University of Nebraska Lincoln

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TOXICOLOGY AND EXPOSURE GUIDELINES

(For assistance, please contact EHS at (402) 472-4925, or visit our web site at http://ehs.unl.edu/)

"All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy."

This early observation concerning the toxicity of chemicals was made by Paracelsus (1493-1541). The classic connotation of toxicology was "the science of poisons." Since that time, the science has expanded to encompass several disciplines. Toxicology is the study of the interaction between chemical agents and biological systems. While the subject of toxicology is quite complex, it is necessary to understand the basic concepts in order to make logical decisions concerning the protection of personnel from toxic injuries.

Toxicity can be defined as the relative ability of a substance to cause adverse effects in living organisms. This "relative ability is dependent upon several conditions. As Paracelsus suggests, the quantity or the dose of the substance determines whether the effects of the chemical are toxic, nontoxic or beneficial. In addition to dose, other factors may also influence the toxicity of the compound such as the route of entry, duration and frequency of exposure, variations between different species (interspecies) and variations among members of the same species (intraspecies). To apply these principles to hazardous materials response, the routes by which chemicals enter the human body will be considered first. Knowledge of these routes will support the selection of personal protective equipment and the development of safety plans. The second section deals with dose-response relationships. Since dose-response information is available in toxicology and chemistry reference books, it is useful to understand the relevance of these values to the concentrations that are actually measured in the environment. The third section of this chapter includes the effects of the duration and frequency of exposure, interspecies variation and intraspecies variation on toxicity. Finally, toxic responses associated with chemical exposures are described according to each organ system.

Routes of Exposure

There are four routes by which a substance can enter the body: inhalation, skin (or eye) absorption, ingestion, and injection.

- **Inhalation**: For most chemicals in the form of vapors, gases, mists, or particulates, inhalation is the major route of entry. Once inhaled, chemicals are either exhaled or deposited in the respiratory tract. If deposited, damage can occur through direct contact with tissue or the chemical may diffuse into the blood through the lung-blood interface. Upon contact with tissue in the upper respiratory tract or lungs, chemicals may cause health effects ranging from simple irritation to severe tissue destruction. Substances absorbed into the blood are circulated and distributed to organs that have an affinity for

that particular chemical. Health effects can then occur in the organs, which are sensitive to the toxicant.

- **Skin (or eye) absorption**: Skin (dermal) contact can cause effects that are relatively innocuous such as redness or mild dermatitis; more severe effects include destruction of skin tissue or other debilitating conditions. Many chemicals can also cross the skin barrier and be absorbed into the blood system. Once absorbed, they may produce systemic damage to internal organs. The eyes are particularly sensitive to chemicals. Even a short exposure can cause severe effects to the eyes or the substance can be absorbed through the eyes and be transported to other parts of the body causing harmful effects.
- **Ingestion**: Chemicals that inadvertently get into the mouth and are swallowed do not generally harm the gastrointestinal tract itself unless they are irritating or corrosive. Chemicals that are insoluble in the fluids of the gastrointestinal tract (stomach, small, and large intestines) are generally excreted. Others that are soluble are absorbed through the lining of the gastrointestinal tract. They are then transported by the blood to internal organs where they can cause damage.
- **Injection**: Substances may enter the body if the skin is penetrated or punctured by contaminated objects. Effects can then occur as the substance is circulated in the blood and deposited in the target organs.

Once the chemical is absorbed into the body, three other processes are possible: metabolism, storage, and excretion. Many chemicals are metabolized or transformed via chemical reactions in the body. In some cases, chemicals are distributed and stored in specific organs. Storage may reduce metabolism and therefore, increase the persistence of the chemicals in the body. The various excretory mechanisms (exhaled breath, perspiration, urine, feces, or detoxification) rid the body, over a period of time, of the chemical. For some chemicals elimination may be a matter of days or months; for others, the elimination rate is so low that they may persist in the body for a lifetime and cause deleterious effects.

The Dose-Response Relationship

In general, a given amount of a toxic agent will elicit a given type and intensity of response. The dose-response relationship is a fundamental concept in toxicology and the basis for measurement of the relative harmfulness of a chemical. A dose-response relationship is defined as a consistent mathematical and biologically plausible correlation between the number of individuals responding and a given dose over an exposure period.

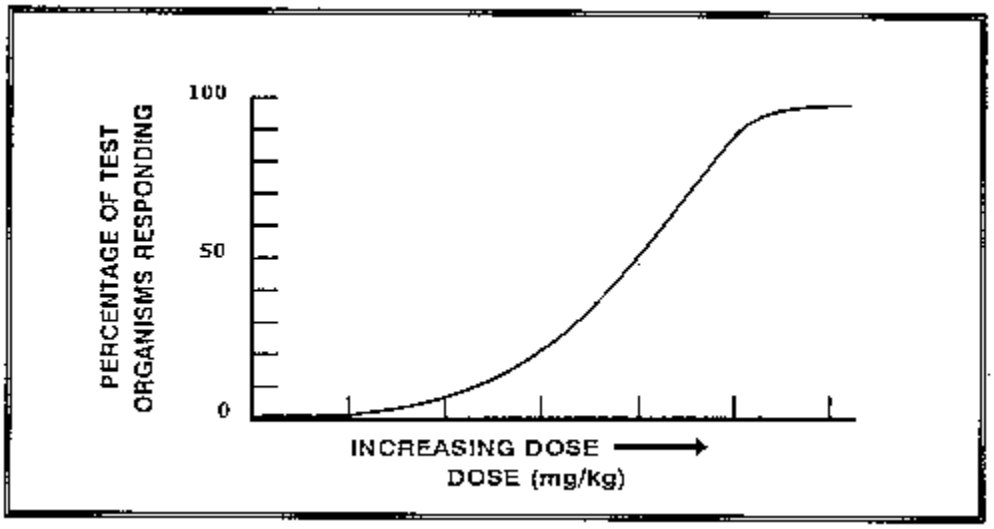
Dose Terms. In toxicology, studies of the dose given to test organisms is expressed in terms of the quantity administered:

- **Quantity per unit mass (or weight)**. Usually expressed as milligram per kilogram of body weight (mg/kg).
- **Quantity per unit area of skin surface**. Usually expressed as milligram per square centimeter (mg/cm^2).
- **Volume of substance in air per unit volume of air**. Usually given as microliters of vapor or gas per liter of air by volume (ppm). Particulates and gases are also given as milligrams of material per cubic meter of air (mg/m^3).

The period of time over which a dose has been administered is generally specified. For example, 5 mg/kg/3 D is 5 milligrams of chemical per kilogram of the subject's body weight administered over a period of three days. For dose to be meaningful it must be related to the effect it causes. For example, 50 mg/kg of chemical "X" administered orally to female rats has no relevancy unless the effect of the dose, say sterility in all test subjects, is reported.

Dose-Response Curves. A dose-response relationship is represented by a dose-response curve. The curve is generated by plotting the dose of the chemical versus the response in the test population. There are a number of ways to present this data. One of the more common methods for presenting the dose-response curve is shown in **Graph 1**. In this example, the dose is expressed in "mg/kg" and depicted on the "x" axis. The response is expressed as a "cumulative percentage" of animals in the test population that exhibits the specific health effect under study. Values for "cumulative percentage" are indicated on the "y" axis of the graph. As the dose increases, the percentage of the affected population increases.

Dose-response curves provide valuable information regarding the potency of the compound. The curves are also used to determine the dose-response terms that are discussed in the following section.



Graph 1
Hypothetical Dose-Response Curve

Dose-Response Terms. The National Institute for Occupational Safety and Health (NIOSH) defines a number of general dose-response terms in the "Registry of Toxic Substances" (1983, p. xxxii). A summary of these terms is contained in **Table 1**.

- **Toxic dose low (TD_{LO})**: The lowest dose of a substance introduced by any route, other than inhalation, over any given period of time, and reported to produce any toxic effect in humans or to produce tumorigenic or reproductive effects in animals.
- **Toxic concentration low (TC_{LO})**: The lowest concentration of a substance in air to which humans or animals have been exposed for any given period of time that has

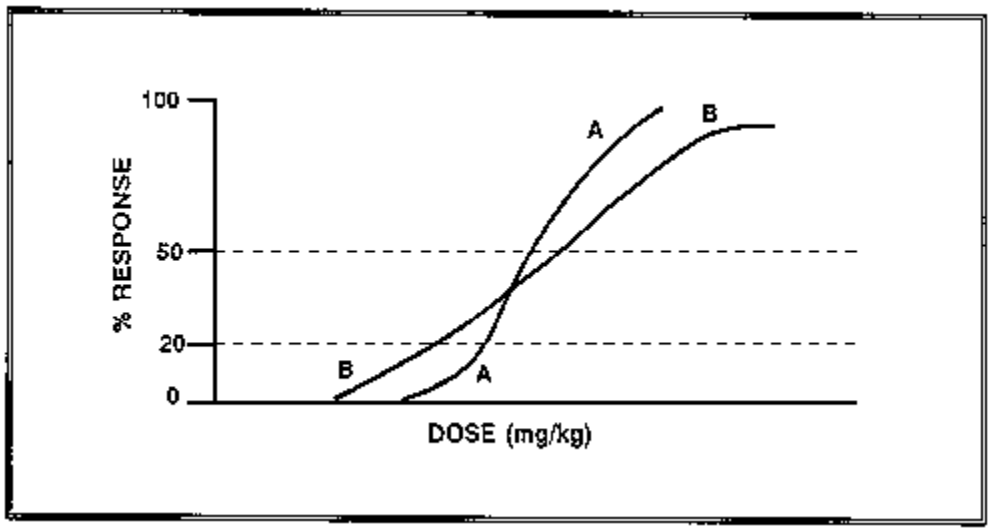
produced any toxic effect in humans or produced tumorigenic or reproductive effects in animals.

- **Lethal dose low (LD_{LO})**: The lowest dose, other than LD_{50} of a substance introduced by any route, other than inhalation, which has been reported to have caused death in humans or animals.
- **Lethal dose fifty (LD_{50})**: A calculated dose of a substance which is expected to cause the death of 50 percent of an entire defined experimental animal population. It is determined from the exposure to the substance by any route other than inhalation.
- **Lethal concentration low (LC_{LO})**: The lowest concentration of a substance in air, other than LC_{50}, which has been reported to cause death in humans or animals.
- **Lethal concentration fifty (LC_{50})**: A calculated concentration of a substance in air, exposure to which for a specified length of time is expected to cause the death of 50 percent of an entire defined experimental animal population.

Limitations of Dose-Response Terms. Several limitations must be recognized when using dose-response data. First, it is difficult to select a test species that will closely duplicate the human response to a specific chemical. For example, human data indicates that arsenic is a carcinogen, while animal studies do not demonstrate these results. Second, most lethal and toxic dose data are derived from acute (single dose, short-term) exposures rather than chronic (continuous, long-term) exposures. A third shortcoming is that the LD_{50} or LC_{50} is a single value and does not indicate the toxic effects that may occur at different dose levels. For example, in **Graph 2** Chemical A is assumed to be more toxic than Chemical B based on LD_{50}, but at lower doses the situation is reversed. At LD_{20}, Chemical B is more toxic than Chemical A.

TABLE 1
Summary of Dose-Response Terms

Category	Exposure Time	Route of Exposure	Toxic Effects	
			Human	Animal
TD_{LO}	Acute or chronic	All except inhalation	Any nonlethal	Reproductive, Tumorigenic
TC_{LO}	Acute or chronic	Inhalation	Any nonlethal	Reproductive, Tumorigenic
LD_{LO}	Acute or chronic	All except inhalation	Death	Death
LD_{50}	Acute	All except inhalation	Not applicable	Death (statistically determined)
LC_{LO}	Acute or chronic	Inhalation	Death	Death
LC_{50}	Acute	Inhalation	Not applicable	Death (statistically determined)



Graph 2
Comparison of Dose-Response Curves for Two Substances

Factors Influencing Toxicity. Many factors affect the reaction of an organism to a toxic chemical. The specific response that is elicited by a given dose varies depending on the species being tested and variations that occur among individuals of the same species. These must be considered when using information such as that found in (**Table 2**).

- **Duration and Frequency of Exposure**. There is a difference in type and severity of effects depending on how rapidly the dose is received (duration) and how often the dose is received (frequency). Acute exposures are usually single incidents of relatively short duration--a minute to a few days. Chronic exposures involve frequent doses at relatively low levels over a period of time ranging from months to years.
  If a dose is administered slowly so that the rate of elimination or the rate of detoxification keeps pace with intake, it is possible that no toxic response will occur. The same dose could produce an effect with rapid administration.

TABLE 2
Classification of Factors Influencing Toxicity

Type	Examples
Factors related to the chemical	Composition (salt, free base, etc.); physical characteristics (particle size, liquid, solid, etc.); physical properties (volatility, solubility, etc.); presence of impurities; break down products; carrier.
Factors related to exposure	Dose; concentration; route of exposure (ingestion, skin absorption, injection, inhalation); duration.
Factors related to person exposed	Heredity; immunology; nutrition; hormones; age; sex; health status; preexisting diseases.
Factors related	Carrier (air, water, food, soil); additional chemical present (synergism,

to environment	antagonism); temperature; air pressure.

- **Routes of Exposure**. Biological results can be different for the same dose, depending on whether the chemical is inhaled, ingested, applied to the skin, or injected. Natural barriers impede the intake and distribution of material once in the body. These barriers can attenuate the toxic effects of the same dose of a chemical. The effectiveness of these barriers is partially dependent upon the route of entry of the chemical.
- **Interspecies Variation**. For the same dose received under identical conditions, the effects exhibited by different species may vary greatly. A dose which is lethal for one species may have no effect on another. Since the toxicological effects of chemicals on humans is usually based on animal studies, a test species must be selected that most closely approximates the physiological processes of humans.
- **Intraspecies Variations**. Within a given species, not all members of the population respond to the same dose identically. Some members will be more sensitive to the chemical and elicit response at lower doses than the more resistant members which require larger doses for the same response.
    - Age and Maturity. Infants and children are often more sensitive to toxic action than younger adults. Elderly persons have diminished physiological capabilities for the body to deal with toxic insult. These age groups may be more susceptible to toxic effects at relatively lower doses.
    - Gender and Hormonal Status. Some chemicals may be more toxic to one gender than the other. Certain chemicals can affect the reproductive system of either the male or female. Additionally, since women have a larger percentage of body fat than men, they may accumulate more fat-soluble chemicals. Some variations in response have also been shown to be related to physiological differences between males and females.
    - Genetic Makeup. Genetic factors influence individual responses to toxic substances. If the necessary physiological processes are diminished or defective the natural body defenses are impaired. For example, people lacking in the G6PD enzyme (a hereditary abnormality) are more likely to suffer red blood cell damage when given aspirin or certain antibiotics than persons with the normal form of the enzyme.
    - State of Health. Persons with poor health are generally more susceptible to toxic damage due to the body's decreased capability to deal with chemical insult.
- **Environmental Factors**. Environmental factors may contribute to the response for a given chemical. For example, such factors as air pollution, workplace conditions, living conditions, personal habits, and previous chemical exposure may act in conjunction with other toxic mechanisms.
- **Chemical Combinations**. Some combinations of chemicals produce different effects from those attributed to each individually:
    - Synergists: chemicals that, when combined, cause a greater than additive effect. For example, hepatotoxicity is enhanced as a result of exposure to both ethanol and carbon tetrachloride.
    - Potentiation: is a type of synergism where the potentiator is not usually toxic in itself, but has the ability to increase the toxicity of other chemicals. Isopropanol,

for example, is not hepatotoxic in itself. Its combination with carbon tetrachloride, however, increases the toxic response to the carbon tetrachloride.

- Antagonists: chemicals, that when combined, lessen the predicted effect. There are four types of antagonists.
    1. functional: Produces opposite effects on the same physiologic function. For example, phosphate reduces lead absorption in the gastrointestinal tract by forming insoluble lead phosphate.
    2. chemical: Reacts with the toxic compound to form a less toxic product. For example, chelating agents bind up metals such as lead, arsenic, and mercury.
    3. dispositional: Alters absorption, metabolism, distribution, or excretion. For example, some alcohols use the same enzymes in their metabolism:
       ethanol--------> acetaldehyde-------> acetic acid
       methanol------> formaldehyde------> formic acid
       The aldehydes cause toxic effects (hangover, blindness). Ethanol is more readily metabolized than methanol, so when both are present, methanol is not metabolized and can be excreted before forming formaldehyde. Another dispositional antagonist is Antabuse which, when administered to alcoholics, inhibits the metabolism of acetaldehyde, giving the patient a more severe prolonged hangover.
    4. receptor: Occurs when a second chemical either binds to the same tissue receptor as the toxic chemical or blocks the action of receptor and thereby reduces the toxic effect. For example, atropine interferes with the receptor responsible for the toxic effects of organophosphate pesticides.

Sources of Toxicity Information

Information on the toxic properties of chemical compounds and dose-response relationships is obtained from animal studies, epidemiological investigations of exposed human populations, and clinical studies or case reports of exposed humans.

- **Toxicity Tests**. The design of any toxicity test incorporates:
    - a test organism, which can range from cellular material and selected strains of bacteria through higher order plants and animals
    - a response or biological endpoint, which can range from subtle changes in physiology and behavior to death
    - an exposure or test period
    - a dose or series of doses.

  The objective is to select a test species that is a good model of humans, a response that is not subjective and can be consistently determined for a given dose, and a test period that is relatively short.
- **Epidemiological and Clinical Studies**. Epidemiological investigations and clinical cases are another means of relating human health effects and exposure to toxic substances. Epidemiological investigations are based upon a human population exposed to a chemical compared to an appropriate, nonexposed group. An attempt is made to determine whether there is a statistically significant association between health effects and chemical exposure. Clinical cases involve individual reports of chemical exposure.

Uses of Toxicity Information

Comparison of Toxicity Data. Comparing the LD_{50} of chemicals in animals gives a relative ranking of potency or toxicity of each. For example, DDT (LD_{50} for rats = 113 mg/kg) would be considered more toxic than ethyl alcohol (LD_{50} for rats = 14,000 mg/kg). Using the LD_{50} (mg/kg) for a test species and multiplying by 70 kg (average mass of man) gives a rough estimate of the toxic potential of the substance for humans, assuming that humans are as sensitive as the subjects tested.

Because the extrapolation of human data from animal studies is complex, this value should only be considered as an approximation for the potency of the compound and used in conjunction with additional data **(Tables 3 and 4)**.

Establishing Exposure Guidelines. Toxicity data from both animal experimentation and epidemiological studies is used to establish exposure guidelines. The method for deriving a guideline is dependent upon the type of chemical as well as duration and frequency of exposure. It is also important to make the distinction between an experimental dose (mg/kg) and an environmental concentration (mg/m^3 or ppm). In order to make safety decisions, exposure guidelines are presented as concentrations so that these values can be compared to concentrations measured by air monitoring instrumentation.

TABLE 3
Toxicity Rating

Toxicity Rating or Class	Oral Acute LD_{50} for Rats
Extremely toxic	1 mg/kg or less (dioxin, botulinum toxin)
Highly toxic	1 to 50 mg/kg (strychnine)
Moderately toxic	50 to 500 mg/kg (DDT)
Slightly toxic	0.5 to 5 g/kg (morphine)
Practically nontoxic	5 to 15 g/kg (ethyl alcohol)

TABLE 4
LD_{50} Values for Rats for a Group of Well-Known Chemicals

Chemical	LD_{50} (mg/kg)
Sucrose (table sugar)	29,700
Ethyl alcohol	14,000
Sodium chloride (common salt)	3,000
Vitamin A	2,000
Vanillin	1,580
Aspirin	1,000
Chloroform	800

Copper sulfate	300
Caffeine	192
Phenobarbital, sodium salt	162
DDT	113
Sodium nitrite	85
Nicotine	53
Aflatoxin B1	7
Sodium cyanide	6.4
Strychnine	2.5

Health Effects

Human health effects caused by exposure to toxic substances fall into two categories: short-term and long-term effects. Short-term effects (or acute effects) have a relatively quick onset (usually minutes to days) after brief exposures to relatively high concentrations of material (acute exposures). The effect may be local or systemic. Local effects occur at the site of contact between the toxicant and the body. This site is usually the skin or eyes, but includes the lungs if irritants are inhaled or the gastrointestinal tract if corrosives are ingested. Systemic effects are those that occur if the toxicant has been absorbed into the body from its initial contact point, transported to other parts of the body, and cause adverse effects in susceptible organs. Many chemicals can cause both local and systemic effects.

Long-term effects (or **chronic effects**) are those with a long period of time (years) between exposure and injury. These effects may occur after apparent recovery from acute exposure or as a result of repeated exposures to low concentrations of materials over a period of years (chronic exposure).

Health effects manifested from acute or chronic exposure are dependent upon the chemical involved and the organ it effects. Most chemicals do not exhibit the same degree of toxicity for all organs.

Usually the major effects of a chemical will be expressed in one or two organs. These organs are known as target organs which are more sensitive to that particular chemical than other organs. The organs of the body and examples of effects due to chemical exposures are listed below.

Respiratory Tract. The respiratory tract is the only organ system with vital functional elements in constant, direct contact-with the environment. The lung also has the largest exposed surface area of any organ on a surface area of 70 to 100 square meters versus 2 square meters for the skin and 10 square meters for the digestive system.

The respiratory tract is divided into three regions: (1) Nasopharyngeal--extends from nose to larynx. These passages are lined with ciliated epithelium and mucous glands. They filter out large inhaled particles, increase the relative humidity of inhaled air, and moderate its temperature. (2) Tracheobronchial--consists of trachea, bronchi, and bronchioles and serves as

conducting airway between the nasopharyngeal region and alveoli. These passage ways are lined with ciliated epithelium coated by mucous, which serves as an escalator to move particles from deep in the lungs back up to the oral cavity so they can be swallowed. These ciliated cells can be temporarily paralyzed by smoking or using cough suppressants. (3) Pulmonary acinus--is the basic functional unit in the lung and the primary location of gas exchange. It consists of small bronchioles which connect to the alveoli. The alveoli, of which there are 100 million in humans, contact the pulmonary capillaries.
Inhaled particles settle in the respiratory tract according to their diameters:

- 5-30 micron particles are deposited in the nasopharyngeal region.
- 1-5 micron particles are deposited in the tracheobronchial region.
- Less than 1 micron particles are deposited in the alveolar region by diffusion and Brownian motion.

In general, most particles 5-10 microns in diameter are removed. However, certain small inorganic particles, settle into smaller regions of the lung and kill the cells which attempt to remove them. The result is fibrous lesions of the lung.

Many chemicals used or produced in industry can produce acute or chronic diseases of the respiratory tract when they are inhaled **(Table 5)**. The toxicants can be classified according to how they affect the respiratory tract.

- **Asphyxiants**: gases that deprive the body tissues of oxygen
- **Simple asphyxiants** are physiologically inert gases that at high concentrations displace air leading to suffocation. Examples: nitrogen, helium, methane, neon, argon.
- **Chemical asphyxiants** are gases that prevent the tissues from getting enough oxygen. Examples: carbon monoxide and cyanide. Carbon monoxide binds to hemoglobin 200 times more readily than oxygen. Cyanide prevents the transfer of oxygen from blood to tissues by inhibiting the necessary transfer enzymes.
- **Irritants**: chemicals that irritate the air passages. Constriction of the airways occurs and may lead to edema (liquid in the lungs) and infection. Examples: hydrogen fluoride, chlorine, hydrogen chloride, and ammonia.
- **Necrosis producers**: Chemicals that result in cell death and edema. Examples: ozone and nitrogen dioxide.
- **Fibrosis producers**: Chemicals that produce fibrotic tissue which, if massive, blocks airways and decreases lung capacity. Examples: silicates, asbestos, and beryllium.
- **Allergens**: Chemicals that induce an allergic response characterized by bronchoconstriction and pulmonary disease. Examples: isocyanates and sulfur dioxide.
- **Carcinogens**: Chemicals that are associated with lung cancer. Examples: cigarette smoke, coke oven emissions, asbestos, and arsenic.

Not only can various chemicals affect the respiratory tract, but the tract is also a route for chemicals to reach other organs. Solvents, such as benzene and tetrachloroethane, anesthetic gases, and many other chemical compounds can be absorbed through the respiratory tract and cause systemic effects.

TABLE 5
Examples of Industrial Toxicants that Produce Disease of the Respiratory Tract

Toxicant	Site of Action	Acute Effect	Chronic Effect
Ammonia	Upper Airways	Irritation, edema	Bronchitis
Arsenic	Upper Airways	Bronchitis, irritation, pharyngitis	Cancer, bronchitis, laryngitis
Asbestos	Lung parenchyma	--	Fibrosis, cancer
Chlorine	Upper airways	Cough, irritation, asphyxiant (by muscle cramps in larynx)	--
Isocyanates	Lower airways, alveoli	Bronchitis, pulmonary edema, asthma	--
Nickel Carbony	Alveoli	Edema (delayed symptoms)	--
Ozone	Bronchi, alveoli	Irritation, edema, hemorrhage	Emphysema, bronchitis
Phosgene	Alveoli	Edema	Bronchitis, fibrosis, pneumonia
Toluene	Upper airways	Bronchitis, edema, bronchospasm	--
Xylene	Lower airways	Edema, hemorrhage	--

Skin. The skin is, in terms of weight, the largest single organ of the body. It provides a barrier between the environment and other organs (except the lungs and eyes) and is a defense against many chemicals.

The skin consists of the epidermis (outer layer) and the dermis (inner layer). In the dermis are sweat glands and ducts, sebaceous glands, connective tissue, fat, hair follicles, and blood vessels. Hair follicles and sweat glands penetrate both the epidermis and dermis. Chemicals can penetrate through the sweat glands, sebaceous glands, or hair follicles.

Although the follicles and glands may permit a small amount of chemicals to enter almost immediately, most pass through the epidermis, which constitutes the major surface area. The top layer is the stratum corneum, a thin cohesive membrane of dead surface skin. This layer turns over every 2 weeks by a complex process of cell dehydration and polymerization of intracellular material. The epidermis plays the critical role in skin permeability.

Below the epidermis lies the dermis, a collection of cells providing a porous, watery, nonselective diffusion medium. Intact skin has a number of functions:

- Epidermis: Prevents absorption of chemicals and is a physical barrier to bacteria.
- Sebaceous glands: Secrete fatty acids which are bacteriostatic and fungistatic.
- Melanocytes (skin pigment): Prevent damage from ultraviolet radiation in sunlight.
- Sweat glands: Regulate heat.

- Connective tissue: Provides elasticity against trauma.
- Lymph-blood system: Provide immunologic responses to infection.

The ability of skin to absorb foreign substances depends on the properties and health of the skin and the chemical properties of the substances. Absorption is enhanced by:

- Breaking top layer of skin by abrasions or cuts.
- Increasing hydration of skin.
- Increasing temperature of skin which causes sweat cells to open up and secrete sweat, which can dissolve solids.
- Increasing blood flow to skin.
- Increasing concentrations of the substance.
- Increasing contact time of the chemical on the skin.
- Increasing the surface area of affected skin.
- Altering the skin's normal pH of 5.
- Decreasing particle size of substance.
- Adding agents which will damage skin and render it more susceptible to penetration.
- Adding surface-active agents or organic chemicals. DMSO, for example, can act as a carrier of the substance.
- Inducing ion movement by an electrical charge.

Absorption of a toxic chemical through the skin can lead to **local effects** through direct contact, such as irritation and necrosis, and **systemic effects**.
Many chemicals can cause a reaction with the skin resulting in inflammation called dermatitis. These chemicals are divided into three categories:

- **Primary irritants**: Act directly on normal skin at the site of contact (if chemical is in sufficient quantity for a sufficient length of time). Skin irritants include: acetone, benzyl chloride, carbon disulfide, chloroform, chromic acid and other soluble chromium compounds, ethylene oxide, hydrogen chloride, iodine, methyl ethyl ketone, mercury, phenol, phosgene, styrene, sulfur dioxide, picric acid, toluene, xylene.
- **Photosensitizers**: Increase in sensitivity to light, which results in irritation and redness. Photosensitizers include: tetracyclines, acridine, creosote, pyridine, furfural, and naphtha.
- **Allergic sensitizers**: May produce allergic-type reaction after repeated exposures. They include: formaldehyde, phthalic anhydride, ammonia, mercury, nitrobenzene, toluene diisocyanate, chromic acid and chromates, cobalt, and benzoyl peroxide.

Eyes. The eyes are affected by the same chemicals that affect skin, but the eyes are much more sensitive. Many materials can damage the eyes by direct contact:

- **Acids**: Damage to the eye by acids depends on pH and the protein-combining capacity of the acid. Unlike alkali burns, the acid burns that are apparent during the first few hours are a good indicator of the long-term damage to be expected. Some acids and their properties are:

    - sulfuric acid. In addition to its acid properties, it simultaneously removes water and generates heat.
    - picric acid and tannic acid. No difference in damage they produce in entire range of acidic pHs.
    - hydrochloric acid. Severe damage at pH 1, but no effect at pH 3 or greater.
- Alkalies: Damage that appears mild initially but can later lead to ulceration, perforation, and clouding of the cornea or lens. The pH and length of exposure have more bearing on the amount of damage than the type of alkali. Some problem alkalies are:
    - sodium hydroxide (caustic soda) and potassium hydroxide.
    - ammonia penetrates eye tissues more readily than any other alkali; calcium-oxide (lime) forms clumps when it contacts eye tissue and is very hard to remove.
- Organic solvents: Organic solvents (for example, ethanol, toluene, and acetone) dissolve fats, cause pain, and dull the cornea. Damage is usually slight unless the solvent is hot.
- Lacrimators: Lacrimators cause instant tearing at low concentrations. They are distinguished from other eye irritants (hydrogen chloride and ammonia) because they induce an instant reaction without damaging tissues. At very high concentrations lacrimators can cause chemical burns and destroy corneal material. Examples are chloroacetophenone (tear gas) and mace.

In addition, some compounds act on eye tissue to form cataracts, damage the optic nerve, or damage the retina. These compounds usually reach the eye through the blood having been inhaled, ingested or absorbed rather than direct contact. Examples of compounds that can provide systemic effects damaging to the eyes are:

- Naphthalene: Cataracts and retina damage.
- Phenothiazine (insecticide): Retina damage
- Thallium: cataracts and optic nerve damage.
- Methanol: Optic nerve damage.

Central Nervous System. Neurons (nerve cells) have a high metabolic rate but little capacity for anaerobic metabolism. Subsequently, inadequate oxygen flow (anoxia) to the brain kills cells within minutes. Some may die before oxygen or glucose transport stops completely.

Because of their need for oxygen, nerve cells are readily affected by both simple asphyxiants and chemical asphyxiants. Also, their ability to receive adequate oxygen is affected by compounds that reduce respiration and thus reduce oxygen content of the blood (barbiturates, narcotics). Other examples are compounds such as arsine, nickel, ethylene chlorohydrin, tetraethyl lead, aniline, and benzene that reduce blood pressure or flow due to cardiac arrest, extreme hypotension, hemorrhaging, or thrombosis.

Some compounds damage neurons or inhibit their function through specific action on parts of the cell. The major symptoms from such damage include: dullness, restlessness, muscle tremor, convulsions, loss of memory, epilepsy, idiocy, loss of muscle coordination, and abnormal sensations. Examples are:

- Fluoroacetate: Rodenticide.

- Triethyltin: Ingredient of insecticides and fungicides.
- Hexachlorophene: Antibacterial agent.
- Lead: Gasoline additive and paint ingredient.
- Thallium: Sulfate used as a pesticide and oxide or carbonate used in manufacture of optical glass and artificial gems.
- Tellurium: Pigment in glass and porcelain.
- Organomercury compounds: Methyl mercury used as a fungicide; is also a product of microbial action on mercury ions. Organomercury compounds are especially hazardous because of their volatility and their ability to permeate tissue barriers.

Some chemicals are noted for producing weakness of the lower extremities and abnormal sensations (along with previously mentioned symptoms):

- Acrylamide: Soil stabilizer, waterproofer.
- Carbon disulfide: Solvent in rayon and rubber industries.
- n-Hexane: Used as a cleaning fluid and solvent. Its metabolic product, hexanedione, causes the effects.
- Organophosphorus compounds: Often used as flame retardants (triorthocresyl phosphate) and pesticides (Leptofor and Mipafox).

Agents that prevent the nerves from producing proper muscle contraction and may result in death from respiratory paralysis are DDT, lead, botulinum toxin, and allethrin (a synthetic insecticide). DDT, mercury, manganese, and monosodium glutamate also produce personality disorders and madness.

Liver. Liver injury induced by chemicals has been known as a toxicologic problem for hundreds of years. It was recognized early that liver injury is not a simple entity, but that the type of lesion depends on the chemical and duration of exposure. Three types of response to hepatotoxins can be identified:

- **Acute**. Cell death from:
    - carbon tetrachloride: Solvent, degreaser.
    - chloroform: Used in refrigerant manufacture solvent.
    - trichloroethylene: Solvent, dry cleaning fluid, degreaser.
    - tetrachloroethane: Paint and varnish remover, dry cleaning fluid.
    - bromobenzene: Solvent, motor oil additive.
    - tannic acid: Ink manufacture, beer and wine clarifier.
    - kepone: Pesticide.
- **Chronic**. Examples include:
    - cirrhosis: a progressive fibrotic disease of the liver associated with liver dysfunction and jaundice. Among agents implicated in cirrhosis cases are carbon tetrachloride, alcohol, and aflatoxin.
    - carcinomas: malignant, growing tissue. For example, vinyl chloride (used in polyvinyl chloride production) and arsenic (used in pesticides and paints) are associated with cancers.

- **Biotransformation of toxicants**. The liver is the principal organ that chemically alters all compounds entering the body. For example:
  ethanol---> acetaldehyde---> acetic acid---> water + carbon dioxide
  This metabolic action by the liver can be affected by diet, hormone activity, and alcohol consumption. Biotransformation in the liver can also lead to toxic metabolities. For example:
  carbon tetrachloride---> chloroform

Kidneys. The kidney is susceptible to toxic agents for several reasons: (1) The kidneys constitute 1 percent of the body's weight, but receive 20-25 percent of the blood flow (during rest). Thus, large amounts of circulating toxicants reach the kidneys quickly. (2) The kidneys have high oxygen and nutrient requirements because of their workload. They filter one-third of the plasma reaching them and reabsorb 98-99% of the salt and water. As they are reabsorbed, salt concentrates in the kidneys. (3) Changes in kidney pH may increase passive diffusion and thus cellular concentrations of toxicants. (4) Active secretion processes may concentrate toxicants. (5) Biotransformation is high.

A number of materials are toxic to the kidneys:

- Heavy metals, may denature proteins as well as produce cell toxicity. Heavy metals (including mercury, arsenic, gold, cadmium, lead, and silver) are readily concentrated in the kidneys, making this organ particularly sensitive.
- Halogenated organic compounds, which contain chlorine, fluorine, bromine, or iodine. Metabolism of these compounds, like that occurring in the liver, generates toxic metabolites. Among compounds toxic to the kidneys are carbon tetrachloride, chloroform, 2,4,5-T (a herbicide), and ethylene dibromide (a fumigant).
- Miscellaneous, including carbon disulfide (solvent for waxes and resins) and ethylene glycol (automobile antifreeze).

Blood. The blood system can be damaged by agents that affect blood cell production (bone marrow), the components of blood (platelets, red blood cells, and white blood cells), or the oxygen-carrying capacity of red blood cells.

Bone Marrow. Bone marrow is the source of most components in blood. Agents that suppress the function of bone marrow include:

- Arsenic, used in pesticides and paints.
- Bromine, used to manufacture gasoline antiknock compounds, ethylene dibromide, and organic dyes.
- Methyl chloride, used as a solvent, refrigerant, and aerosol propellant.
- Ionizing radiation, produced by radioactive materials and x-rays is associated with leukemia.
- Benzene, a chemical intermediate associated with leukemia.

Blood Components. Among platelets (thrombocytes) are blood components that help prevent blood loss by forming blood clots. Among chemicals that affect this action are:

- Aspirin, which inhibits cloning.
- Benzene, which decreases the number of platelets.
- Tetrachloroethane, which increases the number of platelets.

Leukocytes (white blood cells) are primarily responsible for defending the body against foreign organisms or materials by engulfing and destroying the material or by producing antibodies. Chemicals that increase the number of leukocytes include naphthalene, magnesium oxide, boron hydrides, and tetrachloroethane. Agents that decrease the number of leukocytes include benzene and phosphorous.

Erythrocytes (red blood cells) transport oxygen in the blood. Chemicals that destroy (hemolyze) red blood cells include arsine (a gaseous arsenic compound and contaminant in acetylene), naphthalene (used to make dyes), and warfarin (a rodenticide).

Oxygen Transport. Some compounds affect the oxygen carrying capabilities of red blood cells. A notable example is carbon monoxide which combines with hemoglobin to form carboxyhemoglobin. Hemoglobin has an affinity for carbon monoxide 200 times greater than that for oxygen.

While carbon monoxide combines reversibly with hemoglobin, some chemicals cause the hemoglobin to change such that it cannot combine reversibly with oxygen. This condition is called methemoglobinemia. Some chemicals that can cause this are:

- Sodium nitrite, used in meat curing and photography.
- Aniline, used in manufacture of rubber accelerators and antioxidants, resins, and varnishes.
- Nitrobenzene and dinitrobenzene, used in manufacture of dyestuffs and explosives.
- Trinitrotoluene (TNT), used in explosives.
- Mercaptans, used in manufacture of pesticides and as odorizers for hazardous odorless gases.
- 2-nitropropane, used as a solvent.

Spleen. The spleen filters bacteria and particulate matter (especially deteriorated red blood cells) from the blood. Iron is recovered from the hemoglobin for recycling. In the embryo, the spleen forms all types of blood cells. In the adult, however, it produces only certain kinds of leukocytes. Examples of chemicals that damage the spleen are:

- Chloroprene, used in production of synthetic rubber.
- Nitrobenzene, used as chemical intermediate.

Reproductive System. Experimental results indicate that certain agents interfere with the reproductive capabilities of both sexes, causing sterility, infertility, abnormal sperm, low sperm count, and/or affect hormone activity in animals. Many of these also affect human reproduction. Further study is required to identify reproductive toxins and their effects. Some examples of chemicals that have been implicated in reproductive system toxicity include:

- Male: Anesthetic gases (halothane, methoxyflurane) cadmium, mercury, lead, boron, methyl mercury, vinyl chloride, DDT, kepone, chlordane, PCBs, dioxin, 2,4-D, 2,4,5-T, carbaryl, paraquat, dibromochloropropane, ethylene dibromide, benzene, toluene, xylene, ethanol, radiation, and heat.
- Female: DDT, parathion, carbaryl, diethylstilbestrol (DES), PCBs, cadmium, methyl mercury, hexafluoroacetone, and anesthetic gases.

Types of Toxic Effects

Teratogenic. Teratology is derived from Latin and means the study of monsters. In a modern context, teratology is the study of congenital malformations. Teratology is a relatively new discipline that started in 1941 with the correlation of German measles to birth defects. In the 1960s, the first industrial link to teratogens was discovered. The chemical involved was methyl mercury.

The following conditions have been associated with **congenital malformations**: heredity, maternal diseases such as German measles and viral infections during pregnancy, maternal malnutrition, physical injury, radiation, and exposure to chemicals.

Most major structural abnormalities occur during the embryonic period, 5-7 weeks, whereas physiologic and minor defects occur during the fetal period, 8-36 weeks. Studies using lab animals show the need to evaluate exposure of chemicals for each day of pregnancy. Thalidomide, for example, caused birth defects in rats only when administered during the 12th day of gestation.

A number of chemicals are reactive or can be activated in the body during the gestation period. The degree and nature of the fetal effects then depend upon:

- Developmental state of embryo or fetus when chemical is administered.
- Dose of chemical, route, and exposure interval.
- Transplacental absorption of chemical and levels in tissues of embryo/fetus.
- Ability of maternal liver and placenta to metabolize or detoxify chemical.
- Biologic half-life of chemical or metabolites.
- State of cell cycle when chemical is at toxic concentrations.
- Capacity of embryonic/fetal tissues to detoxify or bioactivate chemicals.
- Ability of damaged cells to repair or recover.

Teratogenic potential has been suggested by animal studies under various conditions:

- Dietary deficiency: Vitamins A, D, E, C, riboflavin, thiamine, nicotinamide, folic acid, zinc, manganese, magnesium, and cobalt.
- Hormonal deficiency: Pituitary, thyroxin, and insulin.
- Hormonal excess: Cortisone, thyroxin, insulin, androgens, estrogens, and epinephrine.
- Hormone and vitamin antagonists: 3-acetylpyridine, 6-aminonicotinamide, and thiouracils.

- Vitamin excess: Vitamin A and nicotinic acid.
- Antibiotics: Penicillin, tetracyclines, and streptomycin.
- Heavy metals: Methyl mercury, mercury salts, lead, thallium, selenium, and chelating agents.
- Azo dyes: Trypan blue, Evans blue, and Niagara sky blue 6B.
- Producers of anoxia: Carbon monoxide and carbon dioxide.
- Chemicals: Quinine, thiadiazole, salicylate, 2,3,7,8-TCDD, caffeine, nitrosamines, hydroxyurea, boric acid, insecticides, pesticides, DMSO, chloroform, carbon tetrachloride, benzene, xylene, cyclohexanone, propylene glycol, acetamides, formamides, and sulfonamides.
- Physical conditions: hypothermia, hyperthermia, radiation, and anoxia.
- Infections: Ten viruses (including German measles and cytomegalovirus), syphilis, and gonorrhea.

Far fewer agents have been conclusively shown to be teratogenic in humans: anesthetic gases, organic mercury compounds, ionizing radiation, german measles and thalidomide.

Mutagenic. Mutagens are agents that cause changes (mutations) in the genetic code, altering DNA. The changes can be chromosomal breaks, rearrangement of chromosome pieces, gain or loss of entire chromosomes, or changes within a gene.

Among agents shown to be mutagenic in humans are:

- Ethylene oxide, used in hospitals as a sterilant.
- Ethyleneimine, an alkylating agent.
- Ionizing radiation.
- Hydrogen peroxide, a bleaching agent.
- Benzene, a chemical intermediate.
- Hydrazine, used in rocket fuel.

The concern over mutagenic agents covers more than the effect that could be passed into the human gene pool (germinal or reproductive cell mutations). There is also interest in the possibility that somatic cell mutations may produce carcinogenic or teratogenic responses.

Carcinogenic. Two types of carcinogenic mechanisms have been identified.

- **Genotoxic**: Electrophilic carcinogens that alter genes through interaction with DNA. There are three types:
    - Direct or primary carcinogens: Chemicals that act without any bioactivation; for example, bis(chloromethyl) ether, ethylene dibromide, and dimethyl sulfate.
    - Procarcinogens: Chemicals that require biotransformation to activate them to a carcinogen; for example, vinyl chloride and 2-naphthylamine.
    - Inorganic carcinogen: Some of these are preliminarily categorized as genotoxic due to potential for DNA damage. Other compounds in the group may operate through epigenetic mechanisms.

- **Epigenetic**: These are carcinogens that do not act directly with genetic material. Several types are possible:
    - Cocarcinogen: Increases the overall response of a carcinogen when they are administered together; for example, sulfur dioxide, ethanol, and catechol.
    - Promoter: Increases response of a carcinogen when applied after the carcinogen but will not induce cancer by itself; for example, phenol and dithranol.
    - Solid-state: Works by unknown mechanism, but physical form vital to effect; for example, asbestos and metal foils.
    - Hormone: Usually is not genotoxic, but alters endocrine balance; often acts as promoter (e.g. DES and estrogens).
    - Immunosuppressor: Mainly stimulates virally induced, transplanted, or metastatic neoplasms by weakening host's immune system (e.g., antilymphocytic serum, used in organ transplants).

Genotoxic carcinogens are sometimes effective after a single exposure, can act in a cumulative manner, or act with other genotoxic carcinogens which affect the same organs. Some epigenetic carcinogens, however, only cause cancers when concentrations are high and exposure long. The implication is that while there may be a "safe" threshold level of exposure for some carcinogens, others may have "zero" threshold; that is, one molecule of the chemical can induce a cancer. Various considerations indicate that **DNA** is a critical target for carcinogens:

- Many carcinogens are or can be metabolized so that they react with DNA. In these cases, the reaction can usually be detected by testing for evidence of DNA repair.
- Many carcinogens are also mutagens.
- Inhibitors and inducers of carcinogens affect mutagenic activity.
- Chemicals often are tested for mutagenic and carcinogenic activity in the same cell systems.
- Defects in DNA repair predispose to cancer development.
- Several inheritable or chromosomal abnormalities predispose to cancer development.
- Initiated dormant tumor cells persist, which is consistent with a change in DNA.
- Cancer is inheritable at the cellular level and, therefore, may result from an alteration of DNA.
- Most, if not all, cancers display chromosomal abnormalities.

Although cancer ranks as the second most common cause of death in the United States, the process of carcinogenesis is not yet clearly defined. As a result, there are several problems encountered when evaluating the carcinogenic potential of various agents in the environment. First, human health can be affected by a wide range of factors including the environment, occupation, genetic predisposition and lifestyle (i.e., cigarette smoking and diet). Therefore, it is often difficult to determine the relationship between any one exposure and the onset of cancer. Second, many cancers are latent responses; that is, the disease may not be manifested until many years after the initial exposure. Third, the mechanisms for carcinogenesis may differ according to the type and the site of cancer.

EXPOSURE GUIDELINES

It is necessary, during response activities involving hazardous materials, to acknowledge and plan for the possibility that response personnel will be exposed to the materials present at some time and to some degree. Most materials have levels of exposure which can be tolerated without adverse health effects. However, it is most important to identify the materials involved and then determine (1) the exposure levels considered safe for each of these materials; (2) the type and extent of exposure; and (3) possible health effects of overexposure.

Several reference sources are available that contain information about toxicological properties and safe exposure limits for many different materials. These sources can be grouped into two general categories: 1) sources that provide toxicological data and general health hazard information and warnings and 2) sources that describe specific legal exposure limits or recommended exposure guidelines.

Both types of sources, considered together, provide useful information that can be used to assess the exposure hazards that might be present at a hazardous materials incident. In the following discussion, these sources are described in greater detail.

General Guidelines

The effects of chemical exposure with the route and dosage required can be found in NIOSH's Registry of Toxic Effects of Chemical Substances. However, because most of the data is for animal exposures, there may be problems in trying to use the data for human exposure guidelines.

Other sources give some general guides on chemical exposure. They may say that the chemical is an irritant or corrosive, or they may give a warning like "AVOID CONTACT" or "AVOID BREATHING VAPORS." This gives the user information about the possible route of exposure and effects of the exposure. However, this does not give a safe exposure limit. One may question whether the warning means to "AVOID ANY POSSIBLE CONTACT" or whether there is a certain amount that a person can contact safely for a certain length of time.

Two sources of information go a little further and use a ranking system for exposure to chemicals. Irving Sax, in *Dangerous Properties of Industrial Materials*, gives a Toxic Hazard Rating (THR) for certain chemicals. These ratings are NONE, LOW, MODERATE, and HIGH. The route of exposure is also given. For example, butylamine is listed as a HIGH toxic hazard via oral and dermal routes and a MODERATE toxic hazard via inhalation. HIGH means that the chemical is "capable of causing death or permanent injury due to the exposures of normal use; incapacitating and poisonous; requires special handling."

In the book, *Fire Protection Guide on Hazardous Materials*, the National Fire Protection Association (NFPA) also uses a ranking system to identify the toxic hazards of a chemical. These numbers are part of the NFPA 704 M identification system. The numbers used range from 0 to 4 where 0 is for "materials which on exposure under fire conditions would offer no health hazard beyond that of ordinary combustible material" and 4 is for materials where "a few whiffs of the

gas or vapor could cause death; or the gas, vapor, or liquid could be fatal on penetrating the fire fighters' normal full protective clothing which is designed for resistance to heat." The degree of hazard is based upon the inherent properties of the chemical and the hazard that could exist under fire or other emergency conditions. This rating is based on an exposure of "a few seconds to an hour" and the possibility of large quantities of material being present. Thus it is not completely applicable to long-term exposure to small quantities of chemicals. It is more useful for spills or fires where a person could come in contact with a large amount of the chemical.

The Sax and NFPA sources provide information about the routes of exposures and some effects along with a rating system which indicates which chemicals require extra precaution and special protective equipment.

Sources for Specific Guidelines for Airborne Contaminants

While there are many sources for general exposure guidelines, there are only a few that give more specific information about what is considered a safe exposure limit. Many of the following organizations have exposure guidelines for exposures to hazards other than airborne contaminants (e.g., heat stress, noise, and radiation). This part will deal only with chemical exposures.

American Conference of Governmental Industrial Hygienists (ACGIH). One of the first groups to develop specific exposure guidelines was the American Conference of Governmental Industrial Hygienists (ACGIH). In 1941, ACGIH suggested the development of Maximum Allowable Concentrations (MACs) for use by industry. A list of MACs was compiled by ACGIH and published in 1946. In the early 1960s, ACGIH revised those recommendations and renamed them Threshold Limit Values (TLVs).

Along with the TLVs, ACGIH publishes Biological Exposure Indices (BEIs). BEIs are intended to be used as guides for evaluation of exposure where inhalation is not the only possible route of exposure. Since the TLVs are for inhalation only, they may not be protective if the chemical is ingested or is absorbed through the skin. Biological monitoring (e.g., urine samples, breath analysis) can be used to assess the overall exposure. This monitoring uses information about what occurs in the body (e.g., metabolism of benzene to phenol) to determine if there has been an unsafe exposure. The BEIs serve as a reference for biological monitoring just as TLVs serve as a reference for air monitoring.

The TLVs are reviewed yearly and are published in their booklet, *Threshold Limit Values and Biological Exposure Indices*.

American National Standards Institute (ANSI). The American National Standards Institute (ANSI) has published standards that are a consensus of the people who have a concern about the subject the standard covers (e.g., hard hats and respirators). An ANSI standard is intended as a guide to aid manufacturers, consumers, and the general public. ANSI has standards covering many aspects of the working environment. Many of these have been adopted by OSHA (see later discussion) as legal requirements.

Some of the standards were exposure guidelines. They gave "acceptable concentrations" which were "concentrations of air contaminants to which a person may be exposed without discomfort or ill effects." These exposure limits were withdrawn in 1982. However, some were adopted by OSHA before the withdrawal and still may be in use.

Occupational Safety and Health Administration (OSHA). In 1971, the Occupational Safety and Health Administration (OSHA) promulgated Permissible Exposure Limits (PELs). These limits were extracted from the 1968 TLVs, the ANSI standards, and other federal standards. The PELs are found in 29 CFR 1910.1000. Since then, additional PELs have been adopted and a few of the originals have been changed. These have been incorporated into specific standards for chemicals (e.g., 29 CFR 1910.1028 - Benzene). There are also standards for thirteen carcinogens in which there is no allowable inhalation exposure.

In 1989, OSHA published major revisions to the PELs. Since only a few of the PELs had been updated since 1971, it was decided to update the entire list of PELs by changing existing ones and adding new ones. Again, OSHA looked to the TLVs, but also considered recommendations from the National Institute for Occupational Safety and Health (NIOSH).

Because OSHA is a regulatory agency, their PELs are legally enforceable standards and apply to all private industries and federal agencies. They may also apply to state and local employees depending upon the state laws.

National Institute for Occupational Safety and Health (NIOSH). The National Institute for Occupational Safety and Health (NIOSH) was formed at the same time as OSHA to act as a research organization. It is charged, in part, with making recommendations for new standards and revising old ones as more information is accumulated. The exposure levels NIOSH has researched have been used to develop new OSHA standards, but there are many Recommended Exposure Limits (RELs) that have not been adopted. Thus, they are in the same status as the exposure guidelines of ACGIH and other groups. The RELs are found in the "NIOSH Recommendations for Occupational Health Standards" (see Appendix II).

American Industrial Hygiene Association (AIHA). The American Industrial Hygiene Association has provided guidance for industrial hygienists for many years. In 1984, AIHA developed exposure guidelines that it calls Workplace Environmental Exposure Level Guides (WEELs). These are reviewed and updated each year. Appendix III has the current list of WEELs. While the list is not as large as others, AIHA has chosen chemicals for which other groups do not have exposure guidelines. Thus, they are providing information to fill the gaps left by others.

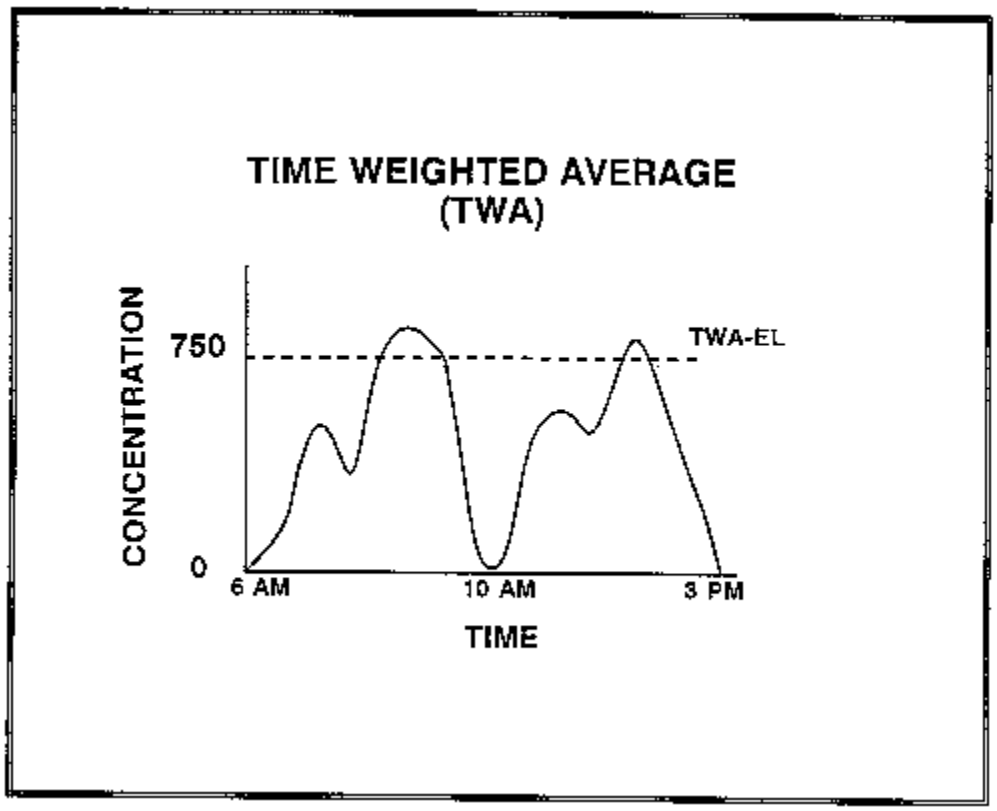
Types of Exposure Guidelines

Several organizations develop exposure guidelines. However, the types of guidelines they produce are similar.

Time-Weighted Average (TWA). This exposure is determined by averaging the concentrations of the exposure with each concentration weighted based on the duration of exposure. For example, an exposure to acetone at the following concentrations and durations:

1000 ppm for 3 hours
500 ppm for 2 hours
200 ppm for 3 hours
would have an 8-hour, TWA exposure of:
[(3hrs)(1000ppm) + (2hrs)(500ppm) + (3hrs)(200ppm)] / 8 hrs
= [3000 ppm + 1000 ppm + 600 ppm] / 8
= 575 ppm
This exposure would be compared to an 8-hour TWA **exposure limit**.

A TWA can be the average concentration over any period of time. However, most TWAs are the average concentration of a chemical most workers can be exposed to during a 40-hour week and a normal 8-hour work day without showing any toxic effects. NIOSH TWA recommendations, on the other hand, can also be based on exposures up to 10 hours. The time-weighted average permits exposure to concentrations above the limit, when they are compensated by equal exposure below the TWA. (**Graph 3**) shows an example that illustrates this point for a chemical with a TWA exposure limit of 750 ppm.

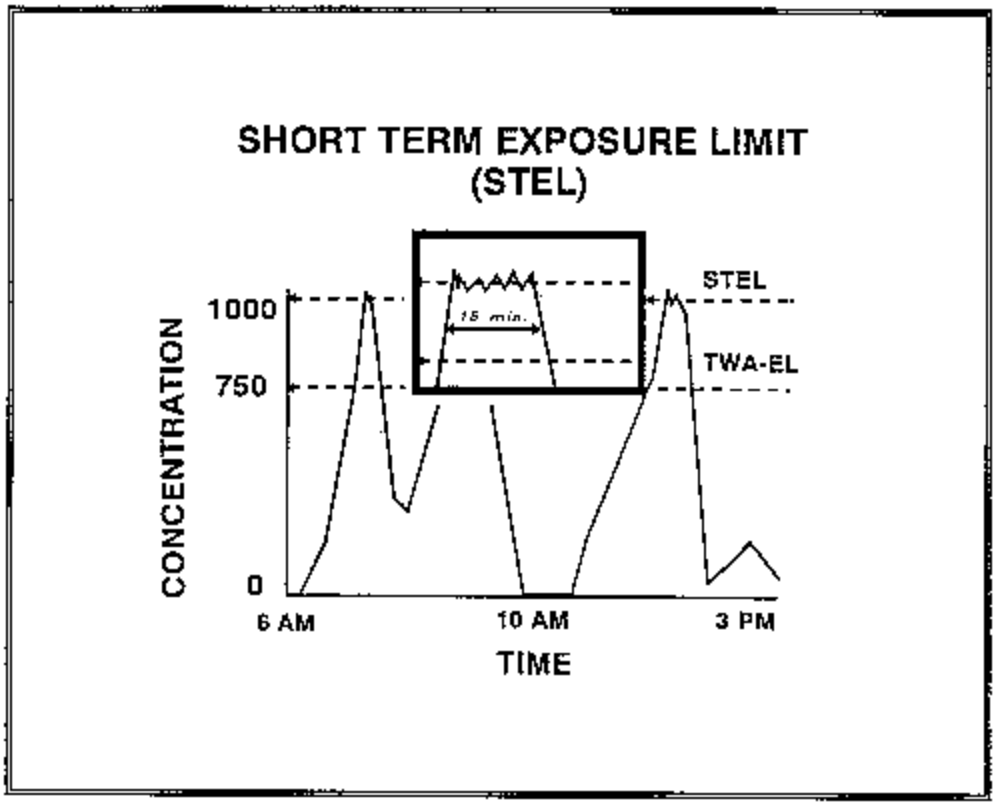


Graph 3
Example of an Exposure Compared to a TWA Exposure Limit

Short-Term Exposure Limit (STEL). The excursions allowed by the TWA could involve very high concentrations and cause an adverse effect, but still be within the allowable average. Therefore, some organizations felt there was a need for a limit to these excursions. In 1976, ACGIH added STELs to its TLVs. The STEL is a 15 minute, TWA exposure. Excursions to the STEL should be at least 60 minutes apart, no longer than 15 minutes in duration and should not be repeated more than 4 times per day. Because the excursions are calculated into the 8-hour TWA, the exposure must be limited to avoid exceeding the TWA. **Graph 4** illustrates an exposure that exceeds the 15 minute limit for an STEL of 1000 ppm.

The STEL supplements the TWA. It reflects an exposure limit that protects against acute effects from a substance which primarily exhibits chronic toxic effects. This concentration is set at a level to protect workers against irritation, narcosis, and irreversible tissue damage. OSHA added STELs to its PELs with the 1989 revisions.

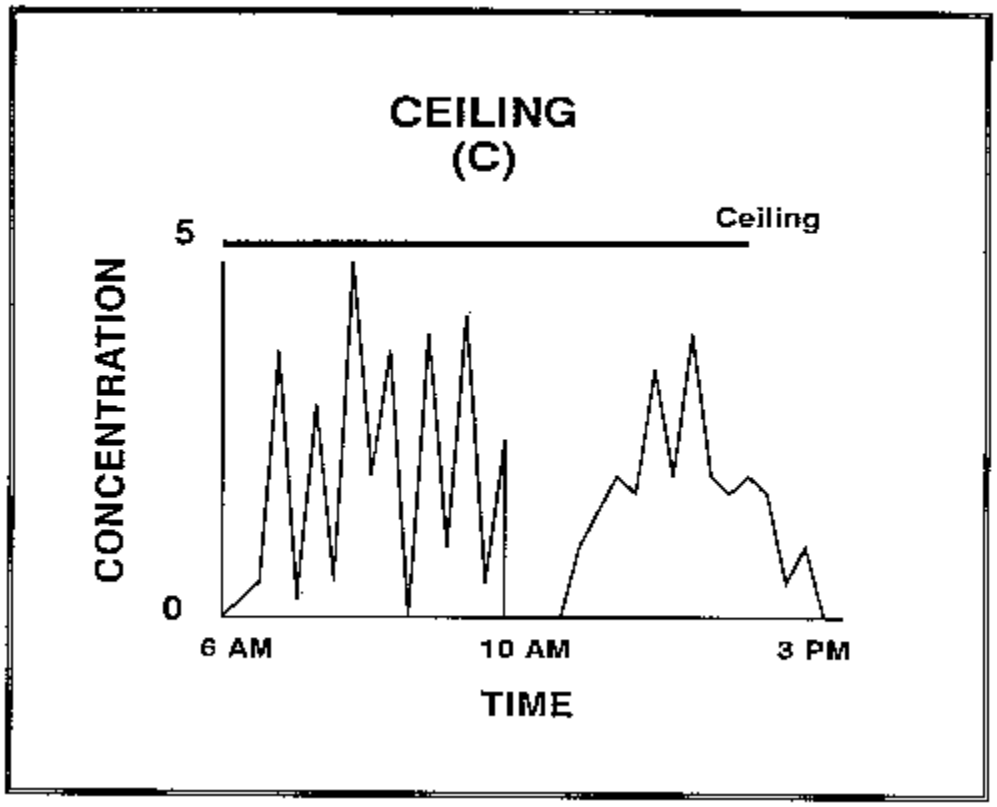
AIHA has some short-term TWAs similar to the STELs. The times used vary from 1 to 30 minutes. These short-term TWAs are used in conjunction with, or in place of, the 8-hour TWA. There is no limitation on the number of these excursions or the rest period between each excursion.



Graph 4
Example of an Exposure Compared to an STEL and a TWA

Ceiling (C). Ceiling values exist for substances where exposure results in a rapid and particular type of response. It is used where a TWA (with its allowable excursions) would not be

appropriate. ACGIH and OSHA state that a ceiling value should not be exceeded even instantaneously. . They denote a ceiling valuely a ACT preceding the exposure limit. NIOSH also uses ceiling values. However, their ceiling values are more like a STEL. Many have time limits (from 5 to 60 minutes) associated with the exposure. **Graph 5** illustrates an exposure that does not exceed a ceiling value of 5 ppm.



Graph 5
Example of an Exposure Compared to a Ceiling Exposure Limit

Peaks. Until recently ANSI, and OSHA where they have adopted ANSI standards, had used a peak exposure limit. This peak exposure is an allowable excursion above their ceiling values. The duration and number of exposures at this peak value is limited. For example, ANSI allowed the 25 ppm ceiling value for benzene to be exceed to 50 ppm but only for 10 minutes during an 8 hour period. ANSI withdrew its exposure limit standards in 1982. With the revision of the PELs in 1989, OSHA has dropped most of its peak values.

"Skin" Notation. While these exposure guidelines are based on exposure to airborne concentrations of chemicals. However, OSHA, NIOSH, ACGIH and AIHA recognize that there are other routes of exposure in the workplace. In particular, there can be a contribution to the overall exposure from skin contact with chemicals that can be absorbed through the skin. Unfortunately, there is very little data available that quantifies the amount of allowable skin contact. But some organizations provide qualitative information about skin absorbable

chemicals. When a chemical has the potential to contribute to the overall exposure by direct contact with the skin, mucous membranes or eyes, it is given a "skin" notation.

This "skin" notation not only points out chemicals that are readily absorbed through the skin, but also notes that if there is skin contact, the exposure guideline for inhalation may not provide adequate protection. The inhalation exposure guidelines are designed for exposures only from inhalation. If additional routes of exposure are added, there can be detrimental effects even if the exposure guideline is not exceeded.

Immediately Dangerous to Life or Health (IDLH). In the May 1987 "NIOSH Respirator Decision Logic", IDLH is defined as a condition "that poses a threat of exposure to airborne contaminants when that exposure is likely to cause death or immediate or delayed permanent adverse health effects or prevent escape from such an environment. The purpose of establishing an IDLH exposure level is to ensure that the worker can escape from a given contaminated environment in the event of failure of the respiratory protection equipment.

Other organizations, such as ANSI, OSHA, and the Mine Safety and Health Administration (MSHA), have defined IDLH similarly. It is accepted by all of these groups that IDLH conditions include not only toxic concentrations of contaminants, but also oxygen-deficient atmospheres and explosive, or near-explosive (above, at, or near the lower explosive limits), environments.

At hazardous material incidents, IDLH concentrations should be assumed to represent concentrations above which only workers wearing respirators that provide the maximum protection (i.e., a positive-pressure, full-facepiece, self-contained breathing apparatus [SCBA] or a combination positive-pressure, full-facepiece, supplied-air respirator with positive-pressure escape SCBA) are permitted. Specific IDLH concentrations values for many substances can be found in the NIOSH "Pocket Guide to Chemical Hazards." Guidelines for potentially explosive, oxygen deficient, or radioactive environments can be found in the U.S. EPA "Standard Operating Safety Guidelines" and the NIOSH/OSHA/USCG/EPA *Occupational Safety and Health Guidance Manual for Hazardous Waste Site Activities*.

Exposure Limits for Chemical Mixtures

The exposure limits that have been discussed are based upon exposure to single chemicals. Since many exposures include more than one chemical, values are adjusted to account for the combination. When the effects of the exposure are considered to be additive, a formula can be used to determine whether total exposure exceeds the limits. The calculation used is:

$E_m = (C_1/L_1 + C_2/L_2) + \ldots (C_n/L_n)$
where:
E_m is the equivalent exposure for the mixture.
C is the concentration of a particular contaminant.
L is the exposure limit for that substance.
The value of E_m should not exceed unity (1).
An example using this calculation would be as follows:

Chemical A : C = 200 ppm, L = 750 ppm
Chemical B : C = 100 ppm, L = 500 ppm
Chemical C : C = 50 ppm, L = 200 ppm
$E_m = 200/750 + 100/500 + 50/200$
$E_m = 0.27 + 0.20 + 0.25$
$E_m = 0.72$
Since E_m is less than unity, the exposure combination is within acceptable limits.

This calculation applies to chemicals where the effects are the same and are additive. If the combination is not additive, the calculation is not appropriate.

Application of Exposure Guidelines

In 29 CFR 1910.120, "Hazardous Waste Operations and Emergency Response" standard, OSHA specifies the use of certain exposure limits. The exposure limits specified are OSHA's permissible exposure limits (PELs) and "published exposure levels." The "published exposure levels" are used when no PEL exists. A "published exposure level" is defined as "the exposure limits published in 'NIOSH Recommendations for Occupational Health Standards' dated 1986 incorporated by reference. If none is specified, the exposure limits published in the standards specified by the American Conference of Governmental Industrial Hygienists in their publication *Threshold Limit Values and Biological Exposure Indices*.

Engineered Controls and Work Practices. 29 CFR 1910.120 (g) (1) (i) states "Engineering controls and work practices shall be instituted to reduce and maintain employee exposure to or below the permissible exposure limits for substances regulated by 29 CFR Part 1910, to the extent required by Subpart Z, except to the extent that such controls and practices are not feasible." (emphasis added) Whenever engineering controls and work practices are not feasible, personal protective equipment shall be used to reduce and maintain exposures.

For those substances or hazards where there is no PEL, the published exposure levels, published literature and material safety data sheets (MSDS) will be used for evaluation. In these circumstances, a combination of engineering controls, work practices and PPE shall be used to reduce and maintain exposures.

Personal Protective Equipment. Since PPE must be selected based on the hazards present at the site, the exposure limits are used to evaluate the effectiveness of the PPE. Comparing the actual or expected exposure to the PEL or other exposure limits gives the wearer information on selection of the proper PPE.

Medical Surveillance. 29 CFR 1910.120(f)(2)(i) requires a medical surveillance program for all employees exposed to substances or hazards above the PEL for 30 or more days per year. If there is no PEL, then the published exposure levels are used for evaluation. The exposures are considered even if a respirator was being used at the time of exposure.

Limitations/Restrictions of Exposure Guideline Use

The exposure guidelines discussed in this part are based on industrial experience, experimental human studies, experimental animal studies, or a combination of the three. The guidelines were developed for workers in the industrial environment. Thus, they are not meant to be used for other purposes. ACGIH in its *Threshold Limit Values and Biological Exposure Indices for 1992-1993* states:

> These limits are intended for use in the practice of industrial hygiene as guidelines or recommendations in the control of potential health hazards and for no other use, e.g., in the evaluation or control of community air pollution nuisances, in estimating the toxic potential of continuous, uninterrupted exposures or other extended work periods, as proof or disproof of an existing disease or physical condition, or adoption by countries whose working conditions differ from those in the United States of America and where substances and processes differ. These limits are not fine lines between safe and dangerous concentration nor are they a relative index of toxicity, and should not be used by anyone untrained in the discipline of industrial hygiene.

As can be seen from this qualifier, these exposure limits are not intended as exposure limits for exposure by the public.

There is the limitation on the use of the exposure guideline as a relative index of toxicity. This is because the exposure limits are based on different effects for different chemicals. For example, the TLV-TWA for acetone is chosen to prevent irritation to the eyes and respiratory system. The TLV- TWA for acrylonitrile is chosen to reduce the risk to cancer. Exposures to these chemicals at other concentration levels could lead to other effects. Thus, when evaluating the risk of chemical exposure, all toxicological data should be consulted.

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