Chapter 2

Toxicology

Toxicology

- Toxicology was defined as the science of poisons

  "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy."
- A fundamental principle of toxicology is

  "There are no harmless substances, only harmless ways of using substances"
- Toxicology is more adequately defined as the qualitative and quantitative study of the adverse effects of toxicants on biological organisms

Toxicology

- Quantity and variety of chemicals used by the chemical process industries,
- Chemical engineers must be knowledgeable about
  - The way toxicants enter biological organisms
  - The way toxicants are eliminated from biological organisms
  - The effects of toxicants on biological organisms
  - Methods to prevent or reduce the entry of toxicants into biological organisms
- The first three areas are related to toxicology
- The last area is essentially industrial hygiene

Toxicology

- Toxicant can be a chemical or physical agent, including dusts, fibers, noise, and radiation

  Example: of a physical agent is asbestos fiber, a known cause of lung damage and cancer.
- Toxicity of a chemical or physical agent is a property of the agent
- The toxic hazard of a substance can be reduced by the application of appropriate industrial hygiene techniques.
- The toxicity, however, cannot be changed

How Toxicants Enter Biological Organisms

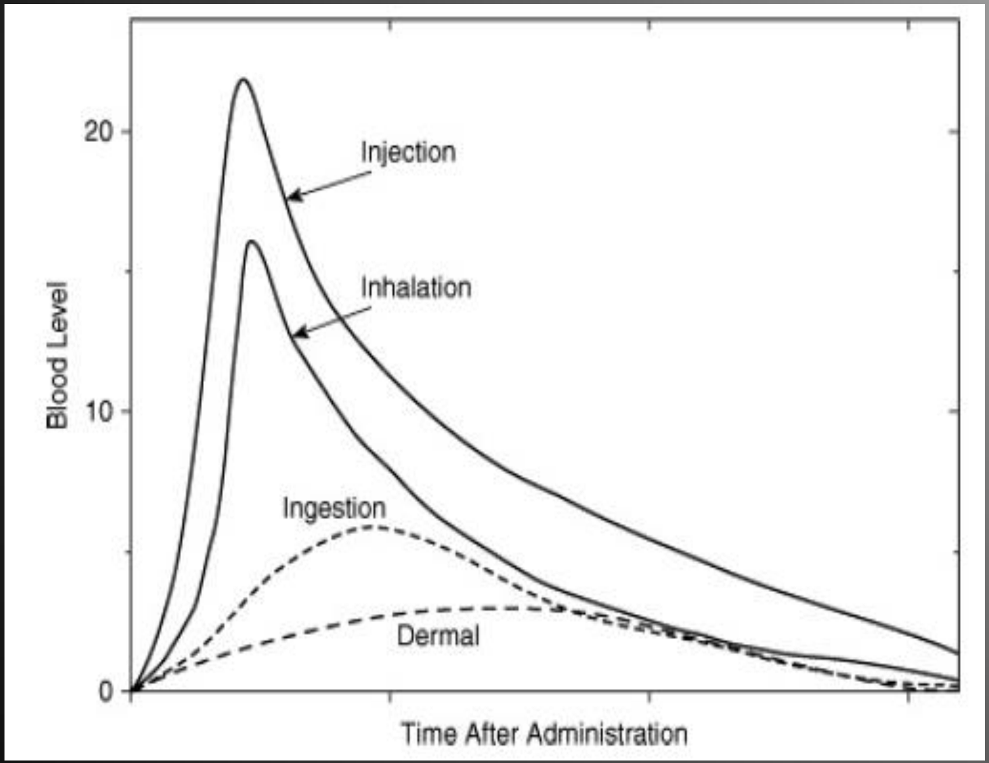
- Toxicants enter biological organisms by the following routes:
  - ✓ Ingestion: through the mouth into the stomach
  - ✓ Inhalation: through the mouth or nose into the lungs
  - ✓ Injection: through cuts into the skin
  - ✓ Dermal absorption: through skin membrane

Entry route	Entry organ	Method for control
Ingestion	Mouth or stomach	Enforcement of rules on eating, drinking, and smoking
Inhalation	Mouth or nose	Ventilation, respirators, hoods, and other personal protection equipment
Injection	Cuts in skin	Proper protective clothing
Dermal absorption	Skin	Proper protective clothing

How Toxicants Enter Biological Organisms

- All these entry routes are controlled by the application of proper industrial hygiene techniques
- Inhalation and dermal routes are the most significant to industrial facilities
- Inhalation is the easiest to quantify by the direct measurement of airborne concentrations
- vapor, but small solid and liquid particles can also contribute
- Toxicants that enter by injection and dermal absorption are difficult to measure and quantify.
- Some toxicants are absorbed rapidly through the skin.

Toxic blood-level concentration as a function of route of exposure



- Blood-level concentration as a function of time and route of entry
- The gastrointestinal (GI) tract, the skin, and the respiratory system play significant roles in the various routes of entry.

How Toxicants Are Eliminated from Biological Organisms

- Toxicants are eliminated or rendered inactive by the following routes
  - Excretion: through the kidneys, liver, lungs, or other organs
  - Detoxification: by changing the chemical into something less harmful by biotransformation
  - Storage: in the fatty tissue
- The toxicants are extracted by the kidneys from the bloodstream and are excreted in the urine
- The digestive tract tends to selectively detoxify certain agents
- Inhalation, injection, or dermal absorption generally arrive in the bloodstream unchanged

Eliminated from Biological Organisms

- The lungs : Volatile Chloroform and alcohol,
  Example: Excreted partially by this route
- The liver: (detoxification) Biotransformation reactions can also occur in the blood, intestinal tract wall, skin, kidneys, and other organs
- Storage: (Depositing) chemical agent mostly in the fatty areas of the organism but also in the bones, blood, liver, and kidney.
- Storage can create a future problem if fatty deposits are metabolized; the stored chemical agents will be released into the bloodstream, resulting in possible damage.

Effects of Toxicants on Biological Organisms

Various Responses to Toxicants

Effects that are irreversible

- *Carcinogen* causes cancer
- *Mutagen* causes chromosome damage
- *Reproductive hazard* causes damage to reproductive system
- *Teratogen* causes birth defects

Effects that may or may not be reversible

- *Dermatotoxic* affects skin
- *Hemotoxic* affects blood
- *Hepatotoxic* affects liver
- *Nephrotoxic* affects kidneys
- *Neurotoxic* affects nervous system
- *Pulmonotoxic* affects lungs

Baseline studies on new employees

- Respiratory problems are diagnosed using a spirometer.

  (1) the total volume exhaled, called the forced vital capacity (FVC), with units in liters;

  (2) the forced expired volume measured at 1 second (FEV1), with units in liters per second;

  (3) forced expiratory flow in the middle range of the vital capacity (FEV 25–75%), measured in liters per second

  (4) ratio of the observed FEV1 to FVC × 100 (FEV1/FVC%).

Respiratory problems

- Reductions in expiration flow (bronchial disease) such as asthma or bronchitis.
- Reductions in FVC are due to reduction in the lung or chest volume (fibrosis) (an increase in the interstitial fibrous tissue in the lung).
- The air remaining in the lung after exhalation is called the residual volume (RV) (emphysema).
- RV measurement : tracer test with helium.

Nervous system disorder

Diagnosed by examining the mental status

- ✓Cranial nerve function
- ✓ Motor system reflexes
- ✓Sensory systems.

An electroencephalogram (EEG) tests higher brain and nervous system functions

Toxic exposures

- ✓Changes in skin texture, pigmentation, vascularity, and hair and nail appearance are indicative of possible toxic exposures
- ✓Blood counts are also used to determine toxic exposures

Toxicological Studies

- Quantify the effects of the suspect toxicant on a target organism
- Toxicological studies animals are used, hope that the results can be extrapolated to humans

  Following items must be identified:

  - The toxicant
  - The target or test organism
  - The effect or response to be monitored
  - The dose range
  - The period of the test
- For studies determining the effects on specific organs such as the lungs, kidneys, or liver, higher organisms

Dose

- Dose units depend on the method of delivery

  Ingestion or injection: Dose is measured in milligrams of agent per kilogram of body weight

  Gaseous airborne substances : the dose is measured in either parts per million (ppm) or milligrams of agent per cubic meter of air (mg/m^3)

  Airborne particulates: the dose is measured in milligrams of agent per cubic meter of air (mg/m^3) or millions of particles per cubic foot (mppcf).

The period of the test depends on whether long- or short-term effects are of interest

Toxicological studies

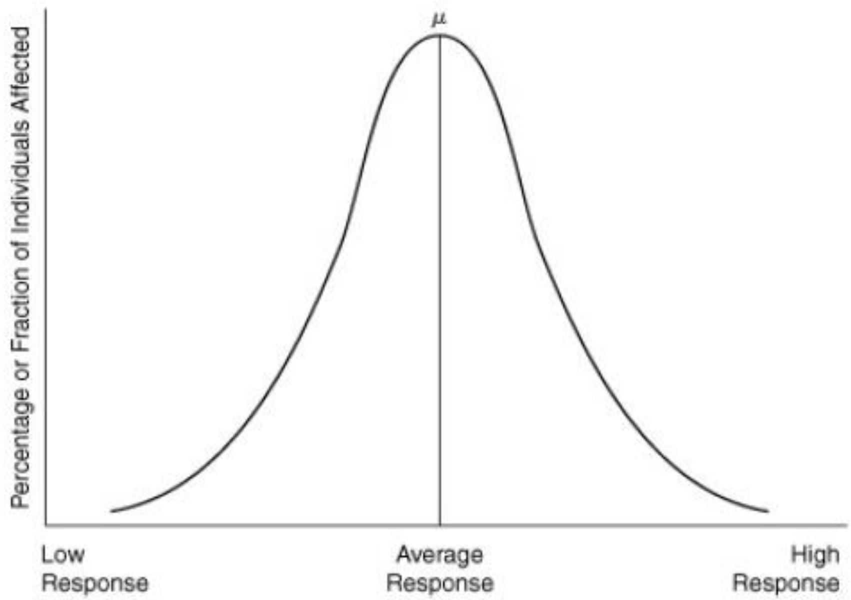
- **Acute toxicity:** effect of a single exposure or a series of exposures close together in a short period of time
- **Chronic toxicity:** Effect of multiple exposures occurring over a long period of time.
- Chronic toxicity studies are difficult to perform because of the time involved;
- most toxicological studies are based on acute exposures.

Dose versus Response

- Biological organisms respond differently to the same dose of a toxicant, depends on age, sex, weight, diet.
- Toxicological test run on a large number of individuals. Each individual is exposed to the same dose and the response is recorded.

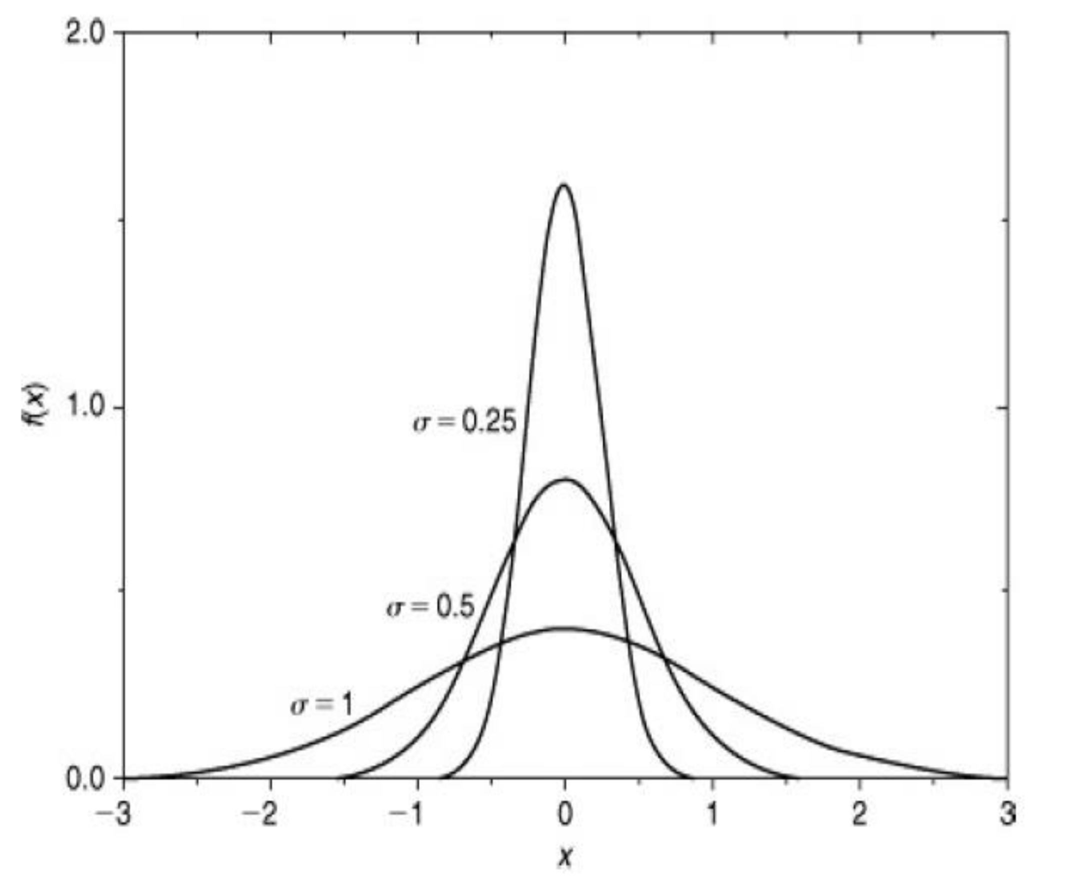
Normal or Gaussian distribution

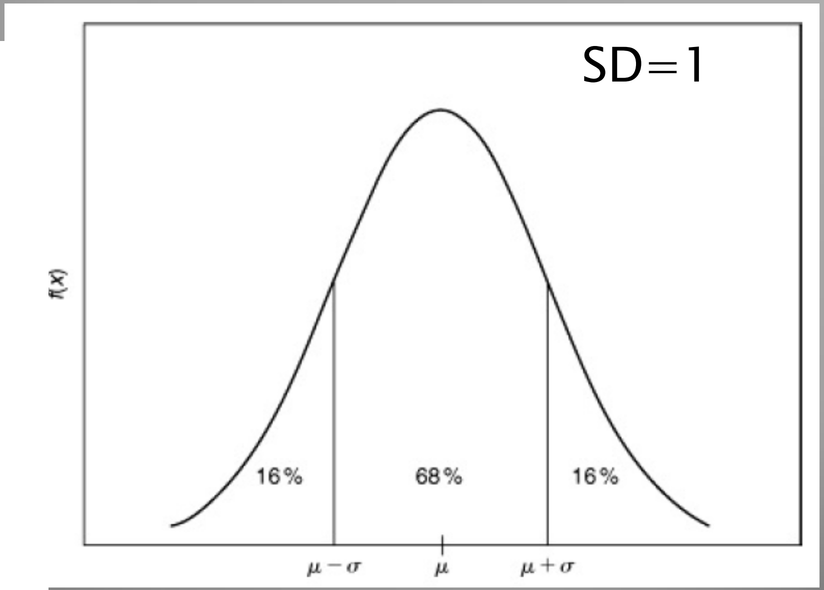
$$f(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{1}{2}\left(\frac{x-\mu}{\sigma}\right)^2},$$

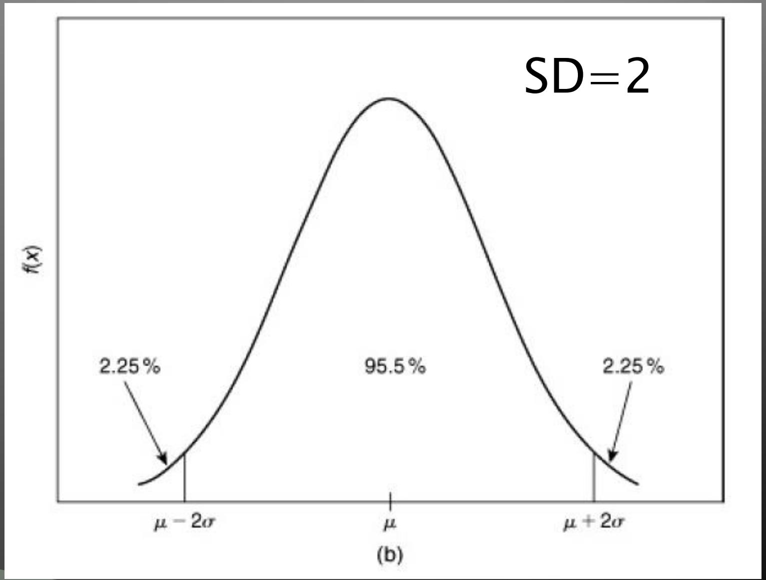


$f(x)$ is the probability (or fraction) of individuals experiencing a specific response,
x is the response,
σ is the standard deviation, and μ is the mean.

Standard deviation on a normal distribution



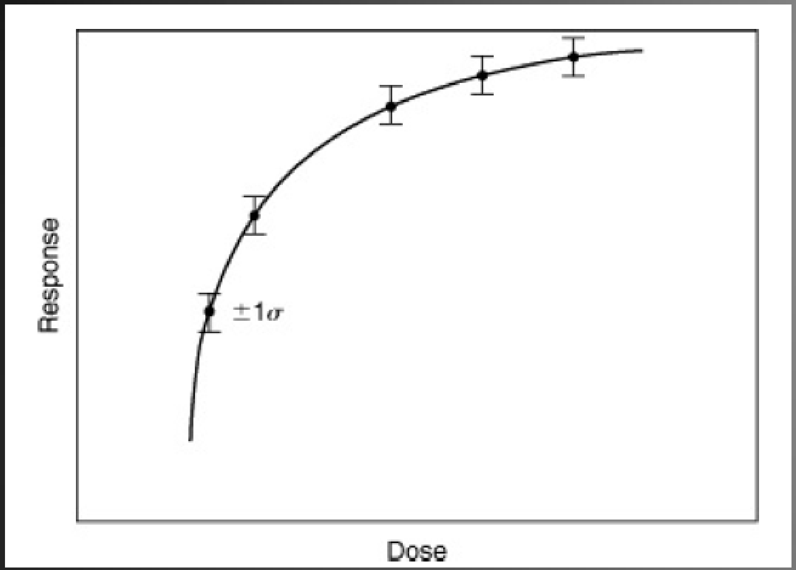


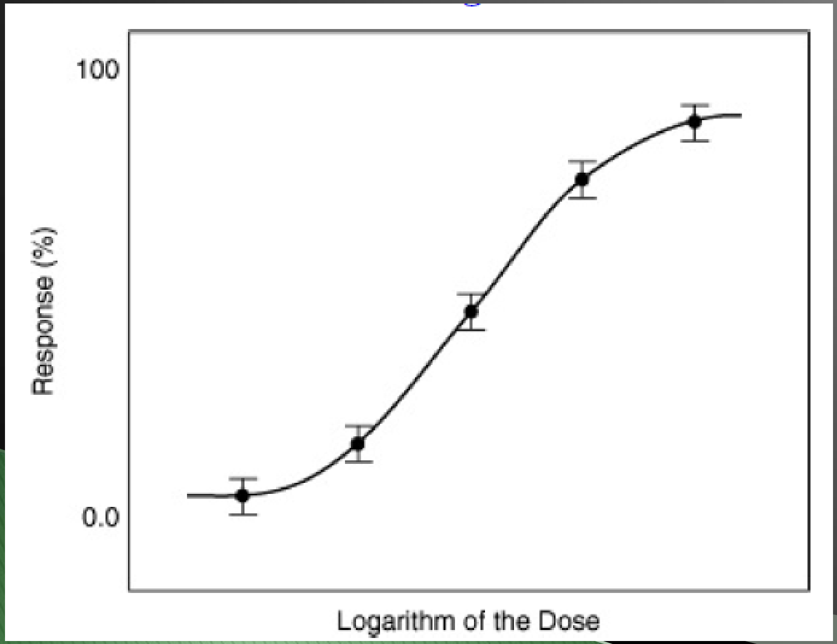


Standard deviation on a normal distribution

- As the standard deviation decreases, the distribution curve becomes more pronounced around the mean value.
- The area under the curve represents the percentage of individuals affected for a specified response interval.
- 1 standard deviation of the mean represents 68% of the individuals
- Response interval of 2 standard deviations represents 95.5% of the total individuals
- The area under the entire curve represents 100% of the individuals.

Dose-response curve



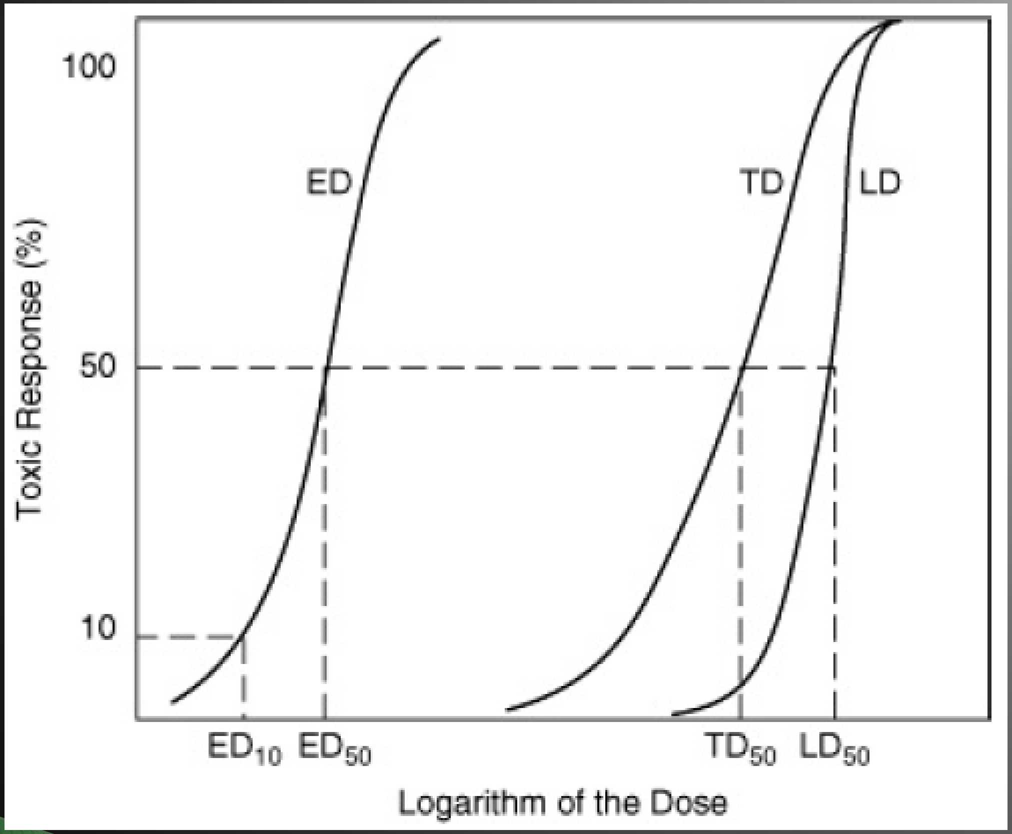


response of interest is death or lethality

- Response versus log dose curve of a lethal dose curve
  - LD_{50} lethal dose for 50% of the subjects
- Gases: LC (lethal conc.)
- Chemical or agent is minor:
  - response–log dose curve is called the effective dose (ED) curve
- Agent is toxic: toxic dose, or
  - TD curve.

Dose-response curve

Response-dose curves are developed using acute toxicity data



- The various types of response versus log dose curves.
- ED (effective dose)

  TD (toxic dose)

  LD (lethal dose)

  gases, LC (lethal concentration)

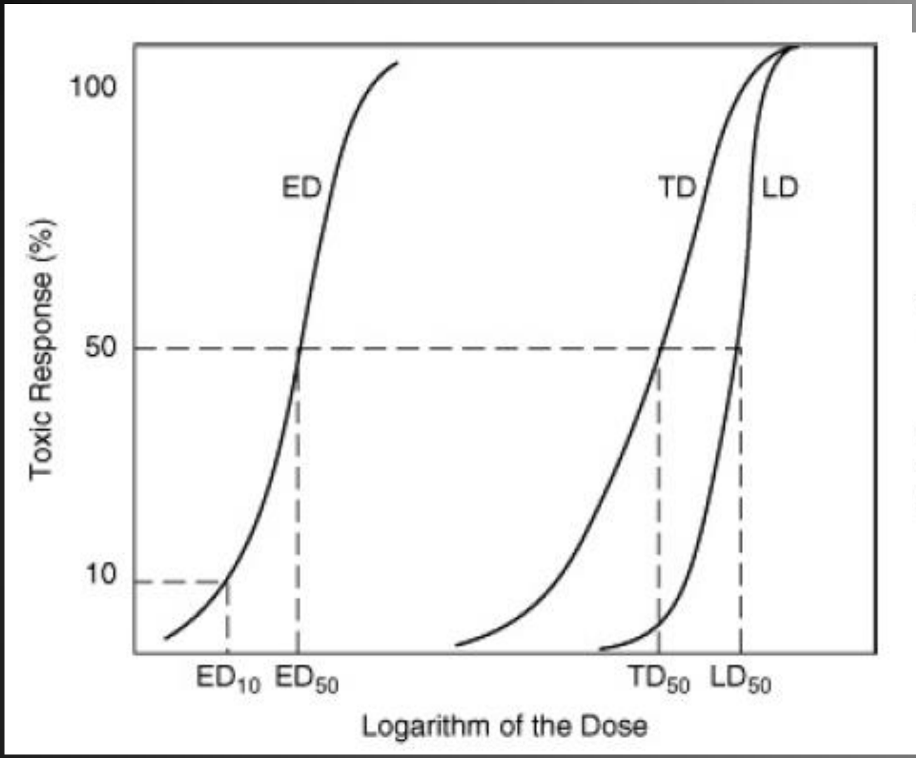
Relative Toxicity

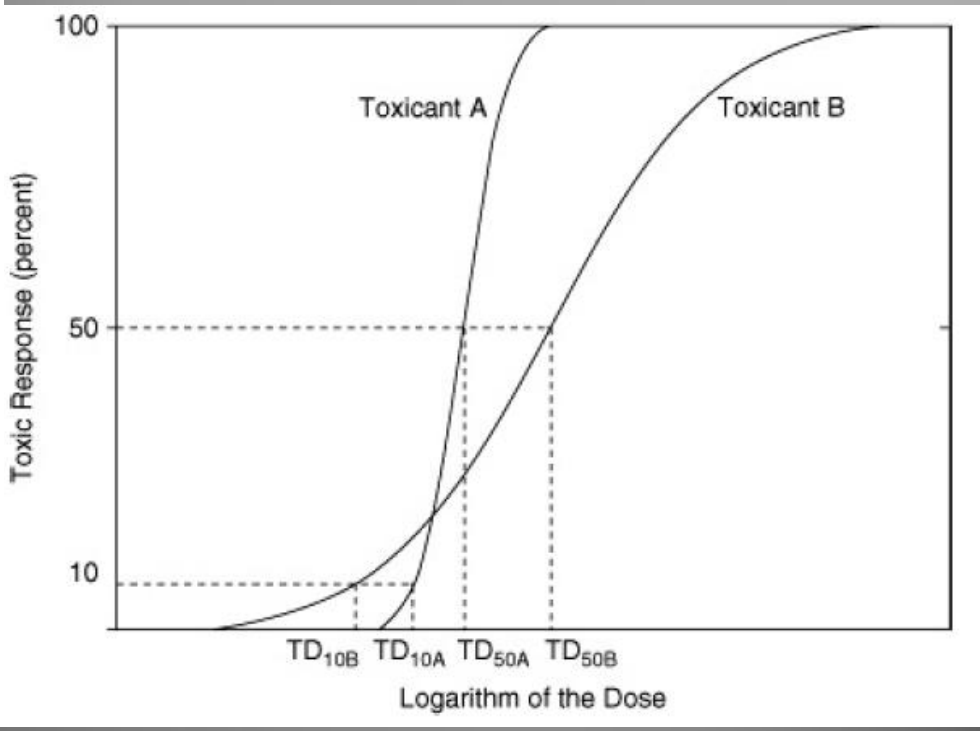
- Hodge-Sterner table for the degree of toxicity

Experimental LD_{50} per kilogram of body weight	Degree of toxicity	Probable lethal dose for a 70-kg person
<1.0 mg	Dangerously toxic	A taste
1.0–50 mg	Seriously toxic	A teaspoonful
50–500 mg	Highly toxic	An ounce
0.5–5 g	Moderately toxic	A pint
5–15 g	Slightly toxic	A quart
>15 g	Extremely low toxicity	More than a quart

- **toxicants with differing relative toxicities at different doses.**

Relative Toxicity





Right of the response-dose curve for chemical is more toxic

Relative Toxicity

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Threshold Limit Values (TLVs)

- The lowest value on the response versus dose curve is called the threshold dose
- The exposure occurs only during normal working hours, eight hours per day and five days per week.
- Below this dose the body is able to detoxify and eliminate the agent without any detectable effects
- The American Conference of Governmental Industrial Hygienists (ACGIH) has established TLVs, for chemical agents
- The TLV was formerly called the maximum allowable concentration (MAC).
- Three different types of TLVs (TLV-TWA, TLV-STEL, and TLV-C)

Threshold Limit Values

TLV type	Definition
TLV-TWA	Threshold limit value—time-weighted average
	The concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect.
TLV-STEL	Threshold limit value—short-term exposure limit
	A 15-minute TWA exposure that should not be exceeded at any time during a workday, even if the 8-hour TWA is within the TLV-TWA. The TLV-STEL is the concentration to which it is believed that workers can be exposed continuously for a short period of time without suffering (1) irritation, (2) chronic or irreversible tissue damage, (3) dose-rate-dependent toxic effects, or (4) narcosis of sufficient degree to increase the likelihood of accidental injury, impaired self-rescue, or materially reduced work efficiency. Exposures above the TLV-TWA up to the TLV-STEL should be less than 15 minutes, should occur no more than four times per day, and there should be at least 60 minutes between successive exposures in this range.
TLV-C	Threshold limit value—ceiling
	The concentration that should not be exceeded during any part of the working exposure.

Threshold Limit Values

- OSHA has defined its own threshold dose, called a permissible exposure level (PEL)
- PEL values follow the TLV-TWA of the ACGIH closely
- Some toxicants (particularly carcinogens) have zero thresholds.
- Another quantity frequently reported is the amount immediately dangerous to life and health (IDLH).
- TLVs are reported using
  - ppm (parts per million by volume),
  - mg/m^3 (milligrams of vapour per cubic meter of air),
  - dusts, mg/m^3
  - mppcf (millions of particles per cubic foot of air).

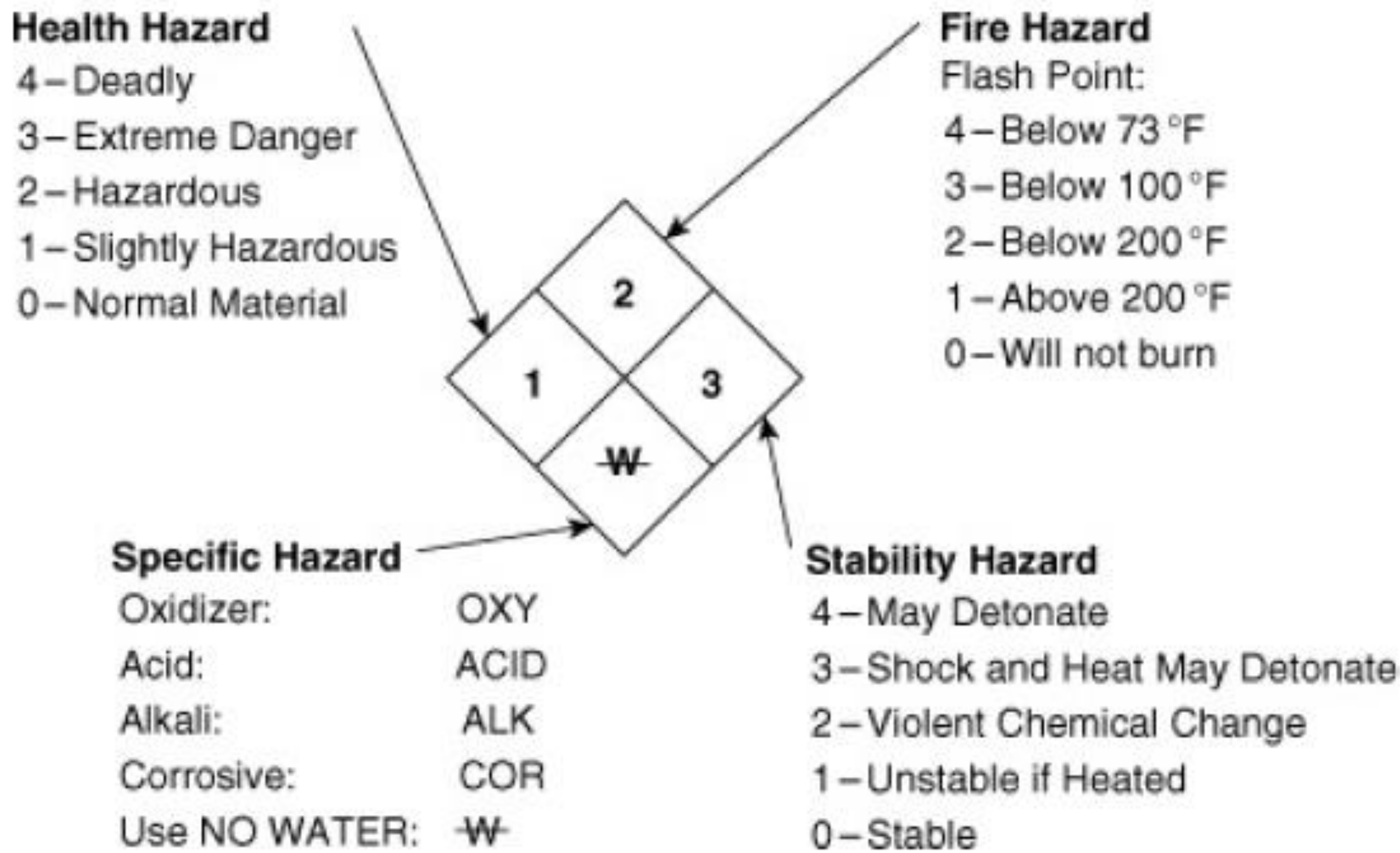
- For vapours, mg/m^3 is converted to ppm using the equation

$$C_{ppm} = \text{Concentration in ppm} = \frac{22.4}{M}\left(\frac{T}{273}\right)\left(\frac{1}{P}\right)(mg/m^3)$$

$$= 0.08205\left(\frac{T}{PM}\right)(mg/m^3),$$

- **National Fire Protection Association (NFPA) Diamond**
- The NFPA is a professional society that was established in 1896 to reduce worldwide fatalities and injuries due to fires and other hazards
- Their primary function is to promote Consensus codes and standards, including the National Electrical Code (NEC).

National Fire Protection Association (NFPA) Diamond



The NFPA diamond frequently appears on chemical containers and storage vessels

On-Line Resources

- American Conference of Governmental Industrial Hygienists (ACGIH), www.acgih.org.
- *NIOSH Pocket Guide to Chemical Hazards.* www.cdc.gov/niosh/npg/
- Society of Toxicology www.toxicology.org.
- TOXNET, Toxicology Data Network provided by the U.S. www.toxnet.nlm.nih.gov.
- U.S. Department of Labor, Occupational Safety and Health Administration.

  www.osha.gov