ENVIRONMENTAL HEALTH AND SAFETY
University of Nebraska-Lincoln

Safe Operating Procedure

(Revised 11/22)

TOXICOLOGY AND EXPOSURE GUIDELINES

Background

"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).

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 that cross the skin barrier can 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 ingested through the mouth 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 a 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. As an example, alcohol is metabolized into an aldehyde. The aldehyde is what causes a hangover effect.

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.

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

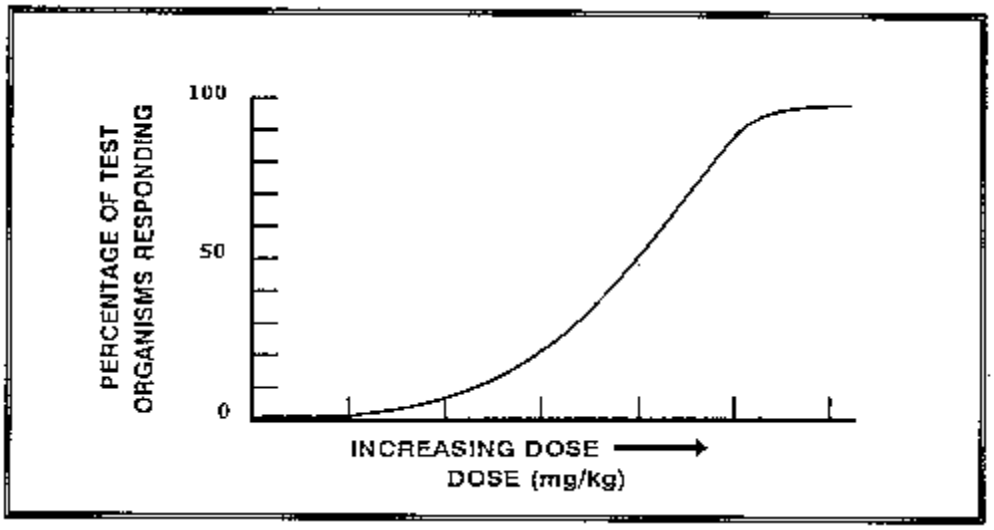
- **Quantity per unit mass (or weight)**. Usually expressed as milligram per kilogram of body weight (mg/kg).

- **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 (parts per million or 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 discussed below.

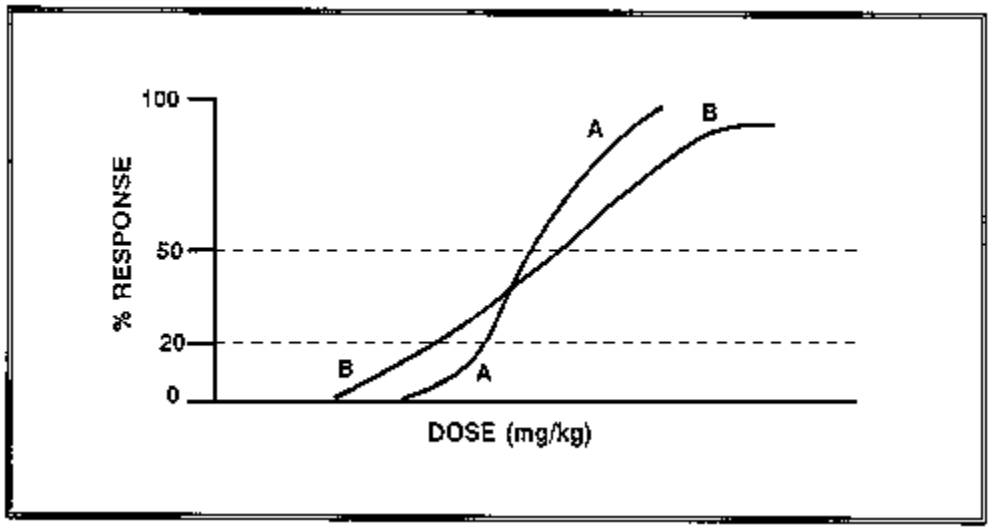


Graph 1
Hypothetical Dose-Response Curve

Dose-Response Terms. Common dose-response terms follow.

- **Toxic dose low (TD_{LO})**: The lowest dose of a substance introduced by a specified route, other than inhalation, over any given period of time, and reported to produce a specified toxic effect in a specified species.
- **Toxic concentration low (TC_{LO})**: The lowest concentration of a substance in air to which a specified species been exposed for any given period of time that has produced a specified toxic effect.
- **Lethal dose low (LD_{LO})**: The lowest dose of a substance introduced by a specified route, other than inhalation, which has been reported to have caused death in a specified species.
- **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 exposure to the substance by any route other than inhalation.
- **Lethal concentration low (LC_{LO})**: The lowest concentration of a substance in airwhich 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 the 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.



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.

- **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.
- **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.
- **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, Antabuse, 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.

Uses of Toxicity Information

Comparison of Toxicity Data. Comparing the LD_{50} of chemicals 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**)**. The following table is a summary of Acute Toxicity categories established by the United States Occupational Safety and Health Administration.

Acute Toxicity	Cat. 1	Cat. 2	Cat. 3	Cat. 4	Cat. 5
Oral (mg/Kg)	≤ 5	>5 ≤ 50	>50 ≤ 300	>300 ≤ 2000	Criteria: Anticipated oral LD50 between 2000 and 5000 mg/kg; Indication of significant effect in humans; Any mortality at class 4; Significant clinical signs at class 4.
Dermal (mg/Kg)	≤ 50	>50 ≤ 200	>200 ≤ 1000	>1000 ≤ 2000	
Gases (ppm)	≤ 100	>100 ≤ 500	>500 ≤ 2500	>2500 ≤ 5000	
Vapors (ml/L)	≤ 0.5	>0.5 ≤ 2.0	>2.0 ≤ 10	>10 ≤ 20	
Dusts & mists (mg/L)	≤ 0.05	>0.05 ≤ 0.5	>0.5 ≤ 1.0	>1.0 ≤ 5	

Establishing Exposure Guidelines. Toxicity data from both animal experimentation and epidemiological studies is used to establish exposure guidelines. Exposure guidelines are established by various entities and are discussed later in this document.

Exposure Limits

Several organizations publish exposure limits for certain chemicals. Typically, exposure limits vary from one source to another because each use differing criteria when establishing their own unique exposure limit. Each organization uses unique terminology to describe their exposure limits.

- **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). ACGIH calls their exposure limits

Threshold Limit Values or TLVs. ACGIH also 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.

- **Occupational Safety and Health Administration (OSHA)**. The Occupational Safety and Health Administration (OSHA) promulgates Permissible Exposure Limits (PELs). PELs are found in 29 CFR 1910.1000. Because OSHA is a regulatory agency, their PELs are legally enforceable standards. OSHA has promulgated PELs for only a few dozen chemicals.
- **National Institute for Occupational Safety and Health (NIOSH)**. The National Institute for Occupational Safety and Health (NIOSH) publishes Recommended Exposure Limits (RELs).
- **American Industrial Hygiene Association (AIHA)**. The American Industrial Hygiene Association publishes Workplace Environmental Exposure Level Guides (WEELs). These are reviewed and updated each year. AIHA focuses on establishing exposure limits for chemicals for which other groups do not have exposure guidelines. Thus, they are providing information to fill the gaps left by others.

Expression of Exposure Guidelines

Airborne exposures and exposure limits are usually expressed as 8-hour Time-Weighted Averages (TWAs), Short-Term Exposure Limits, and Ceiling Values.

- **Time-Weighted Average (TWA)**. TWAs are expressed as the average concentration of a chemical that a worker is exposed to during a normal 8-hour work day. When exposures vary throughout the day, the actual exposure must be calculated to account for these variations and then compared to established exposure limits expressed as an 8-hour TWA. For example, consider a worker exposed to acetone at a concentration of 1000 ppm for 3 hours, 500 ppm for 2 hours, and 200 ppm for three hours in an 8-hour work day. The workers calculated average 8-hour exposure is 575 ppm.

$$[(3hrs)(1000ppm) + (2hrs)(500ppm) + (3hrs)(200ppm)] / 8\ hrs = 575\ ppm$$

This exposure would be compared to the desired 8-hour TWA **exposure limit**. OSHA's PEL expressed as a TWA is 1000 ppm; NIOSH's REL expressed as a TWA is 250 ppm;

ACGIH's TLV expressed as TWA is 500 ppm. In this example, the worker's exposure exceeds the more conservative NIOSH and ACGIH values, but not OSHA's

- **Short-Term Exposure Limit (STEL)**. Exposure limits expressed as an 8-hour TWA do not consider potential adverse effects that could occur when exposed to high concentrations of a chemical but for very short periods of time. This is why STELs were developed. A STEL is expressed as a 15-minute TWA exposure that should not be exceeded during a workday, even if the 8-hour TWA is within the exposure limit. 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. Continuing with our acetone exposure example above, ACGIH has established a STEL for acetone of 750 ppm. In this example, the worker has been exposed above both the STEL (3 hours of exposure at 1000 ppm) and TLV (8-hour TWA of 575 ppm).

- **Ceiling Limit (C)**. In some cases, a worker should not be exposed to a particular chemical above a certain concentration for any period of time, regardless of whether their cumulative exposure throughout the day remains below the 8-hour TWA exposure limit. In such cases, a "Ceiling Limit" may be established. In those cases where a Ceiling Limit have been established, it shall not be exceed for any period of time regardless of any established STEL or 8-hour TWA exposure limit.

- **"Skin" Notation**. 8-hour TWA, STEL, and Ceiling limits are specific to airborne exposures. 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

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.

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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