APPENDIX 1

Toxicology

Exposure to hazardous chemicals may produce a wide range of adverse health effects. The likelihood of an adverse health effect occurring, and the severity of the effect, are dependent on the toxicity of the chemical, route of exposure, and the nature and extent of exposure to dose from that substance. In order to better understand potential health effects, emergency personnel should have an understanding of the basic principles and terminology of toxicology.

Toxicology is the study of the adverse effects of chemicals on living organisms.

Types of Toxic Hazards

1. Systemic poisons - Systemic poisons are chemical agents which act on specific target organs or organ systems. Systemic poisons are divided into the following categories:

- Anesthetics/narcotics (e.g. ethyl ether).
- Compounds damaging liver function (e.g. carbon tetrachloride and tetrachloroethane).
- Compounds damaging kidney function (e.g. halogenated hydrocarbons such as chloroform).

- Compounds damaging the nervous system (e.g. ethanol, carbon disulfide, and organophosphates).

- Compounds damaging blood/circulatory system (e.g. benzene and phenols).

2. Asphyxiants - Asphyxiants are agents which deprive the tissues of oxygen. This group is divided into simple or chemical asphyxiants and both simple and chemical asphyxiants.

- The simple asphyxiants act by diluting or displacing atmospheric oxygen, which lowers the concentration of oxygen in air. Breathing air with a low oxygen concentration causes insufficient oxygen in the blood and tissues. This can cause headache, loss of consciousness, and eventually death. Examples of simple asphyxiants are aliphatic hydrocarbons, nitrogen, hydrogen, and methane.

- Chemical asphyxiants act in one of two ways:

  - The first type of chemical asphyxiant prevents the uptake of oxygen in the blood. For example, carbon monoxide interferes with the transport of oxygen to the tissues by strongly binding with hemoglobin to form carboxy hemoglobin which leaves inadequate hemoglobin available for oxygen transport.

  - The second type of chemical asphyxiant does not permit normal oxygen transfer from the blood to the tissues or within the cell itself. Hydrogen cyanide is an example of this type.

- Some compounds can act as both simple and chemical asphyxiants. Hydrogen sulfide, which is extremely toxic, is an example.

An important aspect of asphyxia and respiratory toxicants is the effect of oxygen-deficient atmospheres. Normal oxygen

oxygen content in air ranges from 19.5 percent to 23.5 percent. Some atmospheres, such as those generated during a fire or hazardous material release, contain less oxygen. For this reason, it is imperative that the oxygen content of any atmosphere be determined before the selection of respiratory protective equipment. Confined space entries represent an especially hazardous exposure situation. Particular attention should be paid to the presence of combustible or explosive atmospheres, as volatile organic vapors can collect rapidly within a confined space. Attention should also be paid to low-lying areas, where vapors heavier than air can collect.

EFFECTS OF OXYGEN CONCENTRATION ON HUMANS

PERCENT OXYGEN	EFFECTS
>23.5	Explosive atmosphere, keep out!
21-16	Nothing abnormal
16-12	Loss of peripheral vision Rapid breathing and heart rate Impaired coordination
12-10	Poor judgement and coordination Excessive fatigue Permanent heart damage Sparse breathing
10-6	Nausea Loss of movement Unconsciousness followed by death
Less than 6	Spasmodic breathing Convulsive movements Death

3. Irritants - Irritants are materials that cause inflammation of tissues. The mechanism of irritation is by either corrosive or drying action and may affect the eyes, skin, respiratory membranes or gastrointestinal tract. The irritant must come in direct contact with tissue to cause an inflammation reaction. Consequently, skin, eye, and respiratory irritants are the greatest concern for response personnel.

- Examples of skin irritants are acids, alkalies, solvents, and detergents.

- Examples of respiratory irritants are ozone, ammonia, hydrogen chloride, and nitrogen dioxide.

4. Pneumoconiosis - Pneumoconiosis is the reaction of the tissues due to accumulation of dust in the lungs. Chronic inhalation of mineral dust such as silica and asbestos can result in pneumoconiosis.

5. Allergic sensitizers - Sensitizers affect the immune system of the exposed person, causing a delayed hypersensitivity to the sensitizing agent. The allergic reaction shows one or more symptoms, which can range from discomfort from poison ivy to a fatal reaction from isocyanates.

- Examples of skin sensitizers are poison ivy and formaldehyde.

- Examples of respiratory sensitizers are sulfur dioxide and isocyanate.

6. Mutagens - A mutagen is any substance that affects genetic material in the lab or in a live animal. Thousands of mutagens have been identified through the use of tests like the Ames Salmonella Assay. Mutagenesis is not a symptom or a disease, but a mechanism by which diseases may develop.

- Examples of mutagens are ionizing radiation, benzene and hydrogen peroxide.

7. Carcinogens - Carcinogens cause cancer in lab animals or in humans.

- Examples of carcinogens are poly bis-chloromethyl ether, polynuclear aromatics, and 13-napthtylamine.

8. Teratogens - Teratogens cause damage to the unborn children of the exposed person by a number of mechanisms. Maternal alcohol abuse throughout pregnancy is the most important single cause of drug-induced teratogenesis. Another example of a teratogen is thalidomide.

9. Biological agents - Categories of biological agents include:

- viruses, such as HIV (which causes AIDS)
- bacteria, such as *Streptococcus*
- fungi, such as yeasts and ringworm
- parasites, such as *Entamoeba histolytica*
- rickettsia, such as *Rickettsia rickettsi*

Routes of Exposure

The route by which personnel are exposed to a compound plays a role in determining the total amount of the compound taken up by the body because a compound may be absorbed following exposure by one route more readily than by another. In addition to the route of exposure, the amount of the compound absorbed by the body depends on the duration of exposure to the compound and the concentration of the compound to which one is exposed. Therefore, a complex relationship exists between the total amount of the compound absorbed by the body (dose) and the concentration of that compound in the environment. This relationship is important for emergency response personnel to understand because the adverse effects produced by a toxic compound are often related to the dose of that compound received by the person. However, because we usually only monitor the concentration of the toxic substance in the environment (e.g., parts per million (ppm) of a compound in air), the actual dose of the compound received by the person is seldom known. Factors specific to the

exposed person, such as size of the skin surface area exposed, presence of an open wound or breaks in the skin, and rate and depth of respiration, are important in estimating the dose of the compound received by the person.

There are only four pathways for substances to enter the body:

- contact with skin, eye, and hair
- inhalation
- ingestion
- injection

Inhalation

Inhalation of toxic agents generally results in a rapid and effective absorption of the compounds into the blood stream because of the large surface area of the lung tissue and number of blood vessels in the lungs.

The toxic effects of particulates depend on the physical and chemical properties of the particles in question and on the particle size. Larger particles settle in the upper portions of the system to be removed by ciliary action. The smaller the particle, however, the greater ability it has to travel deep into the small spaces of the lung, thus potentially causing greater harm. Once small particles are deposited in the lower portions of the lungs, their fate includes:

- Absorption into the bloodstream (particles of greater than 5.0 micrometers do not normally diffuse through cell walls).

- Removal through phagocytosis, a process in which immune cells attempt to remove the particles by incorporating them into their cell structure.

- Cell toxicity resulting in fibrotic (scar-like) tissue formation and decreased gas exchange area.

Certain types of particulates, such as asbestos and silica, can not be effectively eliminated by the body. Incomplete removal results in

irritation and death of the cell, causing further immune response. Irritation may be severe enough to cause fibrosis of portions of the lung or a cancerous growth.

Absorption

Absorption of toxic agents as a route of exposure refers to the passage of toxicants through either the skin, eyes, or other openings in the body. Absorption is the second most common route of exposure to hazardous materials, and frequently occurs through direct contact between the chemical and the skin of the exposed person.

The skin serves as a barrier to prevent most foreign substances from entering the body. It also functions to preserve the components of the body. The skin has three layers: 1) the epidermis, the outermost layer, is composed of mostly dead cells that adhere to the living tissue underneath and is responsible for the skin's effectiveness as a barrier; 2) the dermis, a layer of loose connective tissue, contains the blood vessels closest to the skin surface and is actively involved in wound repair; and 3) the hypodermis, the innermost layer, contains connective and adipose (fat) tissue.

The absorption of chemicals through the skin is called percutaneous absorption. It depends upon:

- The integrity of the skin.
- The vehicle through which the toxicant is administered.
- The type of toxicant.

Factors that facilitate percutaneous absorption include:

- Reduced integrity of the outer skin layer.
- Increased hydration of the skin.
- Increased temperature of the skin.
- Altered skin pH.
- Increased blood flow to the skin.
- Increased concentration of the toxicant.
- Decreased particle size of the toxicant.
- Electrically induced movement of the toxicant.
- The addition of agents that react with the skin surface.

Skin contact does not typically result in as rapid of a systemic dosage as inhalation, although some chemicals are readily absorbed through the skin. Many organic compounds are lipid (fat) soluble and can therefore be rapidly absorbed through the skin.

The same chemicals that can damage the skin can damage the eye. The eyes are actually more sensitive to exposure than the skin due to their high fluid content and lack of a barrier. The primary concerns with exposure to ocular toxicants are:

- Local effects - direct effects caused by the application of a chemical to the cornea.

- Systemic effects - effects to other organs or organ systems in the body, caused by the application of a chemical to the eye.

- Ocular side effects - effects which occur in the eye from exposure to toxicants through other routes of exposure such as inhalation and ingestion.

The types of chemicals noted for their ocular toxicity are acids, bases, organic solvents, detergents, and lacrimators. Acids affect the eye by reacting with protein in the tissues and by dehydrating the tissues. Treatment involves flushing the eye with large amounts of water. Generally, the greater the concentration of the acid, the greater ability it has to induce harm.

Alkaline substances (bases) act on the eye in a very different manner than acidic ones. Bases produce the same initial effects as acids, due to the pH of the base and the heat produced during reaction. However, contrary to acid burns, the effects observed immediately after exposure to an alkaline substance are not a good indication of the total effects of exposure because latent effects may continue to occur up to two weeks after exposure. An example of the impact of an alkaline substance on the eye is exposure to sodium hydroxide (NaOH); irrigation of the eye with a concentrated solution of NaOH for more than three minutes could cause catastrophic changes in the cornea leading to complete opacification (clouding) within a week to ten days after exposure. Other alkaline substances that are potent ocular toxicants include potassium hydroxide and ammonia.

Organic solvents react with the proteins and fats in the eye, causing severe pain. Damage is usually not extensive and can be reversed. In the case of heated solvents, there is the threat of burning, resulting in damage that is often severe and unpredictable. Examples of organic solvents include ethanol, toluene, and acetone.

Detergents react to lower the surface tension of the liquids in the eye, causing pronounced irritation followed by extensive tearing. Concentrated doses can cause severe burns with permanent fogging of the cornea. Examples of detergents include household cleaning agents, emulsifying agents, wetting agents, and antifoaming agents.

Lacrimators are chemical compounds or mixtures which have the ability to induce instant tearing at very low concentrations without reacting with the tissues of the eye. High concentrations can cause tissue damage. Examples include mace (tear gas) and smog.

Ingestion

The ingestion of hazardous substances is the third most frequent route of exposure in humans. Ingestion of hazardous substances occurs through the consumption of:

- Contaminated waters.
- Fish from contaminated waters.
- Contaminated plants and animals.
- Incidental ingestion of soils and dusts.

Exposure to toxicants through ingestion is of most concern with young children who can ingest large amounts of soil every day in the course of normal play activities. Young children are also particularly susceptible to the adverse effects of some contaminants (lead, for example) that may be ingested.

Once a toxicant is ingested, it enters the gastrointestinal (GI) tract. The GI tract is essentially a long tube beginning at the lips and ending at the anus, and includes the mouth, esophagus, stomach, and small and large intestine. Throughout the course of the GI tract, ingested toxicants can be absorbed into the bloodstream. Absorption primarily occurs in three main areas of the GI tract: the stomach, the small intestine, and the large intestine.

The human liver has sophisticated mechanisms for the detoxification of foreign substances. These mechanisms include enzymatic reactions and excretion to the bile and urine. Liver functions can, however, convert a substance into an even more toxic form. In addition, detoxification mechanisms are easily overridden, particularly in cases of exposure to multiple agents or to large doses of a single agent.

Exposure to toxic chemicals through the GI tract can result in both local and systemic effects. Local effects include the reaction of the chemical with the exposed internal surface of the GI tract, as in the case of burns from acid ingestion. Systemic effects result from absorption of the chemical into the bloodstream and transport to critical organs.

Ingestion is a less common route of exposure for emergency personnel at hazardous material incidents, although incidental hand to mouth contact, smoking and swallowing saliva and mucus containing trapped airborne contaminants can cause exposure by this route. Even so, toxicity by mouth is of a lower order because the gastrointestinal lining resists the transport of most toxic agents.

Injection

Injection refers to the combination of toxic exposure with a physical trauma, such as a laceration. This route of exposure, although less common than the others, should be considered very dangerous, since the toxicant is being directly injected into the bloodstream of the exposed person. Proper site safety practices (e.g., the buddy system) can be effective in preventing injection exposures.

Some significant exposures have occurred by injection. Animal bites fall into this category.

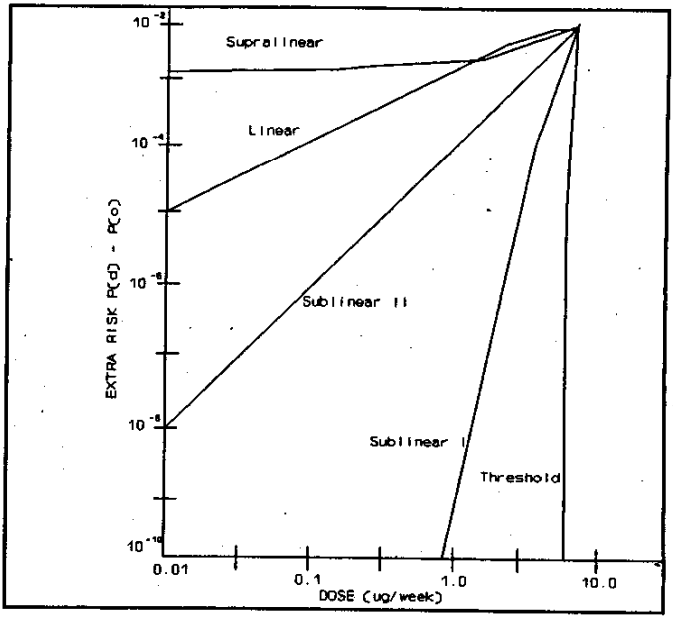
Biological Variation

Biological variation is the term used for the occurrence of differing susceptibilities in a population exposed to a toxic chemical. Factors that contribute to biological variation include sex, age, nutritional status, weight, metabolic type, and state of health. Biological variation is accounted for in all models of toxicological testing.

Dose-Response Relationship

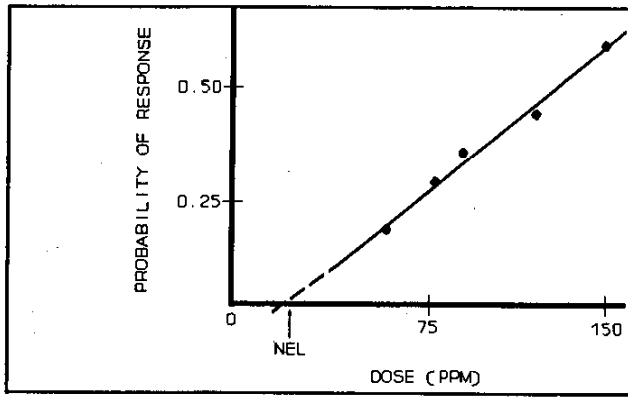
The effect produced by a toxic compound is a function of the dose of the compound received by the organism. This principle, termed the dose-response relationship, is a key concept in toxicology. Typically, as the dose increases, the severity of the toxic response increases.

1. The carcinogens - Carcinogenesis does not have a threshold. Thus, there can never be a zero response (or risk); even the smallest dose will result in some finite risk. It should be noted that the most conservative model is the linear (or one-hit) model. This is the most conservative, because the model predicts a given response (or risk) at the lowest allowable level of exposure.



Results of alternative extrapolation models for the same experimental data. NOTE: Dose-response functions were developed (Crump, in press) for data from a benzopyrene carcinogenesis experiment with mice conducted by Lee and O'Neill (1971).

2. Non-carcinogens - A dose response curve is sought from the literature for the most sensitive biological system in an experimental animal model.



No effect level (NEL): NEL is the dose which will produce no effect in the most sensitive biological system for which data can be found. To add an additional measure of safety for extrapolation to humans, this NEL is further divided by a safety factor of 100 to yield an allowable level of exposure for humans. If other data, either animal or human epidemiologic, suggest a lower level of concern for the compound under review, then the NEL may be divided by 10. Conversely, if other data suggests a higher level of concern, then the NEL may be divided by 1,000. This approach of a threshold "no effect level," coupled with the use of a safety factor ranging from 10 to 1,000 has served the FDA, the food industry and the American public.

Exposure to Chemical Mixture

Emergency health threat determinations involving mixtures are complex and difficult to make because little is known about the toxic properties of a mixture of compounds. Chemicals in a mixture can interact with each other and with the body to produce any one of the four following effects:

- Additive Effects (e.g., 2+3+4=9). These effects are produced when the combined effect of the chemicals is equal to the sum of the individual effects of all the chemicals in the mixture. Examples of a mixture that produces additive effects are organophosphate pesticides such as parathion and malathion.

- Synergistic Effects (e.g., 2+3+4=27). Effects that are greater than the sum of the component chemicals in the mixture are said to be synergistic effects. An example of a synergistic effect is the combined effects of cigarette smoke and asbestos; smokers show a strikingly higher cancer rate from asbestos exposure than do nonsmokers.

- Potentiation Effects (e.g., 0+2=10). One of the chemicals in a mixture may not itself be particularly toxic, but it reacts to increase the toxicity of another chemical in the mixture, producing potentiation effects. An example of a potentiation effect is the increased toxicity observed with carbon tetrachloride (CCl_4) exposure accompanied by isopropanol. Isopropanol is considered to be relatively nontoxic when administered by itself. However, when administered with CCl_4, it excerbates the toxicity of CCl_4 by preventing detoxification mechanisms in the liver from reacting with CCl_4 molecules.

- Antagonistic Effects (e.g., 4+(-4)=0). A mixture in which one or more of the chemicals present inhibits the toxicity of other compounds in the mixture is said to produce antagonistic effects. Antagonistic actions between chemicals serve as the basis for antidotal therapy.

NOTE: Exposure criteria for chemical mixtures do not exist and other information can be very difficult to gather. In situations involving exposure to a mixture of chemicals, it is advisable to assemble a team of experts, including chemists and toxicologists, to characterize the situation completely.

Toxicity Information

Toxicity information is often expressed as the dose of the compound that causes an effect in a percentage of the exposed subjects, which are mostly experimental animals. These dose-response terms are often found in Material Safety Data Sheets (MSDS) and other sources of health information. One dose-response term that is commonly used is the lethal dose 50 (LD_{50}), the dose which is lethal to 50 percent of an animal population from exposure by any route other than inhalation when given all in one dose. Another similar term is the lethal concentration 50 (LC_{50}), which is the concentration of a material in air that on the basis of respiratory exposure in laboratory tests is expected to kill 50 percent of a group of test animals when administered as a single exposure (usually 1 hour).

ACUTE LD_{50} VALUES FOR REPRESENTATIVE CHEMICALS WHEN ADMINISTERED ORALLY TO RATS

Chemical	Acute Oral LD_{50} (mg/kg)*
Sodium cyanide	6.4 - 10
Pentachlorophenol	50 - 230
Chlordane	83 - 560
Lindane	88 - 91
Toluene	2600 - 7000
Tetrachloroethylene	3000 - 3800

* Milligrams of the compound administered per kilogram body weight of the experimental animal.

From the above table it can be seen that a dose of 3000 to 3800 mg/kg tetrachloroethylene is lethal to 50 percent of rats that received the compound orally; however, only 6.4 to 10 mg/kg of sodium cyanide is required to produce the same effect. Therefore, compounds with lower LD_{50} values are more acutely toxic than substances with higher LD_{50} values.

The LD_{50} values that appear in an MSDS or in literature must be used with caution by emergency medical personnel. These values are an index of only one type of response and give no indication of the ability of the compound to cause non-lethal, adverse or chronic effects. Furthermore, LD_{50} values typically come from experimental animal studies.

FACTORS INFLUENCING TOXICITY	
TYPE	**EXAMPLES**
Factors related to the chemical.	Composition (salt, freebase, etc.); physical characteristics (size, liquid, solid, etc.); physical properties (volatility, solubility, etc.); presence of impurities; breakdown products; carriers.
Factors related to exposure.	Dose; concentration; route of exposure (inhalation, ingestion, etc.); duration.
Factors related to person exposed.	Heredity; immunology; nutrition; hormones; age; sex; health status; pre-existing diseases.
Factors related to environment.	Media (air, water, soil, etc.); additional chemicals present; temperature; air pressure.

Exposure Limits

The concept of the various occupational exposure limits which are found in literature or in an MSDS, are based primarily on time-weighted average limits, ceiling values or ceiling concentration limits to which the worker can be exposed without adverse effects.

EXAMPLES OF OCCUPATIONAL EXPOSURE LIMITS		
Value	**Abbreviation**	**Definition**
Threshold Limit Value 3 types (ACGIH)*	TLV	Refers to airborne concentrations of substances and represents conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effect.
1) Threshold Limit Value - Time-Weighted Average (ACGIH)*	TLV-TWA	The time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.
2) Threshold Limit Value - Short-Term Exposure Limit (ACGIH)*	TLV-STEL	The concentration to which workers can be exposed continuously for a short period of time without suffering from: 1) irritation, 2) chronic or irreversible tissue damage, or 3) narcosis of sufficient degree to increase the likelihood of accidental injury, impair self-rescue, or materially reduce work efficiency, and provided that the daily TLV-TWA is not exceeded.
3) Threshold Limit Value - Ceiling (ACGIH)*	TLV-C	The concentration that should not be exceeded during any part of the working exposure.

EXAMPLES OF OCCUPATIONAL EXPOSURE LIMITS		
Value	**Abbreviation**	**Definition**
Permissible Exposure Limit (OSHA)**	PEL	Same as TLV-TWA.
Immediately Dangerous to Life and Health (OSHA)**	IDLH	A maximum concentration (in air) from which one could escape within 30-minutes without any escape-impairing symptoms or any irreversible health effects.
Recommended Exposure Limit (NIOSH)***	REL	Highest allowable airborne concentration that is not expected to injure a worker; expressed as a ceiling limit or time-weighted average for an 8 or 10 hour work day.

* American Conference of Governmental Industrial Hygienists
** Occupational Safety and Health Administration
*** National Institute for Occupational Safety and Health

The values listed in the above table were established to provide worker protection in occupational settings. Because the settings in which those values are appropriate are quite different from an uncontrolled spill site, it is difficult to interpret how these values should be used by emergency personnel dealing with a hazardous materials incident. At best, TLV, PEL, IDLH, and REL values can be used as benchmarks for determining relative toxicity, and perhaps to assist in selecting appropriate levels of personal protective equipment (PPE). Furthermore, these occupational exposure limits are only useful if the

appropriate instrumentation is available for measuring the levels of toxic chemicals in the air at the chemical spill site. It should be noted that with the above Occupational Exposure Limit values, only the OSHA values are regulatory limits. The ACGIH values are for guidance only and are not regulatory limits.

MCL

MCL (Maximum Contaminant Level). MCLs are mandated by the Safe Drinking Water Act (SWDA) of 1972 and are established by the National Academy of Sciences and EPA to regulate contaminants in public drinking water supplies. MCL values are changed regularly to reflect improvements in treatment technologies.

Frequently, one chemical will have several exposure values associated with it. The field investigator should evaluate these numbers on the basis of the tasks to be performed on site and the personal protection equipment to be used to ensure exposure limits are not exceeded. Within this context, the most conservative exposure value (i.e., the lowest value) should be chosen to provide for the greatest site security.

Practical Considerations

The answers to the following questions will dictate how response personnel are protected (type of respiratory and protective gear employed):

- What toxic agent is present?
- How much of the agent is present?
- How will it enter the body?
- How will it affect the body?