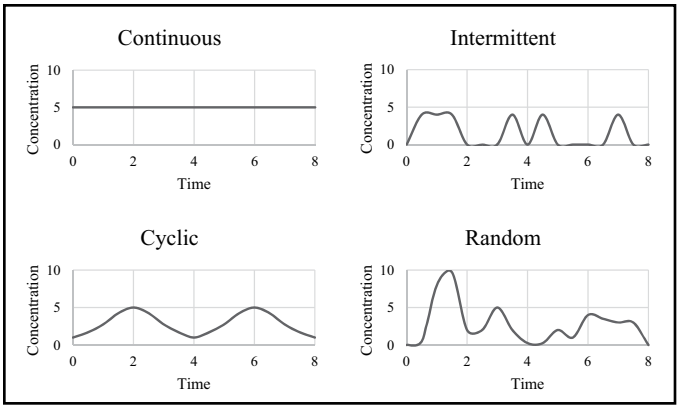

Figure 31.1 — Examples for exposure profiles.

Sample Duration and Toxicology

Many exposure standards and guidelines are based on an 8-hour workday exposure. Comparisons to such standards and guidelines using samples that reflect the 8-hr, time-weighted average (TWA) are usually the most desirable. Sometimes sample data are limited to short-term samples, and the industrial hygienist has to estimate the intervening exposure based on work practices. For example, if a worker uses benzene-containing solvents to clean metal engine parts for only a total of one hour per day, the exposure during the remaining seven hours is assumed to be zero (in the absence of other data). Computation of 8-hour TWA is described in the American Conference of Governmental Industrial Hygienists (ACGIH®) Threshold Limit Values (TLV®) booklet.[8]

ACGIH® includes Short-Term Exposure Limits (STELs) along with the TLV® for some substances. The STEL is a 15-minute TWA exposure level that should not be exceeded at any time during a workday. These limits are designed to limit short-term excursions for substances that could be harmful due to a short-term exposure, even though averaging out the short exposure over eight hours could be below the 8-hr TWA. Ceiling limits are levels that should not be exceeded at any time during the workday due to the potential for adverse effects even if the exposure is very brief. For example, glutaraldehyde has only a relatively low ceiling limit (0.05 ppm) because it is an irritant at low levels, and is also a sensitizer.[9] Thus, it follows that toxicological effects determine the guideline or standard exposure interval, which in turn will determine the sample duration. The sample duration will usually dictate the sampling method(s) that can be used.

In some cases, both short term samples and full-shift samples are indicated by exposure standards/guidelines that have both short term and 8-hour TWA exposure values. For example, benzene standard has both an 8-hr TWA TLV® (0.5ppm), and a STEL (2.5 ppm). In the example of the cleaning metal parts with benzene-containing solvents, it may be necessary to collect 15-minute samples during the actual cleaning activity. Longer duration samples may need to determine the 8-hour time-weighted exposure if, for example, the worker is also near others using benzene-containing solvents.[10] In all cases, it is critical to consult the applicable exposure guideline or standard to determine the sample duration.

The sampling part of exposure assessment needs to be in line with the expected intensity and duration. Sampling for an agent with respect to the STEL may require different methods than sampling for the same agent in order to compare the results to the 8-hr TWA. Short intervals with high intensity are lost when samples are collected over long intervals for many common sampling methods. Short duration samples or real-time sampling instruments may be needed to assess exposures for comparison to STELs or CLs.

Personal versus Area or Source Sampling

In keeping with the goal to measure agents in a way that is representative of the route of human exposure, samples are collected on or near the individual worker rather than in the general area of the worker. The preference for personal versus general area samples comes from the need to collect samples that mimic exposure for a person performing a particular job or task. Air samples collected in the "breathing zone" are thought to more accurately reflect individual exposure than "general area" samples. Skin patches collected from areas of exposed skin better represent exposure than environmental surface samples. When employing sample methods that are less reflective of exposure routes, for example, as with general area or source sampling, the measurements are usually less accurate representatives of exposure or dose. In some cases, general area measurements can be used to estimate the exposure of bystanders or co-workers who have no direct contact with the substance but work in the area of those working with it directly.

Even when the sampling method is representative of the route of exposure, the measured levels may not be easily correlated with dose. For example, total dust measurements likely include non-respirable particles that in some cases do not add to dose, but contribute significant mass to the sample. Many particle methods require the collection of respirable dust to account for this.

Exposure assessment plans should be framed with the following questions:

- Does exposure to the substance have the potential to produce adverse health effects?
- What is the substance of interest and where does it occur? Is it a particle, gas or vapor?
- What are the routes of exposure? Can it be inhaled, ingested and/or absorbed through the skin, or some combination?
- What is the time course or periodicity of the exposure? Is the potential for exposure occasional or continuous?
- What is the likely intensity of exposure and how does the intensity vary with time?
- What assessment methods exist for the substance? Is there a NIOSH or other validated method available?
- What exposure standard or guideline will be used to interpret results? Is there a health-risk based OSHA PEL, TERA-OARS WEEL®, or TLV®? If not, what criteria will be used to interpret the results of assessment?

Exposure measurement methods can be generally grouped into the categories of inhalation, dermal, and biological exposure assessment. However, there are substances for which more than one route of exposure is possible. For example, exposure to benzene can occur through inhalation and dermal exposure routes. There are no sampling methods to directly measure exposure by ingestion; however, contribution from ingestion exposure may be included in biological exposure indices measures. Surface contamination measurements are used to estimate the possible exposure via hand-to-mouth with the use of models. Methods are lacking to directly assess the dose via dermal exposure from surface samples. Surface samples generally cannot be used to estimate airborne concentrations though they may be correlated.

Exposures can also be assessed using computational programs that "model" or estimate exposures, for individuals or activities

with no specific sample data, using existing exposure data from similar exposure circumstances, or source strength and related data. Exposure modeling techniques use data from all assessment methods and can be applied to all routes of exposures.

Measurement of Exposure via Inhalation

Assessment of potential inhalation exposure is probably the most common and important measurement activity for the IH. It is the primary route of exposure for a vast array of agents in particulate and vapor form, so inhalation exposure assessment often includes air sampling measurements of aerosols of particles or gases and vapors. Exposure assessments of airborne agents can provide data to allow toxicological estimation of inhaled dose and/or the dose reaching the upper and/or lower airway. Important features of gaseous or particulate agents that influence the dose for a measured exposure include their solubility and reactivity in the mucosa and size (particles).

Aerosols are generally categorized by the physical form of the substance and the method of generation.[11] Particles that may be aerosolized may be in the form of dusts, fumes, or mists. Dusts may be comprised of particles or fibers. Although there is no strict classification of aerosols, the following list of terms corresponds to common usage; adapted from Hinds[11]:

Aerosols: A suspension of solid or liquid particles in a gas. Particle size ranges from 0.001 to over 100 μm.

Dust: A solid particle aerosol formed by mechanical disintegration of a parent material, such as by crushing or grinding.

Fume: A solid-particle aerosol produced by the condensation of vapors or gaseous combustion products. Particle size is generally less than 1 μm. Note that this definition is different from the popular use of the term to refer to any noxious contaminant in the atmosphere.

Smoke: A visible aerosol resulting from incomplete combustion. Particles may be solid or liquid and are usually less than 1 μm in diameter.

Mist: A liquid-particle aerosol formed by condensation or atomization. Particle size ranges from sub-micrometer to about 20 μm.

Fog: A visible mist.

Smog: Photochemical reaction products, usually combined with water vapor. Particles are generally less than 1 or 2 μm. The term is derived from the words smoke and fog.

Cloud: A visible aerosol with defined boundaries.

Assessment of Exposure to Particles

Much historical and current IH work has been devoted to assessing exposures to airborne particles. The large scope of this work is demonstrated by a section in this text devoted to the subject of the *Toxicology of Particulate Matter*, with chapters for nano- and ultrafine particles, atmospheric particles ($PM_{1.0}$/$PM_{2.5}$), silica, coal, synthetic mineral fibers and diesel particulate matter. The use of size-selective measurements for airborne particles contributes important additional information for determining the dose from the particles or their constituents, since aerodynamic particle size determines where in the respiratory tract the particles will deposit and how much of the particle constituents (mass) can be deposited. Both of these factors can influence or dictate what will become the target organ(s). For example, exposure to the relatively large particles of wood dust results in deposition in the nose, and studies indicate nasal cancer is caused by some hard wood dusts; whereas asthma and respiratory effects are associated with the respirable fraction of wood dusts.[12] Examples of some particles of IH interest and their sampling methods follow.

Particles, non-Fibrous

Dust particles may be comprised of minerals (asbestos, quartz), and other elements (magnesium, lead), organic/biological material (fungal spores, bacteria, pollen, grain dust). The toxicological effect of the particle is determined by its size and physical/chemical properties. Particles of IH interest are typically of irregular shape and varying density, which influences their ability to penetrate and deposit in the respiratory tract. "Particles are often described by their aerodynamic equivalent diameter (AED) which is the diameter of the unit density sphere that has the same settling velocity as the irregular particle. The AED be conceptualized as the diameter of a water droplet having the same aerodynamic properties as the particle."[11] The particle shape is usually ignored, although long, thin fibers are treated as simplified non-spherical shapes in different orientations.[11] The size and shape of the particle determines if it can be inhaled, and where and how in the respiratory system deposition will occur. Larger particles (>10 μm) deposit in the nose, mouth, and upper respiratory tract by the processes of impaction, sedimentation and diffusion. Particles <5 μm AED deposit mainly in the tracheobronchial region. Smaller particles (<2.5 μm AED) can be deposited in the lower airways including the alveoli. Once deposited, the physical/chemical properties of the particle determine whether it will dissolve or be vulnerable to clearance mechanisms (e.g., macrophages). Any mechanical irritation or deposition of chemicals into the respiratory system will be dependent on these properties of the particles.

Exposure assessment of particles involves measurement of mass concentration (mg/m^3) or particle number (usually, $number/cm^3$). Whether the particle mass or number is measured depends ideally on the toxicological mechanism of action. The number of particles may be of interest for small insoluble particles such as asbestos fibers that are found in great number for relatively low mass; or for extremely small particles with low mass and large surface areas such as nanoparticles. The mass of particles may be of more interest if the particles contain or are made of agents that are soluble in the tracheal-bronchial region and lung, since few large particles will contribute greater total mass than numerous small particles.

Measurement of mass concentration is usually done by collecting particles on sample media and weighing the amount collected. To determine particle numbers, particles are collected on media, such as micropore filters, and counting the particles using light or electronic microscopy. Often, particles are counted

depending on some type of size selection criteria. For example, the NIOSH Method 7400 asbestos fiber counting method "A" rules specifies counting only fibers longer than 5 µm.[13] Real time particle-counts are measured indirectly using electronic particle counters that employ techniques such as light-scattering technology.

Assessment of exposure to particles, whether by mass or number, often needs to be tailored to measure particles that preferentially deposit in the part of the respiratory tract that is important for the site of action for that particular dust. Sampling methods for dusts that take into account the need for size-selective sampling are available. For example, use of the TLV® for silica requires the use of a cyclone collection device because the guideline is specific for respirable particulate mass (0.25 mg/m^3).[14] The cyclone allows collection of dust that is in the respirable size range. For some dusts the total mass of inhalable dust is more important because deposition and health effect occurs in all parts of the respiratory tree. Or, exposure standards have been developed using total dust measurements. For example, some wood dusts have been implicated in nasal cancer, so an estimate of inhalable particles is needed.[15]

The combination of particle size and chemical composition is measured in some cases. This is done when sampling for silica under the OSHA Standard for silica.[16] The OSHA standard requires adherence to an exposure limit that takes into account the mass of respirable dust and the proportion of certain types of silica (cristobalite, tridymite) in the dust. Note that the current TLV® for crystalline silica (0.025 mg/m^3) is based simply on the mass of respirable dust.[14]

Fibers

Fibers are generally defined as particles with a diameter to length ratio of greater than 3 to 1. Respirable fibers have AEDs in the range of 5 to 10 µm, with diameters less than 3 µm.

The lung deposition, retention and health effects of fiber exposure are dependent on fiber characteristics including fiber size and durability.[17] Small fibers (< 2 µm long) are considered to be nuisance dusts, whereas respirable fibers longer than 5 µm have the potential to cause disease.[18] Size-selective sampling methods for fibers were introduced in the 1960's. Prior to the development of these methods, all sizes and shapes of particles, fibers or not, were counted as particles. Results were reported in terms of "mmpcf" million particles per cubic foot (1 ft^3 = 0.028 m^3). Methods for selectively sampling fibers evolved as the realization that health effects of fibers are different from other particles. These methods generally involve counting particles that meet the criteria for a fiber. Typically, fibers are collected on filters and the filter contents are examined using optical microscopes. These methods do not distinguish between fiber types. Electron microscopy (SEM with EDXA and TEM) methods are used when there is need to know the identity of the fiber (asbestos or fiberglass) and/or the chemical composition of the fibers present. A common method for collecting and analyzing asbestos fibers is the NIOSH Method 7400.[13] Counting rules dictate that only those fibers greater than 5 µm are counted. If the "B" rules of the method are used, then fibers with diameters over 3.5 µm are not counted.

Biological Particles

Many sampling methods exist for collecting airborne bacteria and fungi. The most commonly employed method is the Andersen sampler. This device uses impaction to collect bacterial and fungal spores on nutrient agar. The six-stage Andersen bioaerosol sampler allows size-selective sampling of particles in the size ranges of 0.65–1.1, 1.1–2.1, 2.1–3.3, 3.3–4.7, 4.7–7.0 and >7.0 micrometers, AED.[19] Collected spores are grown to visible colony size, and the colonies are identified and counted. Another method for collecting fungal spores, "spore trap" samplers, are impaction method collection devices. The collection media is usually a sticky surface, upon which spores are trapped from the moving air stream. The sample is examined for the presence of spores. Since spores don't need to be viable to be counted, this method will detect both viable (culturable) and non-viable (non-culturable) spores. However, there is no currently validated NIOSH method for this type of sampler and the analytical variability is unknown.

Gases & Vapors

A vapor is defined as a gas derived from evaporation or sublimation of a substance that is a liquid or solid at "room temperature." A gas is simply a substance found only in the gaseous state at "room temperature." For simplicity, the term "gas" will be used instead of "gases and vapors." Unlike particle samples, sampling methods for gases are not selective for the likelihood of deposition at the target organ. The sample is collected to determine the concentration of the gas in the environment. Although the concentration measured can be used as a surrogate for dose, the dose in different organs and tissues is dependent on the bioactive properties of the substance and human factors such as breathing rate. Most methods are designed to collect a single substance, but the sampled environment often contains numerous compounds. The chapter on complex mixtures includes discussion of these situations. Some issues involved with mixtures include synergistic health effects, and sample interference or augmentation.

Many methods are available for assessing the concentration of vapors and gases. From the standpoint of the toxicology of the materials being sampled, the sampling method often depends on the time it takes for adverse effects of the substance to appear. Sampling methods are generally one of two types, one that provides instantaneous analysis or display of gas concentration, or one that integrates gas concentration of a period of time. The first type is called a "real time," "direct reading" instrument. Direct reading instruments measure exposure as it occurs, or in "real time." These are useful with substances that require continuous monitoring and/or produce toxicity in a short time frame, such as carbon monoxide; or for capturing peak exposures that may be harmful, such as a high solvent exposure during a short duration task. For example, real-time, direct-reading instruments are usually used to measure carbon

monoxide exposure since instruments can specifically detect CO, and immediate adverse effects are possible. Real-time instruments are also used to measure compounds that are potentially explosive, since levels of these compounds is something you want to know immediately if their presence is anticipated, even if their presence near their lower explosive limit does not create a hazard due to toxicity per se.

Although some real-time instruments have probes that are specific to certain chemicals, some are non-specific and respond to a large number of substances. For many compounds, direct reading instruments are not available that allow identification and quantification of individual compounds. For example, it is not possible to isolate perchlorethylene concentration using an instrument that responds to chlorinated solvents. A substance that is present at potentially toxic levels can be missed if it cannot be distinguished from other substances in the environment. Typically, the user has to assume that entire concentration measured is that of the substance of interest.

To accurately identify and quantify airborne concentration typically requires that samples be collected in or on some sample media, which is later analyzed with an instrument in a laboratory. Bulk gas samples can be collected in a container, such as a Tedlar bag or Suma canister for later analysis, typically for direct injection into a gas chromatograph (GC) with a mass spectrophotometer (MS). Commonly, chemicals present in air are captured as air containing them is passed through an adsorbent or chemical-reactive material in a tube (e.g., activated charcoal, silica gel). The air flow through the media is known, along with the sample duration so the results of analysis can be quantified as the amount of agent in the volume of air (typically mg/m^3). These latter samplers are often compound-specific, and can be selected to measure the substance of interest. For example, solvent vapors or mixtures of solvent vapors are collected on adsorbent charcoal tubes; the sample is later processed using GC or GC/MS. These methods provide identification and quantification of the solvents vapors present in the tested environment. For example, air samples for benzene are collected on charcoal tubes and are later subjected to analysis with the GC. If the exposure to benzene is associated with gasoline, other related compounds, such as toluene, ethyl-benzene and xylene, "BTEX" can be quantified in this analysis. These types of sample integrate the concentration of the substance during the sample interval, so some data about short-term high and low concentrations are lost.

A wide array of methods and instruments are available for use in assessing exposures to gases and vapors. The method or instrument selected will be dependent on the type of gas or vapor expected. For detailed information on available methods and sampling instruments, the reader should consult available resources such as the ACGIH® "Air Sampling Instruments" text[20] and the NIOSH "Manual of Analytical Methods."[21]

Dermal Exposure Assessment

Exposure to chemicals in the workplace can occur through the skin. This is one of the most common ways of contacting chemicals, yet it is a frequently overlooked exposure route when assessing workplace exposures. There is a general lack of knowledge and understanding of how dermal exposures occur and how to quantify these exposures.

Chemicals that come in contact with the skin may remain on the skin's surface or they can be absorbed into the body. Once a chemical penetrates the skin, it can be carried to other parts of the body by the blood and lymph systems. Other organs in the body can be the target for chemicals absorbed through the skin. For example, organophosphate pesticides are readily absorbed through the skin and the target organ is the nervous system. See Chapter 7 for a detailed discussion of dermal toxicology.

The type of chemical and the form it is in will influence whether a chemical will be absorbed. Generally, inorganic chemicals in a dry or powder form are poorly absorbed through intact skin. Organic chemicals in a powder form are less likely to be absorbed than the same chemical in an aqueous solution or suspension. Organic chemicals in an oily solution or solvent form are more likely to be absorbed than aqueous solutions of the same chemicals. Similarly, ionized solutes are less well absorbed than non-ionized substances. Chemicals with a higher affinity for the lipid phase (fat soluble chemicals) will be absorbed through the skin more readily.

Dermal Exposure Assessment Methods

Dermal exposure assessment is a complex issue. Various models have been proposed for quantifying dermal exposures but validation of the models is limited. At best, many of the models realistically provide only a qualitative or semi-quantitative assessment of the exposure and dose because of the data gaps that exist and assumptions that are required. Currently, there is no general agreement on how to measure skin contamination, limited data on absorption of chemicals across the skin (percutaneous absorption), limited data on the potential for skin contamination based on workers' activities and behaviors, and no recognized metric for interpreting dermal exposures.

The practicing industrial hygienist does have some tools to use in evaluating dermal exposures and conducting dermal exposure assessments. Recognition of the potential for dermal exposure is the first step in the dermal exposure assessment. The industrial hygienist should have knowledge of the types and forms of chemicals present and their potential for dermal exposure. The "skin" notation on the TLVs® identifies chemicals with the potential for absorption or toxicity via the skin route of exposure. However, this notation does not include the potential for chemicals to cause skin damage and dermatitis. The OSHA Technical Links internet site includes "Chemical Sampling Information" which lists substances that have a potential for ingestion toxicity, skin absorption, and/or a hazardous effect on skin (see "Health Factors", OSHA 2007). Safety data sheets (SDSs formerly MSDSs) may provide useful information to assess the importance of the dermal exposure pathway. Other resources include the ACGIH biological exposure index (BEI) and supporting data.

The type of exposure, the degree of contact, and the work activities that can contribute to a dermal exposure should be evaluated. Is the potential dermal exposure episodic such as from occasional mixing or splashes? Is the potential for dermal exposure ongoing from immersion of hands or arms in the chemical? Can the chemical be deposited on the skin from mist or transferred from work or other surfaces to the worker's skin? Can chemicals soak through clothing or gloves or be trapped on the skin by the worker's clothing? What is the form of the chemical? How much body surface is potentially affected? How frequent is the exposure? What is the duration of contact? What type or personal protective equipment (PPE) is used? Worker-specific factors such as condition of the skin should also be assessed.

Rating schemes for estimating dermal exposures are available that incorporate the qualitative considerations discussed above.[22] The ranking factors include the dermal contact area, dermal concentration of the chemical, dermal contact frequency, dermal retention time, and the dermal penetration potential.

There are also methods for measuring chemicals in the work environment that have the potential to be absorbed through the skin. Before instituting any sampling program, the industrial hygienist should have developed a hypothesis regarding the potential exposure, develop a sampling plan that will answer that hypothesis, and understand how the resultant data are to be used.

One of the simplest sampling techniques is source sampling of surfaces in the work area. Wipe sampling (also called swipe sampling or smear sampling) can be used to identify potentially hazardous conditions and to evaluate the effectiveness of housekeeping, work practices, decontamination programs, and the use of PPE. There is limited guidance on acceptable surface contamination amounts. Wipe samples do not assess health risk. However, they can identify areas where special cleaning practices are needed or not needed, how effective PPE use is (for example wipe sampling inside gloves or coveralls), or to assess how work practices may transport chemicals in the work environment. The OSHA Technical Manual available on the OSHA web site provides information on media and techniques for wipe sampling including wiping surfaces with filters, gauze squares, charcoal-impregnated pads, or direct-reading colorimetric sampling on surfaces.[23] Wipe sampling techniques can also be used to obtain wipe samples directly from skin surfaces.

A second type of sampling for dermal exposures is the use of patches. This is a passive form of sampling. The purpose of patch sampling is to estimate the amount of a specific chemical deposited on the skin or clothing. Absorbent patches are attached to the worker's skin or clothing prior to exposure. They are then removed at the completion of exposure and analyzed for the chemical of interest. The amount of chemical detected can then be used to estimate the exposure to the surface area of the corresponding body part. The method can have errors associated with it. For example, if a single splash hits the patch directly the exposure may be overestimated; whereas if splashes miss the patch entirely, then the exposure may be underestimated. Similar to patch sampling, whole body sampling can be conducted with workers wearing a suit that is then analyzed for the chemical of interest. The whole body suit sampling technique has largely been used in evaluating pesticide exposures. Soutar et al. provide a discussion on the use of patches and whole body suits in assessing dermal exposure.[24]

A third method of evaluating dermal exposure is the use of fluorescent tracers that are added to the chemical of interest. The deposition and retention of the chemical on skin surfaces is then measured directly using ultraviolet fluorescence imaging detection equipment.

Dermal exposures can also be measured indirectly using biological monitoring methods. Although these methods can be used to detect compounds absorbed through the skin, they cannot distinguish the amount due to skin versus inhalation exposure. For example, benzene is absorbed through the skin, and the TLV® for benzene has a "skin" notation; however, the ACGIH® BEI for benzene can be used only to estimate total benzene exposure, not just that exposure due to dermal contact.[25] In situations where inhalation exposure potential is known, or is limited by respiratory protection, the BEI could be used to estimate absorption due to dermal exposure.

The methods and limitations of some of the methods and models for assessing risks of dermal exposures in the workplace have been recently critically reviewed[26], and extensive discussions of dermal exposure assessment methods and models are available in the exposure assessment chapter of the U.S. EPA document, *Dermal Exposure Assessment: Principles and Applications*[27]; and in Warren et al.[28] Practical information sources for assessing dermal exposure have been compiled by Hebisch.[29]

Biological Exposure Assessment (e.g., BEIs)

Biological exposure measurements are one step closer to measuring absorbed dose. Biological monitoring has been defined as "the measurement and assessment of agents or their metabolites either in tissues, secreta, excreta, expired air or any combination of these to evaluate exposure and health risk compared to an appropriate reference."[30] Thus, these measurements may be of substances or their byproducts in exhaled air, urine and blood, etc., and allow an estimate of absorbed dose to the worker.[31] Biological "effects monitoring" is included in the general category of biologic monitoring. This can include such measures such as pulmonary function, etc. Biological monitoring has been used successfully to assess the renal effects of cadmium, lead effects on hemoglobin synthesis, and organophosphate effects on cholinesterase activity.[30] These are well-validated and widely used.

Biomonitoring is useful in determining exposed groups and estimating delivered dose. Biomonitoring has also been used in the diagnosis of diseases that are exposure-related. This method requires that there is specificity for the substance in the analysis methods, metabolism, and source. Analytical specificity requires that the method used to measure the substance is specific for that substance. Metabolic specificity means that the

substance measured is derived from the parent compound, and does not have contributions from other substances. Since biological monitoring cannot identify the source of a substance, source specificity means that the majority of the substance of interest is derived from the occupational source (or other expected source). Often exposures occur outside of the workplace, from the ambient air and from food and water. Thus, the comparison is made between individual levels and some reference level from the 'unexposed' population. For highly exposed workers, the differences from the population will be large and easily detected, but if the difference is small, then this method is not useful in distinguishing occupational exposure.

Quantitative exposure assessment using biomarkers is possible for a number of compounds for which the main route of exposure is inhalation. The accuracy of the exposure estimate varies among different chemicals. For example, exposure to styrene is well-described and results are uniform. But for other compounds, the relationship is less clear. For example, the relationship between demethylformamide exposure and the concentrations of its metabolite, methylhydroxymethylformamide in urine, have provided widely different results.[30] This may be due to dermal exposure or other causes. This is a major drawback of biomonitoring, in that it does not provide information about the route of exposure, but only represents the total amount absorbed.

The half-life of the substance in the body largely determines the utility and frequency required for biomonitoring. The half-lives of substances vary widely; the half-life for mercury is about 60 days[30], but the half-life for CO is about four hours in room air. For substance with half-lives shorter than two hours, biomonitoring is not often feasible. For half-lives of two to ten hours, a sample at the end of the work shift reflects exposure over the day. The shorter the half-life, the more frequent sampling must be to accurately represent exposure.

Biological monitoring is also a method used to measure effects of substances. For example, the cholinesterase activity in plasma and erythrocytes can be measured in cases where organophosphate insecticide exposure is suspected.[30] Effect biomarkers are not typically used to identify exposed populations. However, in some occupational settings, it may be possible to exclude other exposures that affect the biomarker, and exposures can be determined. Biomarkers have also been used to diagnose exposure-related disease in individuals. For example, the presence of asbestos bodies is a biomarker of exposure to asbestos that is used to diagnose asbestosis.[32]

Although biological exposure monitoring can be used to determine exposed individuals or populations, and to measure dose and effect, alone it cannot be used to identify the sources, routes, and duration of exposures.[33] For example, a ACGIH® BEI® is available for benzene, which could be used to estimate the benzene exposure for the worker using benzene-containing solvents to clean metal parts; however, the BEI results would not allow the industrial hygienist to determine whether other jobs, tasks or processes contributed to the total exposure.[25] Therefore, biomarkers or biological exposure indices should be used to complement traditional industrial hygiene exposure assessment.[31]

Computational Methods of Exposure Assessment

Where comprehensive and scientifically valid exposure and RAs are required, the inclusion of modeling is a critical element of the EA process. Historically, the comprehensive assessment of exposures in a systematic framework has not occurred, and risks due to most personal chemical exposures have not been estimated.[34] Therefore, conclusions about the acceptability of exposure are often made without a formal assessment or collection of data.[35,36]

Modeling: An Integral Part of Exposure Assessment

Models are at the very core of the science of exposure assessment. Consider the four steps in the scientific process:

1. Define the hypothesis
2. Conduct experiments to test the hypothesis
3. Analyze the results
4. Draw conclusions and possibly form new hypotheses

An EA is initiated by the formation of a hypothesis about exposure, however consciously or subconsciously formulated. The hypothesis is in fact a model; it is a qualitative and quantitative expression of what the assessor believes to be taking place. Typically, to test the hypothesis, the industrial hygienist observes the tasks or activities related to the exposure and conducts experiments taking physical measurements or monitoring exposures. In practice, the IH must initially use a simple model to estimate the likely exposure – in order to employ the appropriate sampling method on the right sampling schedule (relevant to activities/jobs/tasks) and sample duration (STEL, 8-hr TWA, etc.). The sample results are then typically compared to the occupational exposure limit (OEL) or some other standard. The comparison lets the assessor accept or reject the hypothesis and perhaps form new hypotheses. It also allows the assessor to calibrate their professional judgment about this kind of exposure scenario. However, in many cases these hypotheses are never tested with experiments (exposure monitoring) due to lack of resources or because the industrial hygienist is confident of the outcome.[35,36]

Physical-Chemical Models

Physical-chemical models are used to predict contaminant concentrations in the environment using first principals (e.g., heat and mass transfer) and empirical observations. These models describe the concentration due to a source such as a leak or an open tank or mixing in an enclosed space.[37] These models need to be validated with measurements over a wide array of conditions.

Physical-chemical models allow the assessor to estimate historical exposures that cannot be readily be recreated. By adjusting the values for room dimensions, air exchange rates, emission rates and other determinants of exposure, the assessor can explore the effects on the airborne concentration in any hypothetical situation. Accordingly, physical-chemical models also lend themselves to estimating possible future exposure scenarios.

The models can be used deterministically; using single, point values for the variables in the algorithm and producing a single value for the airborne concentration. They can also be used probabilistically, in which ranges or distributions of values are used in place of single point values. For example, a single ventilation rate is used in a deterministic model, whereas a range of possible ventilation rates is used in the probabilistic model. The resulting output is a distribution of values of predicted airborne concentrations. The models presented here are neither elegant nor complete. They should be interpreted with careful consideration of the assumptions and inherent limitations.

Simple modeling programs are currently available at no cost to users online from AIHA®. The "IHMOD" is an Excel spreadsheet that includes a user-friendly interface to create graphs displaying concentration over time for twelve modeling scenarios described in *Mathematical Models for Estimating Occupational Exposures to Chemicals*.[38] The user provides basic information, for example, mass emission rate, ventilation rate, room volume and time for simulation for the well-mixed room model, and, using the appropriate equation, the program provides a graph and resulting data for the requested model. Actual data can be added to assess the accuracy of the model.

The discussion of exposure modeling in this chapter is centered on inhalation. While models exist for assessing dermal and incidental oral exposures, they will not be discussed here.

Assumptions in Concentration Exposure Modeling

The models considered here do not estimate human exposure directly; rather, they estimate an airborne concentration. The link to human exposure is made through the association with the time spent in the environment. The use of this and other assumptions is important and necessary in exposure assessment. These assumptions must be understood and acceptable to the assessor before any conclusions can be drawn based on the model under consideration.

Modeling as a Tiered, Iterative Approach

In accordance with the precautionary principle, models are typically applied in a tiered, iterative manner. Conservative assumptions that are expected to over-estimate the true exposure are used in lieu of data; as more information becomes available, more complex and accurate models are applied. Tier I models include very simple screening level tools that require little data, time and expertise. Accordingly, the exposure estimate can be orders of magnitude greater than the 'true' exposure. Their utility lies in screening out *de minimis* exposures; for example, where the predicted exposure; albeit conservative, is less than the occupational or *a priori* acceptable exposure limit, the assessor can quickly conclude the exposure to be acceptable. (And document the basis for such a conclusion.) The following discussion is adapted from and uses equations and language from Jayjock, et al.[39]

Tier 1: Saturation or Zero Ventilation Model

This model estimates the atmospheric concentration of an evaporating chemical in the gas or vapor phase, excluding misting. The model ignores any ventilation that may be in place and estimates a worst-case concentration. This algorithm predicts a worst-case airborne concentration that is less than the OEL so the industrial hygienist is able to classify the exposure as acceptable based on a simple, very conservative model.

The equilibrium saturation concentration (C_{sat}) in volume parts of contaminant per million volume parts of air (ppm, v/v) will be

$$C_{sat} = \frac{(10^6)(\text{vapor pressure})}{(\text{atmospheric pressure})} \quad (2)$$

Units: Vapor pressure and atmospheric pressure can be in expressed as mm Hg, atmospheres, Pascals, etc. as long as both are expressed in the same units.

Vapor pressure at any ambient temperature is an experimentally determined quantity; however, it can also be estimated for any class of liquids from boiling point data either atmospheric pressure or under vacuum.[40] The vapor pressure of the components within mixtures can also be estimated using established procedures[41] such as Henry's law constant (ratio of vapor to solution concentration) or Raoult's law (portion of a substance's pure vapor pressure in the headspace is the same as its mole fraction (in solution)).

Tier 2: General Ventilation Model

One of the oldest and most used models in inhalation exposure modeling is the "box" or general ventilation model. It relies very simply on the concept of the conservation of mass. Imagine a box of air. Now imagine it is a black box; that is, you cannot go into it or look inside it. Now consider that as you begin to put an airborne contaminant into the box you will constantly measure any contaminant that subsequently comes out. We know that the average concentration in the box can be described as:

$$\text{Concentration} = \frac{(\text{Amount going into the Box})-(\text{Amount coming out of the Box})}{(\text{Volume of the Box})} \quad (3)$$

If the contaminant is going into the box at a steady rate and leaving with the outgoing air at the same rate, then we know that the system is at "steady-state" and that the average concentration in the box is constant. This is actually a relatively simple and very useful relationship given by Equation 4 below.

If we are to believe that the concentration in the box is the same or homogeneous throughout the volume of the box then we need to make the assumptions that the contaminant:

- remains airborne (does not absorb onto surfaces)
- does not change chemically within the box and
- upon entering the box is instantly and completely mixed with the air in the box.

This is the so-called Well-Mixed Box construct.

Using this simple steady-state model and assumptions a general ventilation equation for this situation is:

$$C_{eq} = \frac{G}{Q} \quad (4)$$

C_{eq} = steady state concentration, mg/m^3
G = rate going into the box, mg/hr
Q = ventilation rate of air leaving the box, m^3/hr

Of course, the real world is often much more complicated. The mixing of airborne contaminants is often not at equilibrium nor is it complete and instantaneous. Also, some substances of interest are removed by non-ventilatory mechanisms such as adsorption or chemical reaction. Also, the non-steady-state situation is significantly more complicated to describe mathematically. A differential equation that attempts to take all of these factors into account can be written for the pollutant concentration within the box for any time[42]:

$$VdC = Gdt - (C)(Q)(m)dt - (C)(k)dt \quad (5)$$

In Equation 5, V is the assumed volume of the box (m^3), t is the time variable (hr), C is the concentration in the box at any given time (mg/m^3), G is the rate of generation of pollutant within the box (mg/hr), Q is the volume flow rate of air exchange in the box (m^3/hr), m is the dimensionless mixing efficiency of ventilation in the assumed box[40], and k has units of m^3/hr and is the removal rate by mechanisms other than ventilation and filtration.

Typically, we do not have specific information on non-ventilatory loss rate (k), the mixing efficiency (m) or on the time course of exposure. Thus, we assume values for these factors and for the ventilation (Q) and generation rate (G) that render a reasonable upper bound estimate of C. Indeed, we often default to the steady-state condition for our analysis.

Using these assumptions, our general ventilation model that incorporates the mixing factor and ignore "k" (i.e., set k =0) is:

$$C_{eq} = \frac{G}{(Q)(m)+k} = \frac{G}{(Q)(m)} \quad (6)$$

Tier IIa: Dispersion Model

The general ventilation model avoids the question of contaminant mixing in the volume. It also ignores near field exposure or sharp gradients of concentration for workers close to the source. A diffusion model has been developed for heat flow[42] and applied to indoor air modeling.[43,44] The equation for a continuous point source is presented in the references to predict concentration at position r and time t.

$$C = \frac{G}{240\varpi Dr}\left[1 - \text{erf}\left(\frac{r}{\sqrt{4tD}}\right)\right] \quad (7)$$

where "erf" means the error function.

C = concentration, mass/volume (mg/m^3)
G = steady-state emission rate, mass/time (mg/hour)
r = the distance from the source to the worker (meter)
D = the effective or eddy diffusivity, area/time (m^2/hour)
t = elapsed time (hour)

Diffusion of contaminants in workroom air occurs principally because of the turbulent motion of the air.[45] In most industrial environments, molecular diffusion is not significant between the emission source and the worker's breathing zone. Instead, the normal "turbulence" of typical indoor air causes eddies (or packet-like motions) that have the effect of breaking up the contaminant cloud and hastening its mixing with the workroom air. Therefore, applications of diffusion models in industrial environments use experimentally determined diffusion coefficients (D) called eddy or effective diffusivities. These eddy diffusivitity coefficients are 3–5 orders of magnitude larger than molecular diffusivity.

The eddy diffusivity term (D) can be based on experimental measurements at the site being modeled. Some eddy diffusivity values are also available in the literature.[44,46] Measurements of D in indoor industrial environments have ranged from 3 to 690 m^2/hour with 12 m^2/hour being a typical value.

Plotting the predicted airborne concentration (C) at one position, r, for many values of time, t, gives an increasing curve of concentration that approaches a steady-state level.

For sources (emitting into a hemisphere) on a surface and at equilibrium, equation (9) simplifies to:

$$C_{eq} = \frac{G}{120\varpi Dr} \quad (9)$$

There is little doubt that the Eddy Diffusivity model could be a very valuable tool that can potentially provide near and far field exposure estimations; however, this approach in general suffers because it lacks the reasonable characterization of the primary predictor variable, eddy diffusivity (adapted from Jayjock, et al.)[39]

Modeling and Uncertainty

There are generally two types of uncertainty impacting exposure assessment; one is the natural variability associated with a given process or task, and the other is lack of knowledge, or ignorance of input parameter values. It is the latter that drives the predicted output of these models. Recognizing and documenting the uncertainty in any assessment is crucial to the integrity of the process, and this is no less true with modeling.

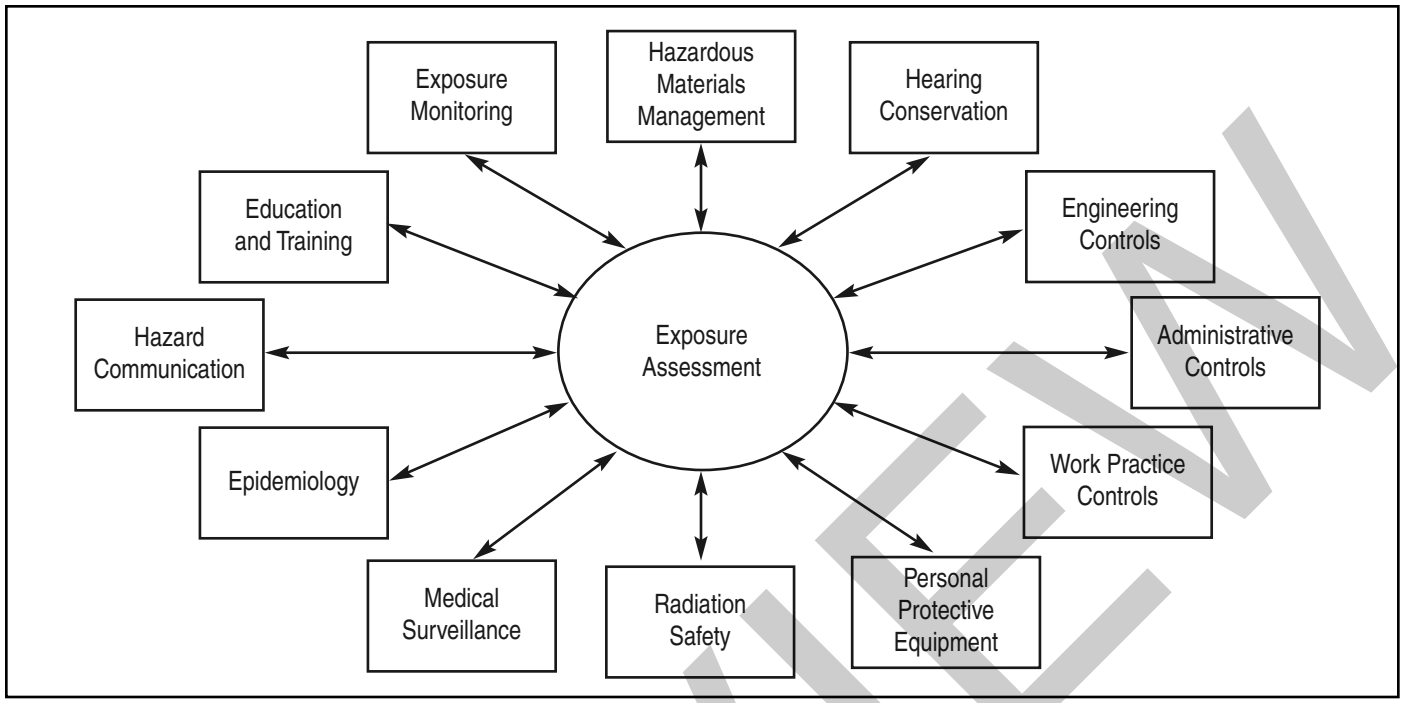

Figure 31.2 — Exposure assessment's central role in industrial hygiene[3]

When using the models deterministically, where the output is a single value, uncertainty can be incorporated and the results communicated as not less than half the predicted value and not more than twice the predicted value. The degree of confidence which the assessor can place on the result of a deterministic model application is appropriately displayed with this approach.

Probabilistic techniques allow for the degree of uncertainty to be quantified. Working with a distribution of outputs, the assessor can quantitatively express the level of confidence for a given predicted concentration. Conversely, the assessor can communicate what fraction of a given population of exposures would be expected to be above or below a given value.

Probabilistic tools can also help the assessor identify the parameters that have the greatest impact on the predicted concentration, and would therefore produce the greatest change in the output when refined. This is valuable information when resources for testing are limited.

Process of Occupational Exposure Assessment

Exposure assessment in industrial hygiene is a large topic and the subject of entire books. It is central to the IH program and supports all of its elements (See Figure 31.2). AIHA® has published a "Generic Exposure Assessment Standard" which calls on OSHA to adopt such a standard.[47] The details of the steps in an OEA vary among authors and authorities; however, all versions include the same essential elements.[3,47,48] The steps include establishing an EA strategy, basic characterization of the workplace and hazards present, exposure measurement prioritization and monitoring, interpretation of EA data and institution of health hazard controls, reporting, and reassessment

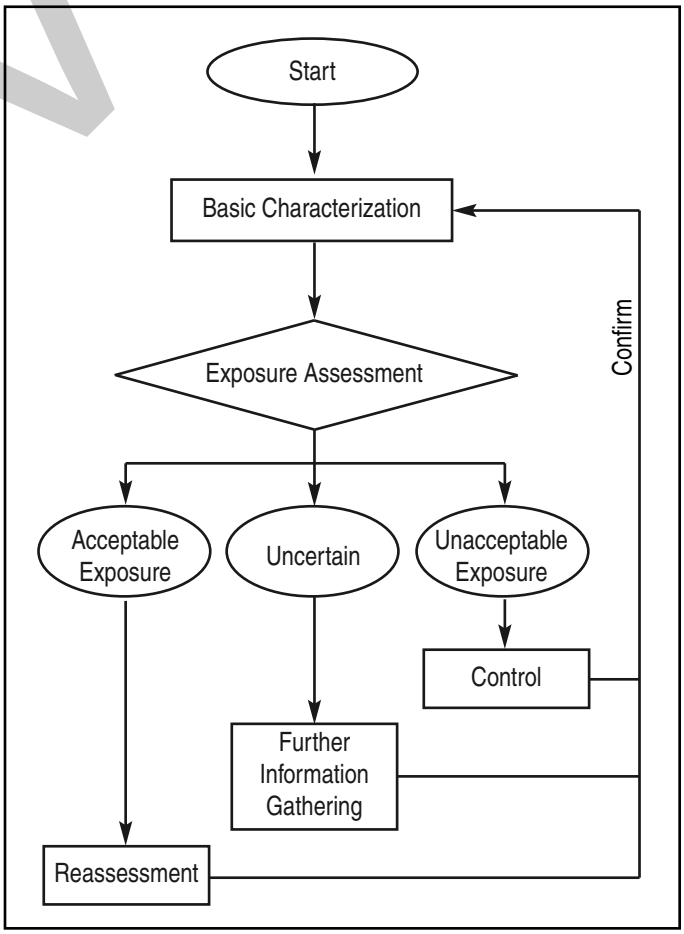

Figure 31.3 — Exposure assessment: the overall process[3]

or re-evaluation (see Figure 31.3). In reality, these steps do not necessarily occur in order in the tidy boxes that are assigned to them. The steps overlap and intertwine, and iterations occur between the steps. The following is adapted from these sources and others as noted.[3,47]

Start. An EA strategy is established. The initial EA strategy defines and documents the role of the industrial hygienist, and the exposure assessment program and goals.[3]

Basic Characterization. This is essentially an inventory of workplace, including the worker population, and physical, chemical and biological hazards present.[47] Basic characterization and qualitative assessment and prioritization are needed to narrow the range of possible substances and workers to monitor. It is rarely feasible to monitor all compounds in the workplace. Basic data gathered include information about the jobs and tasks performed, materials used, processes, and controls in place.[3]

This step usually includes developing groups of workers who are thought to be similarly exposed.[48] These homogeneous exposure groups (HEGs) are "a group of employees who experienced agent exposure similar enough that monitoring agent exposure of any worker in the group provides data useful for predicting exposure of the remaining workers".[3]

Exposure Assessment

Qualitative Exposure Assessment and Prioritization. Information collected through basic characterization is used to determine where EA is not needed, where it is needed, and prioritizing areas that require attention.[47]

Exposure Monitoring. Measurements are carried out to characterize the magnitude and variability of worker exposures that cannot be assessed with qualitative information. Exposure monitoring is conducted to provide baseline data, but is also used to evaluate workplace controls, ensure regulatory compliance, and inform management and workers.

Exposure monitoring may be conducted for compliance with OELs, implementation of an IH program, epidemiologic studies, complaint or problem investigation, worker compensation/toxic tort cases, task/source investigations, RA and management, and evaluation of changes in the workplace.[48] Although the reasons for exposure monitoring appear to be different, the questions in most cases are the same: what is the exposure, what is the potential dose, and can it have an adverse effect at exposure conditions found in the environment studied. The complexity increases as more substances are present; the subject of mixtures is addressed in Chapter 22.

Exposure monitoring is at the center of EA and is the main focus of this chapter. Although methods exist to estimate exposures using agent information and models, exposure monitoring provides input data for these models and is needed to validate the models and calculated exposures.

Interpretation and Decision Making, Health Hazard Control. All of the information from the first three steps is used to determine the acceptability of worker exposures. Prioritized control strategies are implemented for unacceptable exposures. Industrial hygiene control programs are changed and adjusted based on the information gleaned from the previous EA steps.

Further Information Gathering. Additional exposure monitoring or health effects data are collected to resolve uncertain exposures. Exposure monitoring may include personal monitoring or biological monitoring. Mathematical modeling techniques may be used to estimate exposures for new processes and products. It may be necessary to research and collect toxicological and epidemiological data for some agents. Consultation with occupational physicians and toxicologists may be indicated.

Recommendations and Reporting. Recommendations are made based on all information and interpretation, and documented for future reference.

Re-evaluation. Reassessments may need to be made after process or work practice changes, or introduction of new hazards. Similar or homogenous exposure groups may need to be updated after changes that cause rearrangement of these exposure groups that alter their exposure profile.

Exposure Assessment Research Needs

NIOSH has identified priorities in research related to the field of exposure assessment.[5] They recommend research be focused in the areas of study design, on monitoring methods, applied toxicology, and education and communication. Advancing the science of exposure assessment can result in improved: identification of at-risk workers; cost-effective control and intervention strategies; and, improved baseline data for standard setting and RA.

Study Design

The success of any exposure assessment rests on the study design and sampling strategy. Research is needed to refine job exposure matrices, and a national occupational exposure survey of current conditions with continuous updates is called for. Continued research on statistical analysis of exposure data is also a priority.

Monitoring Methods

The first priority is the development of guidelines to evaluate monitoring methods. Development is needed in the areas of dermal exposure assessment, biomonitoring methods, and rapidly deployable field methods.

Applied Toxicology

The first priority is mechanistic research on chemical, physical, and biological agents. The next priority is the need for a toxicity assessment protocol. The third priority is for development and evaluation of pharmacokinetic and predictive models. The final need is a call for more research on a general toxicology approach to assess exposures to mixtures.

Education and Communication

Research is needed to evaluate the curricula of occupational safety and health programs relative to exposure assessment and

to address the effect of external requirements (i.e., Accreditation Board for Engineering and Technology, ABET) on these curricula. Lastly, research is needed to determine the best means of communicating exposure assessment issues and results.

Computational Exposure Assessment Research Needs

In the past, exposure and RAs have been limited to situations in which either a substance had been implicated in some adverse health effect, or new toxicological findings indicate that a substance has new and potentially dreaded adverse health effects. This approach addresses risks after the fact; after some untoward effect has occurred. The reactive approach to exposure and RA did not require the explicit use of modeling thus model development and refinement was not at the forefront of scientific research. However, pressure to embrace a more proactive approach has resulted in enactment of regulations in the European Union and Canada that require a proactive and comprehensive approach to assessing risk to chemicals which may impact consumer as well as occupational exposures. These new regulations will require increased use of computational EA and this will likely result in improvement and expansion of existing methods of computational EA.

Summary

Exposure assessment is at the heart of industrial hygiene and is critical to the recognition, evaluation and control of hazardous exposures in the workplace, but is also applicable to exposures in the general environment, including homes and outdoors. Fundamental to OEA is an understanding of the underlying toxicological relationships between workplace exposure and internal dose, and target-organ dose, pre-clinical and clinical effects. Since the interaction between the toxicity and the exposure is key to determining health risk, EA and RA are overlapping and inseparable for the industrial hygienist.

Although the classical industrial hygiene OEA involves agents in the industrial workplace, the scope of OEA has become much broader over the last fifteen to twenty years because of changes in technology and increased attention to non-industrial work environments.

Monitoring, or actual measurement of potential exposure, is often the central activity for exposure assessment in industrial hygiene. In order for environmental monitoring to represent human exposure, the assessment method must be designed to measure substances in a way that mimics human exposure, e.g., air samples are collected to evaluate inhalation exposures and surface samples are collected to evaluate dermal exposure.

Exposure measurement methods can be generally grouped into the categories of inhalation, dermal, and biological exposure assessment. However, there are substances for which more than one route of exposure is possible. Exposures can also be assessed using computational programs that "model" or estimate exposures using existing exposure data, or source strength and related data.

The process or steps in an EA include: establishing an EA strategy, basic characterization of the workplace and hazards present, exposure measurement prioritization and monitoring, interpretation of EA data and institution of health hazard controls, reporting, and reassessment or re-evaluation.

NIOSH has identified priorities in research related to the field of exposure assessment, which include the areas of study design, monitoring methods, applied toxicology, and education and communication.

There are many opportunities for improving the nescient science of exposure modeling including developing peer reviewed, publicly available parameter data and establishing standardized methods for collecting the data. These data will also facilitate the much needed critical evaluation of the existing models, helping researchers better understand the bounds of their applicability, and promote the refinement of these and development of new models.

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