TRAINING FOR THE HEALTH SECTOR

Introduction to Toxicology

Children's Health and the Environment

CHEST Training Package for the Health Sector

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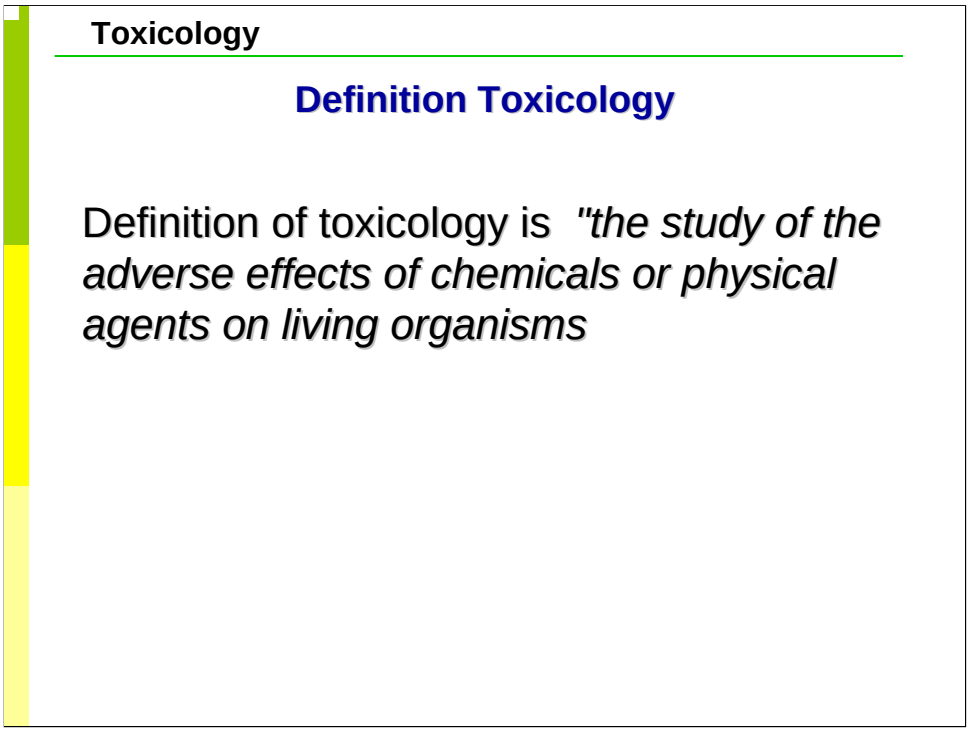


The traditional definition of **toxicology** is ***"the science of poisons."*** As our understanding of how various agents can cause harm to humans and other organisms, a more descriptive definition of toxicology is *"the study of the adverse effects of chemicals or physical agents on living organisms"*.

Adverse effects may occur in many forms, ranging from immediate death to subtle changes not realized until months or years later. They may occur at various levels within the body, such as an organ, a type of cell, or a specific biochemical. Knowledge of how toxic agents damage the body has progressed along with medical knowledge. It is now known that various observable changes in anatomy or body functions actually result from previously unrecognized changes in specific biochemicals in the body.

The textbooks listed below are quite comprehensive and widely used in basic toxicology training courses.
Casarett and Doull's Toxicology (*C. Klaassen, M. Amdur, and J. Doull, eds.)*
Principles and Methods of Toxicology *(A. W. Hayes, ed.)*
Basic Environmental Toxicology *(L. Cockerham and B. Shane, eds.)*

Toxicology

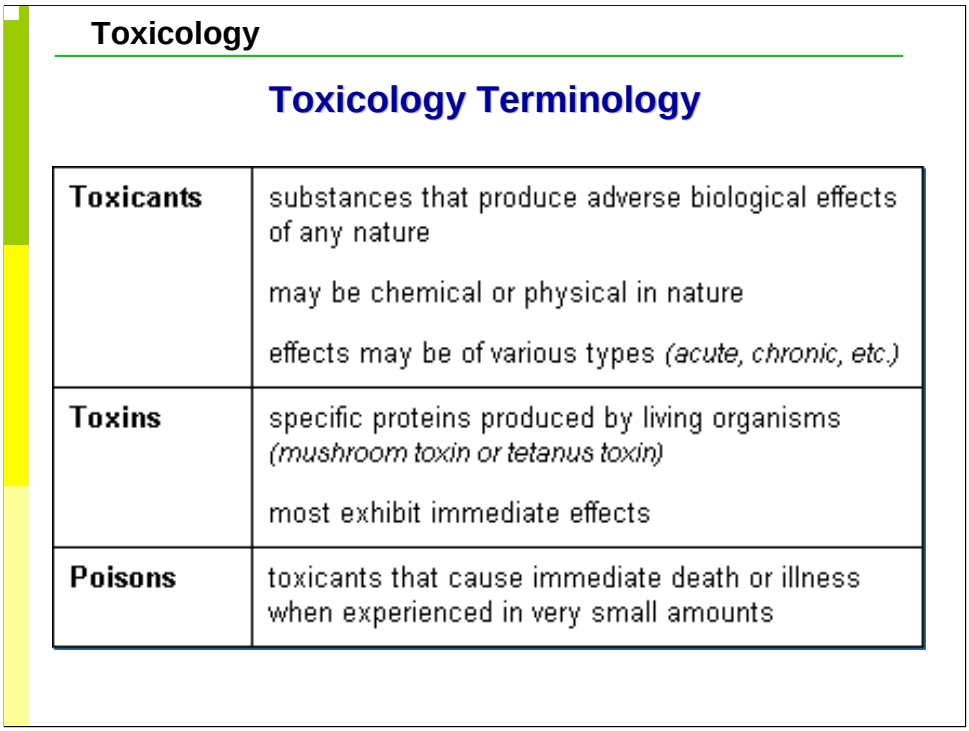
Philippus Theophrastus Aureolus
Bombastus von Hohenheim
PARACELSUS
(Einsiedeln, Zürich, 1493 -
Salzburg, 1541)

All substances are poisons; it is the dose that makes the poison

The **historical development of toxicology** began with early cave dwellers who recognized poisonous plants and animals and used their extracts for hunting or in warfare. By 1500 BC, written recordings indicated that hemlock, opium, arrow poisons, and certain metals were used to poison enemies or for state executions.
With time, poisons became widely used and with great sophistication. Notable poisoning victims include Socrates, Cleopatra, and Claudius. By the time of the Renaissance and Age of Enlightenment, certain concepts fundamental to toxicology began to take shape. The studies of Paracelsus *(~1500AD)* and Orfila *(~1800 AD) are well known.*

Paracelsus determined that specific chemicals were actually responsible for the toxicity of a plant or animal poison. He also documented that the body's response to those chemicals depended on the dose received. His studies revealed that small doses of a substance might be harmless or beneficial whereas larger doses could be toxic. This is now known as the dose-response relationship, a major concept of toxicology. Paracelsus was one of the founders of modern toxicology. His best known quote: *All substances are poisons;* it is the dose that makes the poison.
Orfila, a Spanish physician, is often referred to as the **founder of toxicology**. It was Orfila who first prepared a systematic correlation between the chemical and biological properties of poisons of the time. He demonstrated effects of poisons on specific organs by analyzing autopsy materials for poisons and their associated tissue damage.
The 20th century is marked by an advanced level of understanding of toxicology. DNA *(the molecule of life)* and various biochemicals that maintain body functions were discovered. Our level of knowledge of toxic effects on organs and cells is now being revealed at the molecular level. It is recognized that virtually all toxic effects are caused by changes in specific cellular molecules and biochemicals.

Xenobiotic is the general term that is used for a ***foreign*** substance taken into the body. It is derived from the Greek term *xeno* which means *"foreigner."* Xenobiotics may produce beneficial effects *(such as a pharmaceuticals)* or they may be toxic *(such as lead)*.
As Paracelsus proposed centuries ago, dose differentiates whether a substance will be a remedy or a poison. A xenobiotic in small amounts may be non-toxic and even beneficial but when the dose is increased, toxic and lethal effects may result.



T**oxicology** is the study of the adverse effects of chemicals or physical agents on living organisms. A **toxicologist** is a scientist that determines the harmful effects of agents and the cellular, biochemical, and molecular mechanisms responsible for the effects.

Toxicant, toxin, and poison are often used interchangeably in the literature; however, there are subtle differences as indicated in the table.
Toxic substances may be **systemic toxins** or **organ toxins**.
A **systemic toxin** is one that affects the entire body or many organs rather than a specific site. For example, potassium cyanide is a systemic toxicant in that it affects virtually every cell and organ in the body by interfering with the cell's ability to utilize oxygen.
Toxicants may also affect only specific tissues or organs while not producing damage to the body as a whole. These specific sites are known as the **target organs** or **target tissues**.
Some examples: Benzene is a **specific organ toxin** in that it is primarily toxic to the blood-forming tissues.
Lead is also a specific organ toxin; however, it has three **target organs** *(central nervous system, kidney, and hematopoietic system)*.

Toxic agent or substance

Toxic agent is anything that can produce an adverse biological effect. It may be chemical, physical, or biological in form.

Toxic agents may be:

chemical *(such as cyanide)*,

physical *(such as radiation)* and

biological *(such as snake venom)*.

Toxic substance is simply a material which has toxic properties.

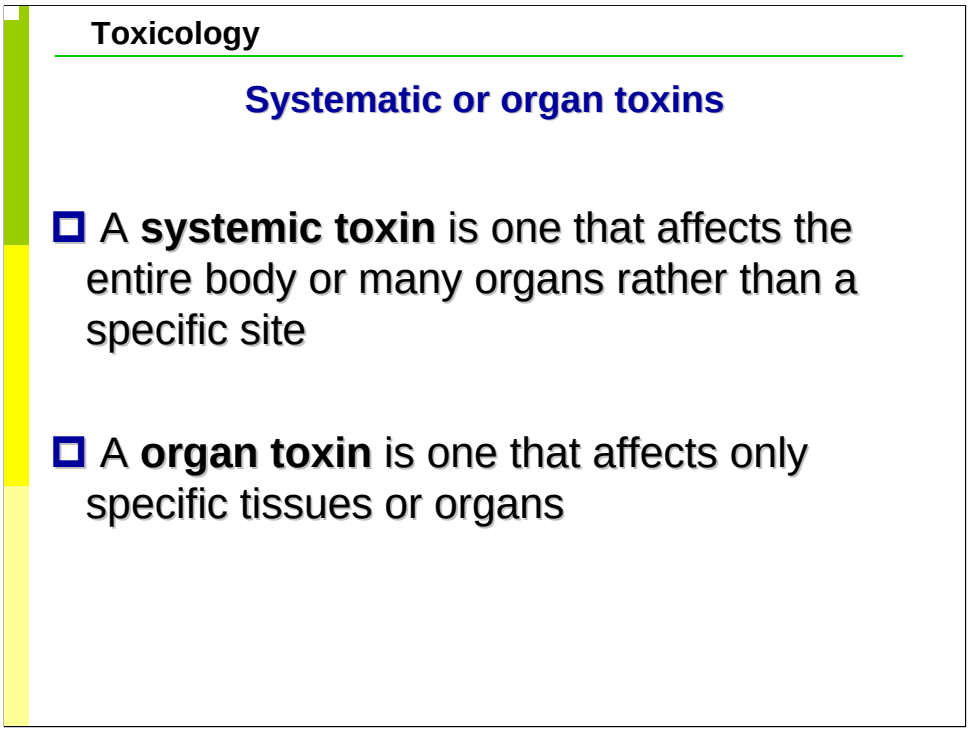
A **toxic agent** is anything that can produce an adverse biological effect. It may be chemical, physical, or biological in form. For example, toxic agents may be chemical *(such as cyanide)*, physical *(such as radiation)* and biological *(such as snake venom)*.

A distinction is made for diseases due to biological organisms. Those organisms that invade and multiply within the organism and produce their effects by biological activity are not classified as toxic agents. An example of this is a virus that damages cell membranes resulting in cell death.

If the invading organisms excrete chemicals which is the basis for toxicity, the excreted substances are known as **biological toxins**. The organisms in this case are referred to as **toxic organisms**. An example is tetanus. Tetanus is caused by a bacterium, *Clostridium tetani*. The bacteria *C. tetani* itself does not cause disease by invading and destroying cells. Rather, it is a toxin that is excreted by the bacteria that travels to the nervous system *(a neurotoxin)* that produces the disease.

A **toxic substance** is simply a material which has toxic properties. It may be a discrete toxic chemical or a mixture of toxic chemicals. For example, lead chromate, asbestos, and gasoline are all toxic substances. Lead chromate is a discrete **toxic chemical.** Asbestos is a **toxic material** that does not consist of an exact chemical composition but a variety of fibers and minerals. Gasoline is also a **toxic substance** rather than a toxic chemical in that it contains a mixture of many chemicals. Toxic substances may not always have a constant composition. For example, the composition of gasoline varies with octane level, manufacturer, time of season, etc.
oxic substances may be organic or inorganic in composition

Organic toxins	substances that were originally derived from living organisms *(thus named organic)* contain carbon and often are large molecules can be synthesized *(that is man-made)* as well as be obtained from natural sources
Inorganic toxins	specific chemicals that are not derived from living organisms *(minerals)* generally small molecules consisting of only a few atoms *(such as nitrogen dioxide)*



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A toxicant may affect a specific type of tissue *(such as connective tissue)* that is present in several organs. The toxic site is then referred to as the **target tissue**.
There are many types of cells in the body and they can be classified in several ways.
basic structure (e.g., cuboidal cells)
tissue type (e.g., hepatocytes of the liver)
germinal cells (e.g., ova and sperm)
somatic cells (e.g., non-reproductive cells of the body)

Germ cells are those cells that are involved in the reproductive process and can give rise to a new organism. They have only a single set of chromosomes peculiar to a specific sex. Male germ cells give rise to sperm and female germ cells develop into ova. Toxicity to germ cells can cause effects on the developing fetus *(such as birth defects, abortions)*.
Somatic cells are all body cells except the reproductive germ cells. They have two sets *(or pairs)* of chromosomes. Toxicity to somatic cells causes a variety of toxic effects to the exposed individual *(such as dermatitis, death, and cancer)*.

Factors determining adverse effects

- **intrinsic toxicity**
- dose
- exposure conditions
- response of host

Several factors will be discussed determining the adverse effects of toxic agents.

Intrinsic toxicity

- **Chemical properties**
  - molecular structure & functional groups
  - solubility - insolubility
  - volatility
  - stability (light, water, acids, enzymes, …)
  - reactivity
- **Physical properties**
  - gas (density, …)
  - liquid (vapour pressure, …)
  - solid (crystal structure, size, shape, …)

Information on chemical properties and physical properties of toxic agents can be found at several websites.

Material Safety Data Sheets are available for most chemicals. US Environmental Protection Agency has a site called IRIS with plenty of data on chemical properties.

Stability means that some compounds might change under influence of light, water, acids or other external factors.

The same data sheets have information about the physical properties of chemicals.

Misunderstandings

- Natural compounds ≠ safe compounds
- Synthetic agents ≠ toxic agents

- Pure substance
  - ≠ pure substance + impurities
  - ≠ pure substance in (complex) mixture

These are some reminders about common misunderstandings.

Sometimes there is confusion about the terminology related to compounds.

Factors determining adverse effects

- intrinsic toxicity
- **dose**
- exposure conditions
- response of host

The second factor determining adverse efects is the **dose**.

Dose

The dose is the amount of a substance administered at one time

Dose by definition is the amount of a substance administered at one time. However, other parameters are needed to characterize the exposure to xenobiotics. The most important are the number of doses, frequency, and total time period of the treatment.

Some examples:

500 mg Asperin as a single dose

500 mg Penicillin every 8 hours for 10 days

15 mg DDT per day for 60 days

Toxicology

Dose

Types of doses, e.g., exposure dose, absorbed dose, administered dose and total dose

Exposure dose	the amount of a xenobiotic encountered in the environment
Absorbed dose	the actual amount of the exposed dose that enters the body
Administered dose	the quantity administered usually orally or by injection
Total dose	the sum of all individual doses

There are numerous **types of doses**, e.g., exposure dose, absorbed dose, administered dose and total dose.
F**ractionating** a total dose usually decreases the probability that the total dose will cause toxicity. The reason for this is that the body often can repair the effect of each subtoxic dose if sufficient time passes before receiving the next dose. In such a case, the total dose, harmful if received all at once, is non-toxic when administered over a period of time. For example, 30 mg of strychnine swallowed at one time could be fatal to an adult whereas 3 mg of strychnine swallowed each day for ten days would not be fatal.

Toxicology

Dose units

Unit	Gram Equivalents	Exp. Form
Kilogram (kg)	1000.0 g	10^{3} g
Gram (g)	1.0 g	1 g
Milligram (mg)	0.001 g	10^{-3} g
Microgram (µg)	0.000,001 g	10^{-6} g
Nanogram (ng)	0.000,000,001 g	10^{-9} g
Picogram (pg)	0.000,000,000,001 g	10^{-12} g
Femtogram (fg)	0.000,000,000,000,001 g	10^{-15} g

The **units** used in toxicology are basically the same as those used in medicine. The **gram** is the standard unit. However, most exposures will be smaller quantities and thus the **milligram (mg)** is commonly used. For example, the common adult dose of Tylenol is 650 milligrams.
The clinical and toxic effects of a dose must be related to age and body size. For example, 650 mg is the adult dose of Tylenol. That would be quite toxic to young children, and thus Children's Tylenol tablets contain only 80 mg. A better means to allow for comparison of effectiveness and toxicity is the amount of a substance administered on a body weight basis. A common dose measurement is **mg/kg** which stands for mg of substance per kg of body weight.
Another important aspect is the **time** over which the dose is administered. This is especially important for exposures of several days or for chronic exposures. The commonly used time unit is one day and thus, the usual dosage unit is **mg/kg/day**.
Since some xenobiotics are toxic in much smaller quantities than the milligram, smaller fractions of the gram are used, such as **microgram (µg)**. Other units are shown in the slide.

In the environmental sciences **Environmental exposure units** are expressed as the amount of a xenobiotic in a unit of the media.
mg/liter (**mg/l**) for liquids
mg/gram (**mg/g**) for solids
mg/cubic meter (**mg/m³**) for air
Smaller units are used as needed, e.g., **µg/ml**.

Other commonly used dose units for substances in media are parts per million **(ppm)**, parts per billion **(ppb)** and parts per trillion **(ppt)**.

The dose level at which a toxic effect is first encountered is known as the threshold dose. Doses below the threshold dose are often referred to as "subthreshold doses."

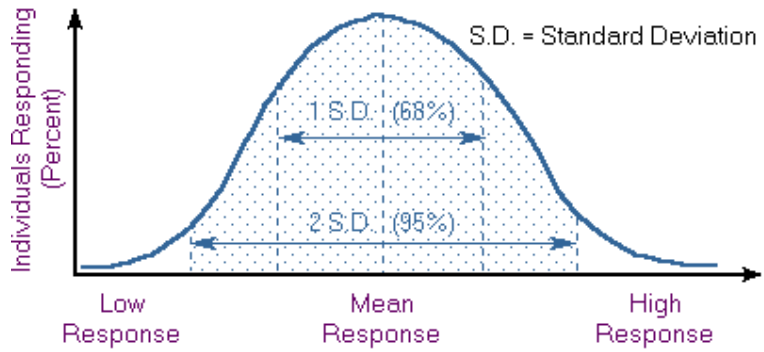
Dose-response relationship

"The dose-response relationship is the most fundamental and pervasive concept in toxicology"

The dose-response relationship is a fundamental and essential concept in toxicology. It correlates exposures and the spectrum of induced effects. Generally, the higher the dose, the more severe the response. The dose-response relationship is based on observed data from experimental animal, human clinical, or cell studies.

Toxicology

Dose-effect relationship

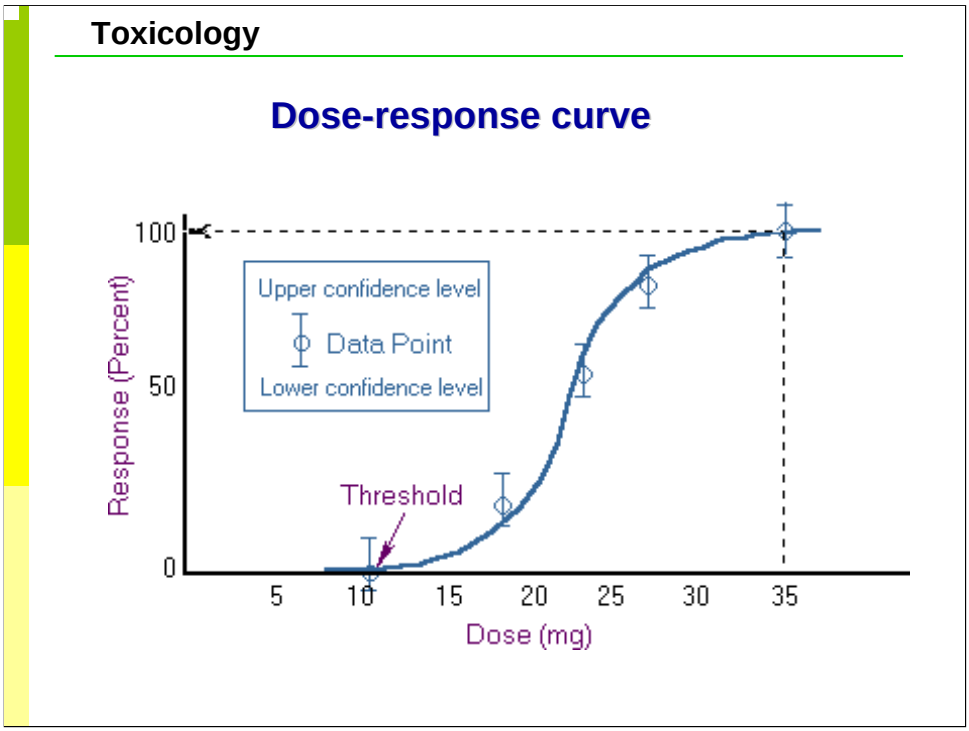


Knowledge of the dose-response relationship:
- establishes causality that the chemical has in fact induced the observed effects
- establishes the lowest dose where an induced effect occurs - the threshold effect
- determines the rate at which injury builds up - the slope for the dose response.

Within a population, the majority of responses to a toxicant are similar; however, a wide variance of responses may be encountered, some individuals are susceptible and others resistant. As demonstrated above, a graph of the individual responses can be depicted as a bell-shaped standard distribution curve.

Dose responses are commonly presented as mean $\pm$ 1 S.D. (*standard deviation*), which incorporates 68% of the individuals. The variance may also be presented as two standard deviations, which incorporates 95% of the responses. A large standard deviation indicates great variability of response. For example, a response of 12 ± 5 mg indicates considerably more variability than 12 ± 1 mg.

Toxicology



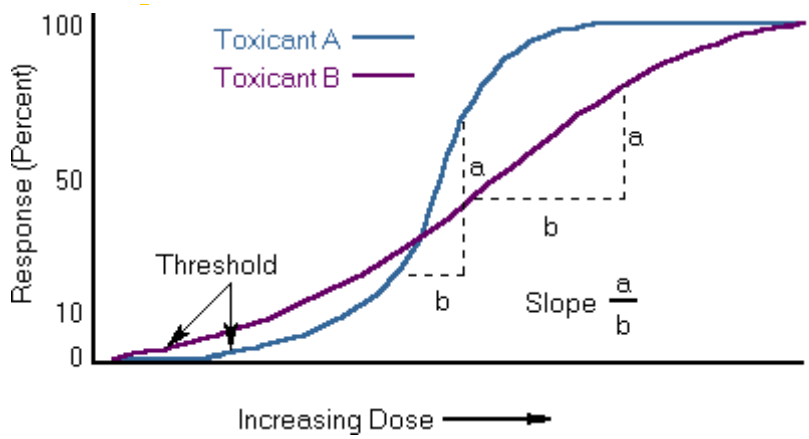
The **dose-response curve** normally takes the form of a sigmoid curve. It conforms to a smooth curve as close as possible to the individual data points. For most effects, small doses are not toxic. The point at which toxicity first appears is known as the **threshold** dose level. From that point, the curve increases with higher dose levels. In the hypothetical curve above, no toxicity occurs at 10 mg whereas at 35 mg 100% of the individuals experience toxic effects.

There is always a relation between dose and effect/response, but for some agents there is a threshold below which no effect occurs.

A **threshold** for toxic effects occurs at the point where the body's ability to detoxify a xenobiotic or repair toxic injury has been exceeded. For most organs there is a reserve capacity so that loss of some organ function does not cause decreased performance. For example, the development of **cirrhosis** in the liver may not result in a clinical effect until over 50% of the liver has been replaced by fibrous tissue.

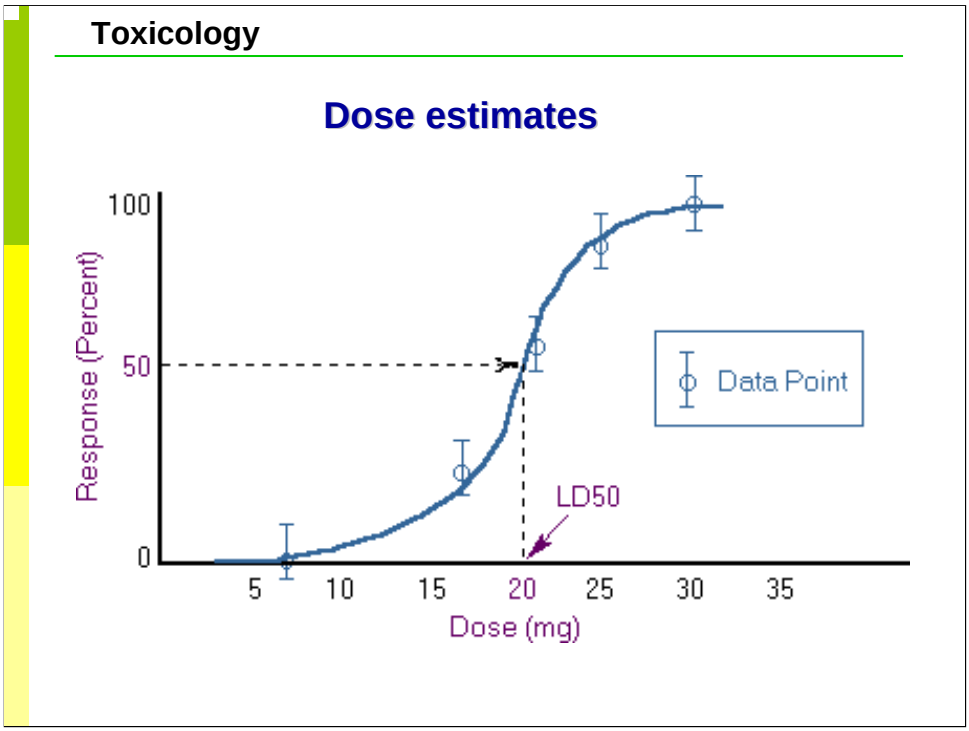
Toxicology

Dose-response curve



Knowledge of the **shape** and **slope** of the dose-response curve is extremely important in predicting the toxicity of a substance at specific dose levels. Major differences among toxicants may exist not only in the point at which the threshold is reached but also in the percent of population responding per unit change in dose (*i.e., the slope*). As illustrated above, Toxicant A has a higher threshold but a steeper slope than Toxicant B.

Knowledge of the dose-response relationship permits one to determine whether exposure has caused an effect, threshold for the effect, and the rate of buildup of the effect with increasing dose levels. Rate of buildup of toxic effects is known as the "slope" of the dose-response curve.



Dose Estimates of Toxic Effects

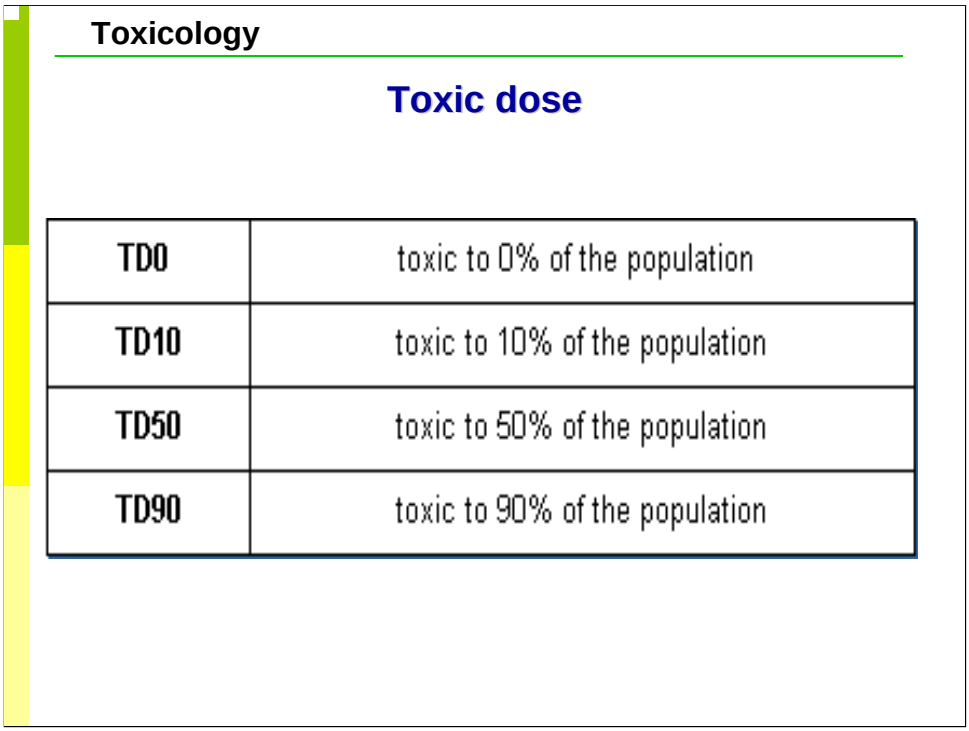
Dose-response curves are used to derive dose estimates of chemical substances. A common dose estimate for acute toxicity is the **LD50** (*Lethal Dose 50%*). This is a statistically derived dose at which 50% of the individuals will be expected to die. The figure illustrates how an LD50 of 20 mg is derived.
Other dose estimates also may be used. LD0 represents the dose at which no individuals are expected to die. This is just below the threshold for lethality. LD10 refers to the dose at which 10% of the individuals will die.

For inhalation toxicity, air concentrations are used for exposure values. Thus, the LC50 is utilized which stands for Lethal Concentration 50%, the calculated concentration of a gas lethal to 50% of a group. Occasionally LC0 and LC10 are also used.

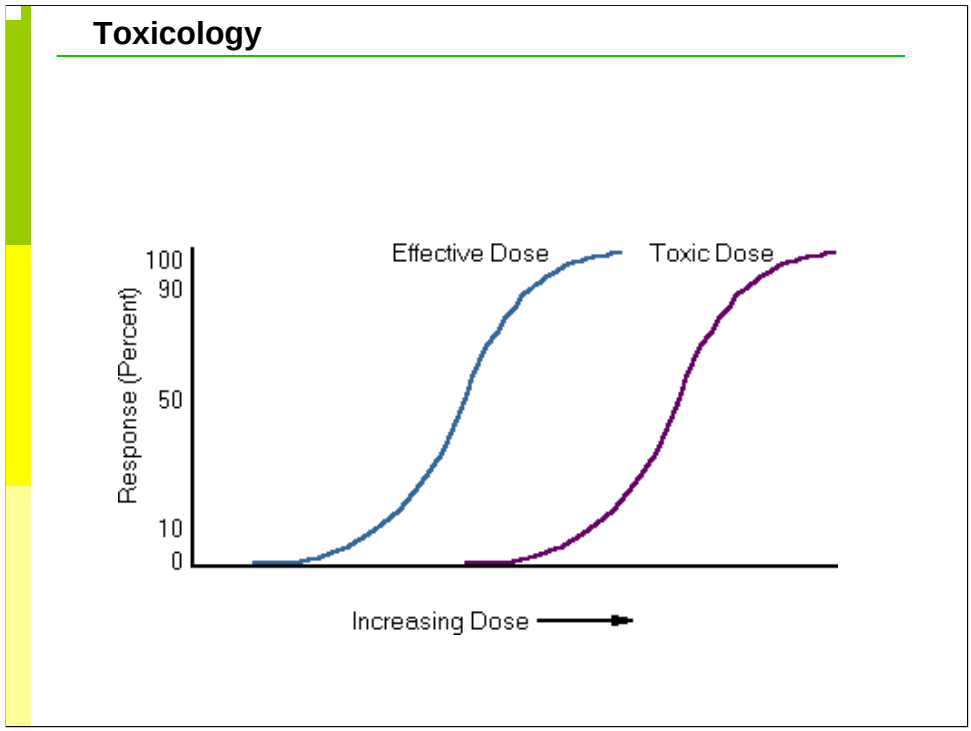
Effective dose

ED0	effective for 0% of the population
ED10	effective for 10% of the population
ED50	effective for 50% of the population
ED90	effective for 90% of the population

Effective Doses (**EDs**) are used to indicate the effectiveness of a substance. Normally, effective dose refers to a beneficial effect *(relief of pain)*. It might also stand for a harmful effect. Thus the specific endpoint must be indicated.



Toxic Doses (**TDs**) are utilized to indicate doses that cause adverse toxic effects. The usual dose estimates are seen in the table.
The knowledge of the **effective** and **toxic dose** levels aides the toxicologist and clinician in determining the relative safety of toxic agents. Two dose-response curves can be presented for the same drug, one for effectiveness and the other for toxicity. In this case, a dose that is 50-75% effective does not cause toxicity whereas a 90% effective dose may result in a small amount of toxicity.

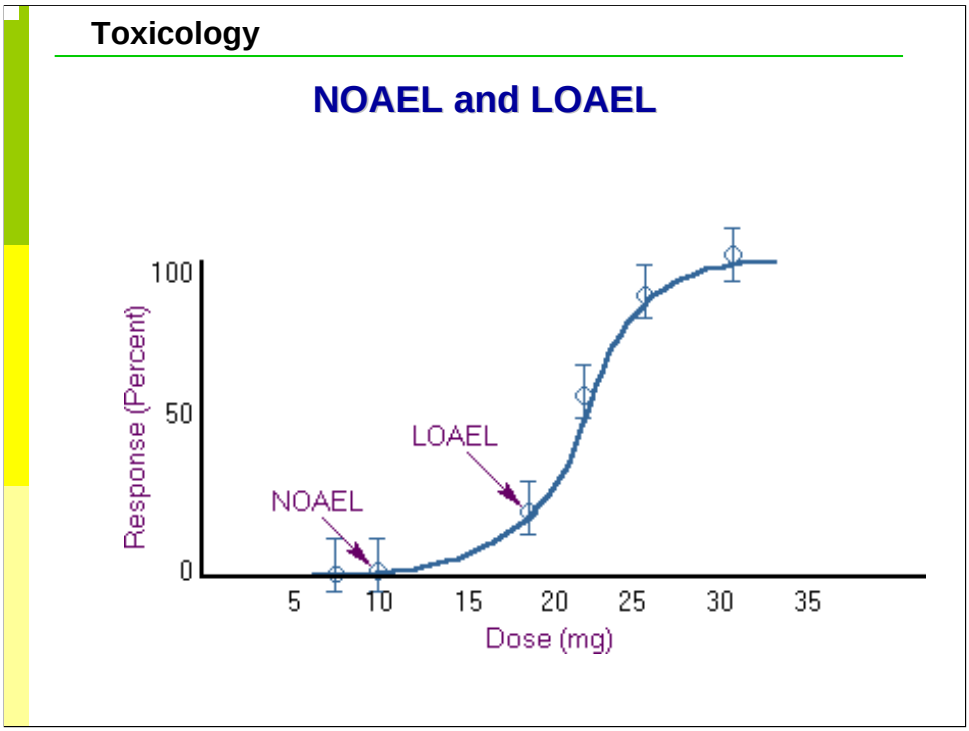


The toxic dose is seen at an increasing dose compared with the effective dose. As can been seen in the graph, it is ppossible to have an overlap of having an effective dose while this is also starting to be toxic.

Question: The quantity of a substance administered to an individual over a period of time or in several individual doses is known as the:

- O Exposure Dose
- O Absorbed Dose
- O Total Dose

Answer: The total dose is the quantity of a substance administered to an individual over a period of time or in several individual doses. It becomes particularly important when evaluating cumulative poisons.



Two terms often encountered are **No Observed Adverse Effect Level (NOAEL)** and **Low Observed Adverse Effect Level (LOAEL)**. They are the ***actual data points*** from human clinical or experimental animal studies.

Sometimes the terms **No Observed Effect Level (NOEL)** and **Lowest Observed Effect Level (LOEL)** may also be found in the literature. NOELs and LOELs do not necessarily imply toxic or harmful effects and may be used to describe beneficial effects of chemicals as well.

The NOAEL, LOAEL, NOEL, and LOEL have great importance in the conduct of risk assessments.

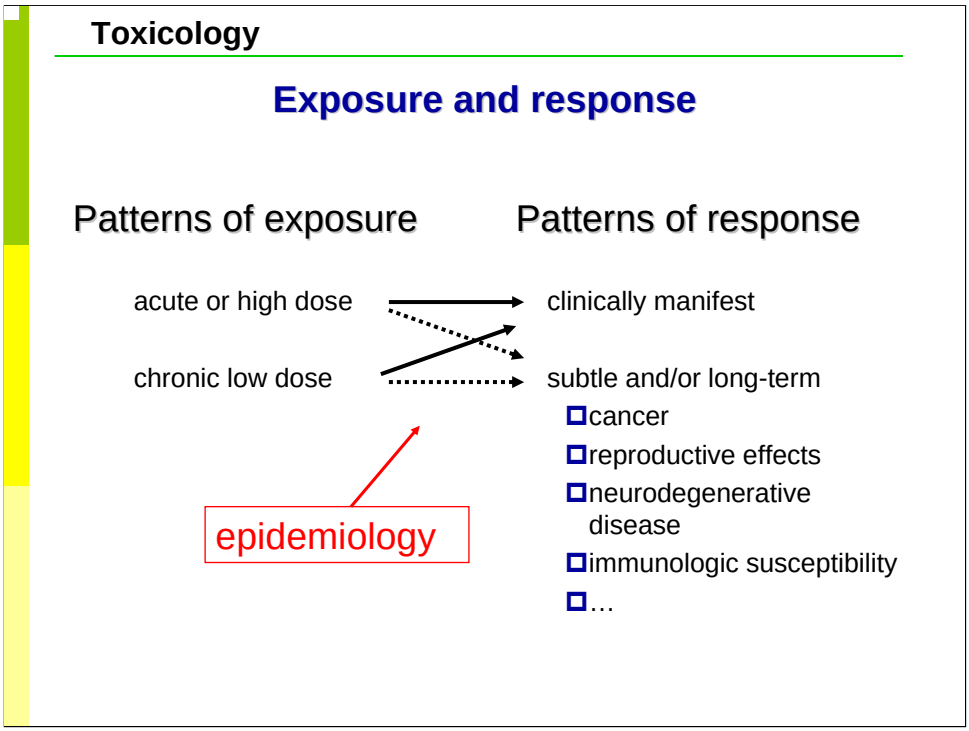
Dose-response relationship

Our knowledge of the effects of chemicals stems mainly from

- clinical and occupational toxicology
  - relatively high doses, limited number of agents
- epidemiology
  - complex exposures, rarely “causal” associations
- animal experiments
  - high doses, single chemicals, statistical limitations, healthy animals, species differences

There are several sources of information to develop dose-repsonse relationships.

Read slide.

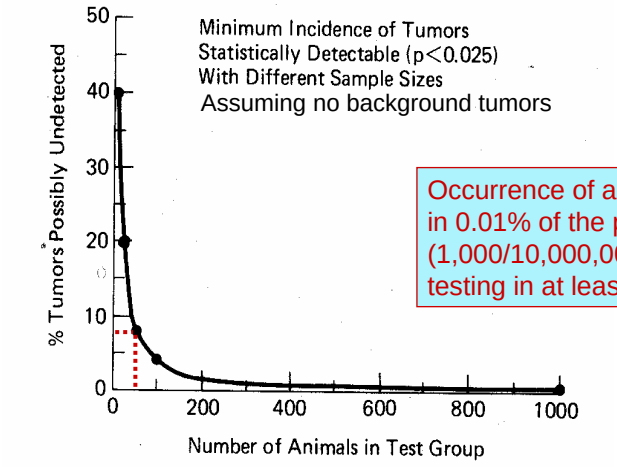


Different patterns of exposure are related to different patterns of response.

Epidemiology can be applied to find knowledge on the dose-response in complex exposures.

Toxicology

Statistical limitations

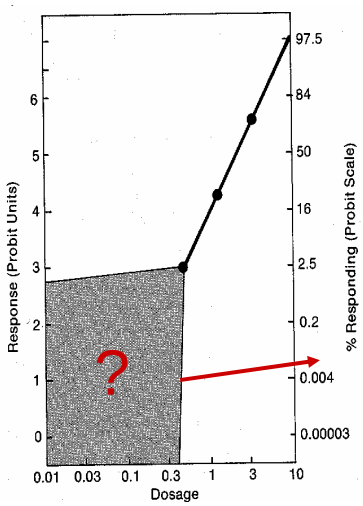


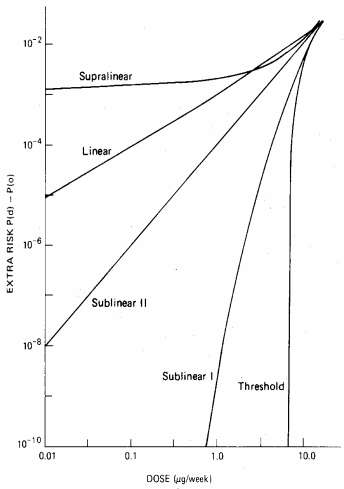
Occurrence of adverse effect in 0.01% of the population (1,000/10,000,000) requires testing in at least 30,000 animals !

To find adverse effects in a population we will find statistical limitations. A adverse effects i 0.01% of the population needs a very large amount of test animals to proof a relationship.

Toxicology

Extrapolation from animal data





In the area where there low response to low dosage we will encounter limitations in research.

The dose-response relationship in the black box is quite often unknown.

There are several options.

Linear dose-response.

Supralinear dose-response where a smaller dose provides a larger effect.

SublinearII where there is still an effect a very small doses.

Sublinear I where the effect steeply decreases at lower doses.

Threshold where at certain doses there is no effect at all.

Factors determining adverse effects

- intrinsic toxicity
- dose
- **exposure conditions**
- response of host

There are several factors that play a role at determining adverse effects.

Read slide. To continue with exposure conditions.

Exposure conditions

- routes of exposure
- frequency & duration of exposure
- mixed exposures
- environmental circumstances

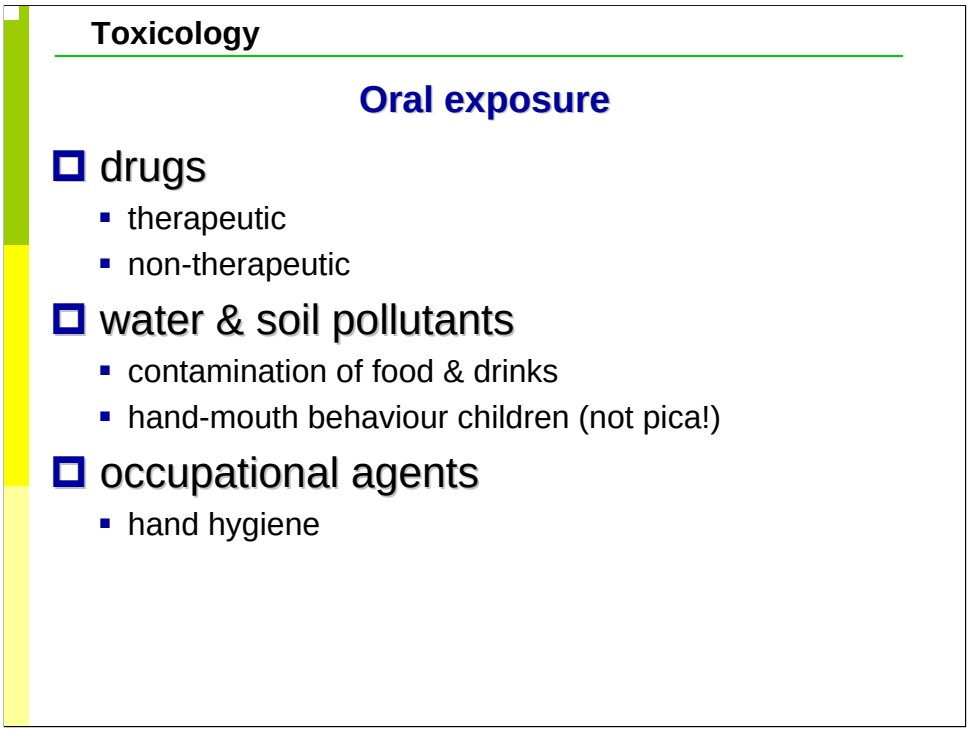
There are several items to be considered in exposure.

Routes of exposure

- Oral
- Inhalation
- Dermal
- Parenteral

Read slide for different routes of exposures.

Parenteral means: application outside the gastro-intestinal tract by e.g. intramuscular, intravenous or subcutaneous application of medicines.



In the slide are examples of oral exposure.

Pica means exessive amount of intake of soil. This relates to abnormal behaviour.

Question: The usual dosage unit that incorporates the amount of material administered or absorbed in accordance with the size of the individual over a period of time is:

O PPM/hour
O mg/kg/day
O kg/100 kg/week

Answer: The usual dosage unit that incorporates the amount of material administered or absorbed in accordance with the size of the individual over a period of time is mg/kg/day. In some cases, much smaller dosage units are used, e.g., µg/kg/day.

Inhalation

- smoking
- indoor air pollution
  - domestic
  - occupational
  - schools
  - hobby & sports
- outdoor air pollution
  - urban, industry & vehicle traffic
  - natural sources

Sources of pollution with inhalation as route of exposure.

Dermal exposure

- occupational agents
  - solvents
  - pesticides
- cosmetics
- some water pollutants

Pollutants as examples for dermal exposure.

Factors determining adverse effects

- intrinsic toxicity
- dose
- exposure conditions
- **response of host**

Next factor to be discussed: response of host

Toxic effects

- A target organ is an organ that is damaged by the xenobiotic or its metabolite. There may be more than one target for toxicity for a particular substance.

  For example, the targets for alcohol are the central nervous system and the liver.

Toxicity is complex with many influencing factors; dosage is the most important. Xenobiotics cause many types of toxicity by a variety of mechanisms. Some chemicals are themselves toxic. Others must be metabolized *(chemically changed within the body)* before they cause toxicity.

Many xenobiotics distribute in the body and often affect only specific **target organs**. Others, however, can damage any cell or tissue that they contact. The target organs that are affected may vary depending on dosage and route of exposure. For example, the target for a chemical after acute exposure may be the nervous system, but after chronic exposure the liver.

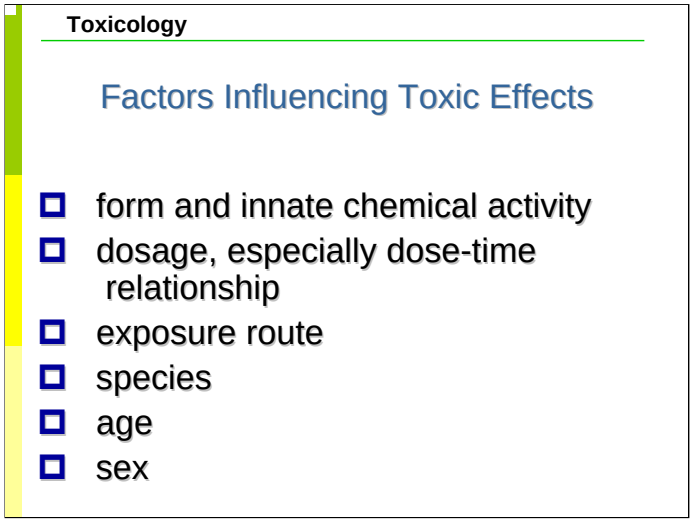
Toxic effects

Cellular, biochemical, or macromolecular changes

- cell replacement, such as fibrosis
- damage to an enzyme system
- disruption of protein synthesis
- production of reactive chemicals in cells
- DNA damage

Toxicity can result from adverse cellular, biochemical, or macromolecular changes. Examples are:
- cell replacement, such as fibrosis
- damage to an enzyme system
- disruption of protein synthesis
- production of reactive chemicals in cells
- DNA damage

Some xenobiotics may also act indirectly by:
- modification of an essential biochemical function
- interference with nutrition
- alteration of a physiological mechanism



The toxicity of a substance depends on the following (to be continued at next slide):
form and innate chemical activity
dosage, especially dose-time relationship
exposure route
species
age
sex
ability to be absorbed
metabolism
distribution within the body
excretion
presence of other chemicals

The **form** of a substance may have a profound impact on its toxicity especially for metallic elements. For example, the toxicity of mercury vapor differs greatly from methyl mercury. Another example is chromium. Cr^{3+} is relatively nontoxic whereas Cr^{6+} causes skin or nasal corrosion and lung cancer.
The **innate chemical activity** of substances also varies greatly. Some can quickly damage cells causing immediate cell death. Others slowly interfere only with a cell's function. For example:

- hydrogen cyanide binds to cytochrome oxidase resulting in cellular hypoxia and rapid death
- nicotine binds to cholinergic receptors in the CNS altering nerve conduction and inducing gradual onset of paralysis

The **dosage** is the most important and critical factor in determining if a substance will be an acute or a chronic toxicant. Virtually all chemicals can be acute toxicants if sufficiently large doses are administered. Often the toxic mechanisms and target organs are different for acute and chronic toxicity.
Exposure route is important in determining toxicity. Some chemicals may be highly toxic by one route but not by others. Two major reasons are differences in absorption and distribution within the body. For example:

- ingested chemicals, when absorbed from the intestine, distribute first to the liver and may be immediately detoxified
- inhaled toxicants immediately enter the general blood circulation and can distribute throughout the body prior to being detoxified by the liver

Frequently there are different target organs for different routes of exposure.
Toxic responses can vary substantially depending on the species. Most species differences are attributable to differences in metabolism. Others may be due to anatomical or physiological differences. For example, rats cannot vomit and expel toxicants before they are absorbed or cause severe irritation, whereas humans and dogs are capable of vomiting.
Selective toxicity refers to **species** differences in toxicity between two species simultaneously exposed. This is the basis for the effectiveness of pesticides and drugs. Examples are:

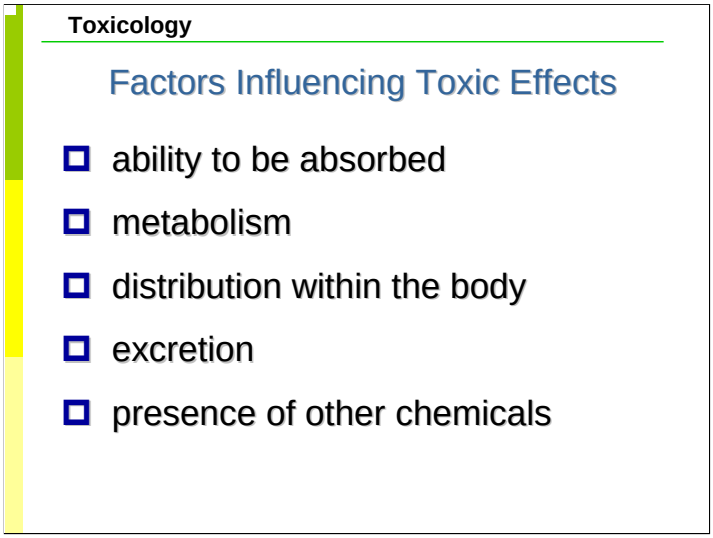
- an insecticide is lethal to insects but relatively nontoxic to animals
- antibiotics are selectively toxic to microorganisms while virtually nontoxic to humans

Age may be important in determining the response to toxicants. Some chemicals are more toxic to infants or the elderly than to young adults. For example:

- parathion is more toxic to young animals
- nitrosamines are more carcinogenic to newborn or young animals

Although uncommon, toxic responses can vary depending on **sex**. Examples are:

- male rats are 10 times more sensitive than females to liver damage from DDT
- female rats are twice as sensitive to parathion as male rats



The toxicity of a substance depends on the following (cotinued form previous slide:
ability to be absorbed
metabolism
distribution within the body
excretion
presence of other chemicals

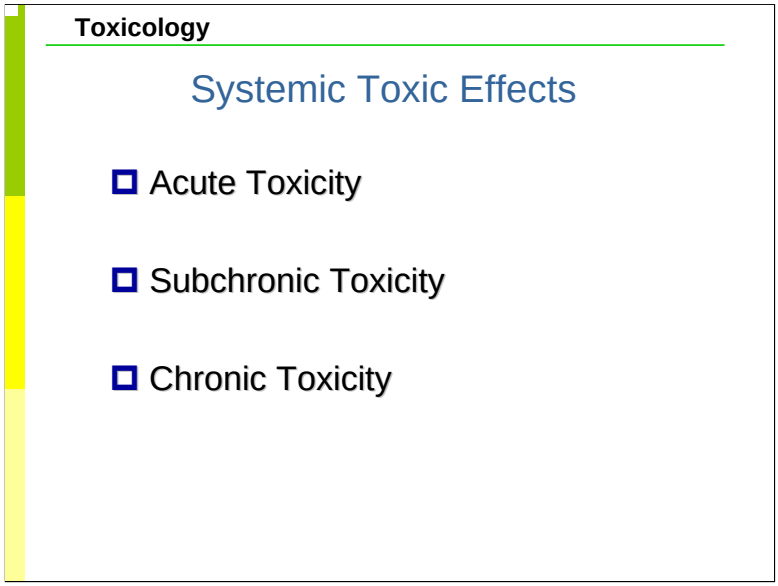
The **ability to be absorbed** is essential for systemic toxicity to occur. Some chemicals are readily absorbed and others poorly absorbed. For example, nearly all alcohols are readily absorbed when ingested, whereas there is virtually no absorption for most polymers. The rates and extent of absorption may vary greatly depending on the form of the chemical and the route of exposure. For example:
- ethanol is readily absorbed from the gastrointestinal tract but poorly absorbed through the skin
- organic mercury is readily absorbed from the gastrointestinal tract; inorganic lead sulfate is not

Metabolism, also known as biotransformation, is a major factor in determining toxicity. The products of metabolism are known as metabolites. There are two types of metabolism - **detoxification** and **bioactivation**. Detoxification is the process by which a xenobiotic is converted to a less toxic form. This is a natural defense mechanism of the organism. Generally the detoxification process converts lipid-soluble compounds to polar compounds. Bioactivation is the process by which a xenobiotic may be converted to more reactive or toxic forms.

The **distribution** of toxicants and toxic metabolites throughout the body ultimately determines the sites where toxicity occurs. A major determinant of whether or not a toxicant will damage cells is its lipid solubility. If a toxicant is lipid-soluble it readily penetrates cell membranes. Many toxicants are stored in the body. Fat tissue, liver, kidney, and bone are the most common storage depots. Blood serves as the main avenue for distribution. Lymph also distributes some materials.

The site and rate of **excretion** is another major factor affecting the toxicity of a xenobiotic. The kidney is the primary excretory organ, followed by the gastrointestinal tract, and the lungs *(for gases)*. Xenobiotics may also be excreted in sweat, tears, and milk.

A large volume of blood serum is filtered through the kidney. Lipid-soluble toxicants are reabsorbed and concentrated in kidney cells. Impaired kidney function causes slower elimination of toxicants and increases their toxic potential.
The **presence of other chemicals** may decrease toxicity ***(antagonism)***, add to toxicity ***(additivity)***, or increase toxicity ***(synergism or potentiation)*** of some xenobiotics. For example:
- alcohol may enhance the effect of many antihistamines and sedatives
- antidotes function by antagonizing the toxicity of a poison *(atropine counteracts poisoning by organophosphate insecticides)*



Toxic effects are generally categorized according to the site of the toxic effect. Sometimes the effect may occur at only one site. This site is referred to as the **specific target organ**. In other cases, toxic effects may occur at multiple sites. This is referred as **systemic toxicity**. Following are types of systemic toxicity:
Acute Toxicity
Subchronic Toxicity
Chronic Toxicity
Carcinogenicity
Developmental Toxicity
Genetic Toxicity *(somatic cells)*

Acute toxicity occurs almost immediately *(hours/days)* after an exposure. An **acute exposure** is usually a single dose or a series of doses received within a 24 hour period. Death is a major concern in cases of acute exposures. Examples are:
- In 1989, 5,000 people died and 30,000 were permanently disabled due to exposure to methyl isocyanate from an industrial accident in Bhopal, India.
- Many people die each year from inhaling carbon monoxide from faulty heaters.
Non-lethal acute effects may also occur, e.g., convulsions and respiratory irritation.

Subchronic Toxicity
Subchronic toxicity results from repeated exposure for several weeks or months. This is a common human exposure pattern for some pharmaceuticals and environmental agents. Examples are:
- Ingestion of coumadin tablets *(blood thinners)* for several weeks as a treatment for venous thrombosis can cause internal bleeding.
- Workplace exposure to lead over a period of several weeks can result in anemia.

Chronic Toxicity
Chronic toxicity represents cumulative damage to specific organ systems and takes many months or years to become a recognizable clinical disease. Damage due to subclinical individual exposures may go unnoticed. With repeated exposures or long-term continual exposure, the damage from these subclinical exposures slowly builds-up *(cumulative damage)* until the damage exceeds the threshold for chronic toxicity. Ultimately, the damage becomes so severe that the organ can no longer function normally and a variety of chronic toxic effects may result.
Examples of chronic toxic affects are:
- cirrhosis in alcoholics who have ingested ethanol for several years;
- chronic kidney disease in workmen with several years exposure to lead;
- chronic bronchitis in long-term cigarette smokers;
- pulmonary fibrosis in coal miners *(black lung disease).*

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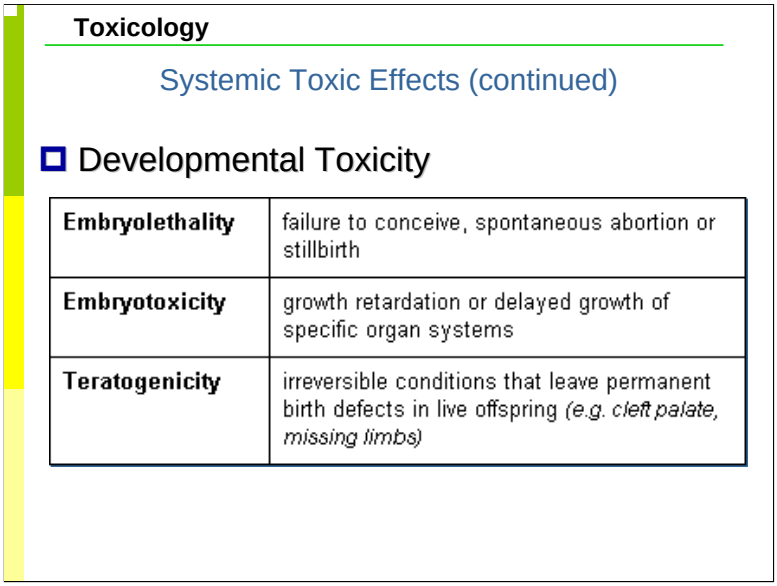

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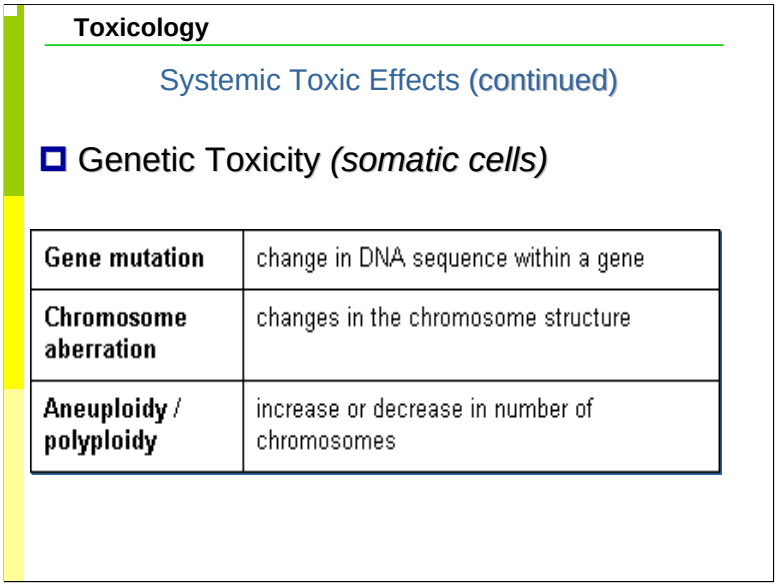
Subchronic Toxicity
Chronic Toxicity
Carcinogenicity
Developmental Toxicity
Genetic Toxicity *(somatic cells)*

continued from previous slide:

Developmental Toxicity

Developmental Toxicity pertains to adverse toxic effects to the developing embryo or fetus. This can result from toxicant exposure to either parent before conception or to the mother and her developing embryo-fetus. The three basic types of developmental toxicity are showbn in the table on the slide.

Chemicals cause developmental toxicity by two methods. They can act directly on cells of the embryo causing cell death or cell damage, leading to abnormal organ development. A chemical might also induce a mutation in a parent's germ cell which is transmitted to the fertilized ovum. Some mutated fertilized ova develop into abnormal embryos.



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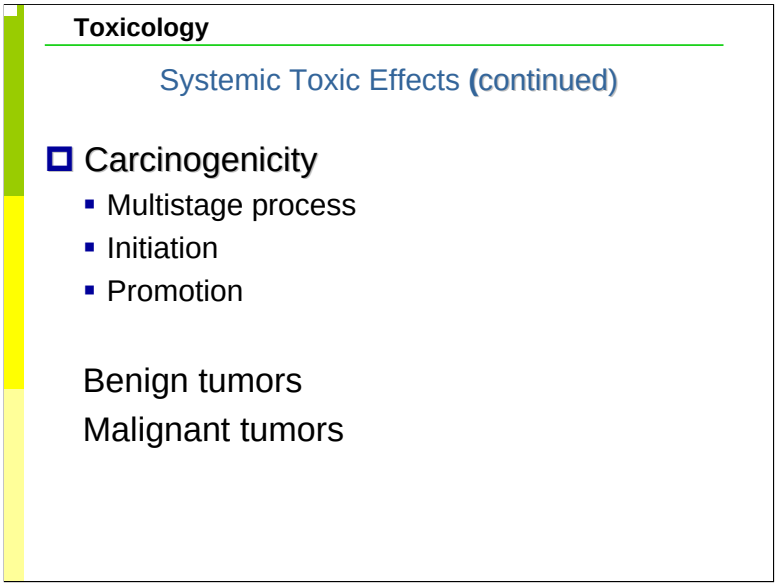
Subchronic Toxicity
Chronic Toxicity
Carcinogenicity
Developmental Toxicity
Genetic Toxicity *(somatic cells)*

continued form previous slide:

Genetic Toxicity

Genetic Toxicity results from damage to DNA and altered genetic expression. This process is known as **mutagenesis**. The genetic change is referred to as a **mutation** and the agent causing the change as a **mutagen**. There are three types of genetic change (see tabel in slide).

If the mutation occurs in a germ cell the effect is **heritable**. There is no effect on the exposed person; rather the effect is passed on to future generations. If the mutation occurs in a **somatic** cell, it can cause altered cell growth *(e.g. cancer)* or cell death *(e.g. teratogenesis)* in the exposed person.



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Acute Toxicity
Subchronic Toxicity
Chronic Toxicity
Carcinogenicity
Developmental Toxicity
Genetic Toxicity *(somatic cells)*

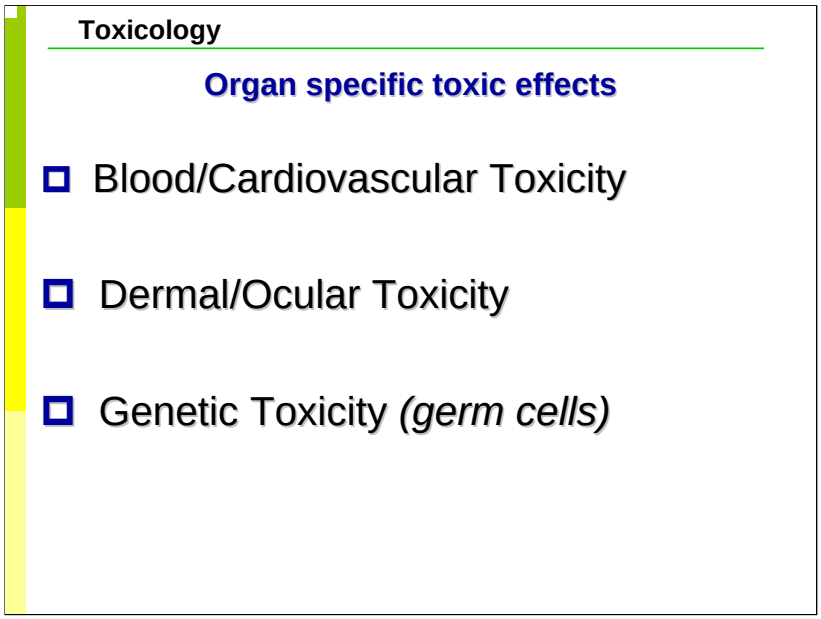
continued form previous slide:

Carcinogenicity

Carcinogenicity is a complex multistage process of abnormal cell growth and differentiation which can lead to cancer. At least two stages are recognized. They are **initiation** in which a normal cell undergoes irreversible changes and **promotion** in which initiated cells are stimulated to progress to cancer. Chemicals can act as **initiators** or **promoters**.

The initial neoplastic transformation results from the mutation of the cellular genes that control normal cell functions. The mutation may lead to abnormal cell growth. It may involve loss of suppresser genes that usually restrict abnormal cell growth. Many other factors are involved *(e.g., growth factors, immune suppression, and hormones)*.

A **tumor *(neoplasm)*** is simply an uncontrolled growth of cells. **Benign tumors** grow at the site of origin; do not invade adjacent tissues or metastasize; and generally are treatable. **Malignant tumors *(cancer)*** invade adjacent tissues or migrate to distant sites ***(metastasis)***. They are more difficult to treat and often cause death.



Types of organ specific toxic effects are:
Blood/Cardiovascular Toxicity, Dermal/Ocular Toxicity and Genetic Toxicity *(germ cells)*

to be continued at next slides: Hepatotoxicity/ Immunotoxicity/ Nephrotoxicity/ Neurotoxicity/ Reproductive Toxicity/ Respiratory Toxicity.

B**lood and Cardiovascular Toxicity** results from xenobiotics acting directly on cells in circulating blood, bone marrow, and heart.

-hypoxia due to carbon monoxide binding of hemoglobin preventing transport of oxygen
- decrease in circulating leukocytes due to chloramphenicol damage to bone marrow cells
- leukemia due to benzene damage of bone marrow cells
- arteriosclerosis due to cholesterol accumulation in arteries and veins

Dermal Toxicity may result from direct contact or internal distribution to the skin. Effects range from mild irritation to severe changes, such as corrosivity, hypersensitivity, and skin cancer. Examples of dermal toxicity are:

- dermal irritation due to skin exposure to gasoline
- dermal corrosion due to skin exposure to sodium hydroxide
- dermal hypersensitivity due to skin exposure to poison ivy
- skin cancer due to ingestion of arsenic or skin exposure to UV light

Eye (Ocular) Toxicity results from direct contact or internal distribution to the eye. The cornea and conjunctiva are directly exposed to toxicants. Thus, conjunctivitis and corneal erosion may be observed following occupational exposure to chemicals. Many household items can cause conjunctivitis. Chemicals in the circulatory system can distribute to the eye and cause corneal opacity, cataracts, retinal and optic nerve damage.
- acids and strong alkalis may cause severe corneal corrosion
- corticosteroids may cause cataracts
- methanol *(wood alcohol)* may damage the optic nerve

Toxicology

Organ specific toxic effects

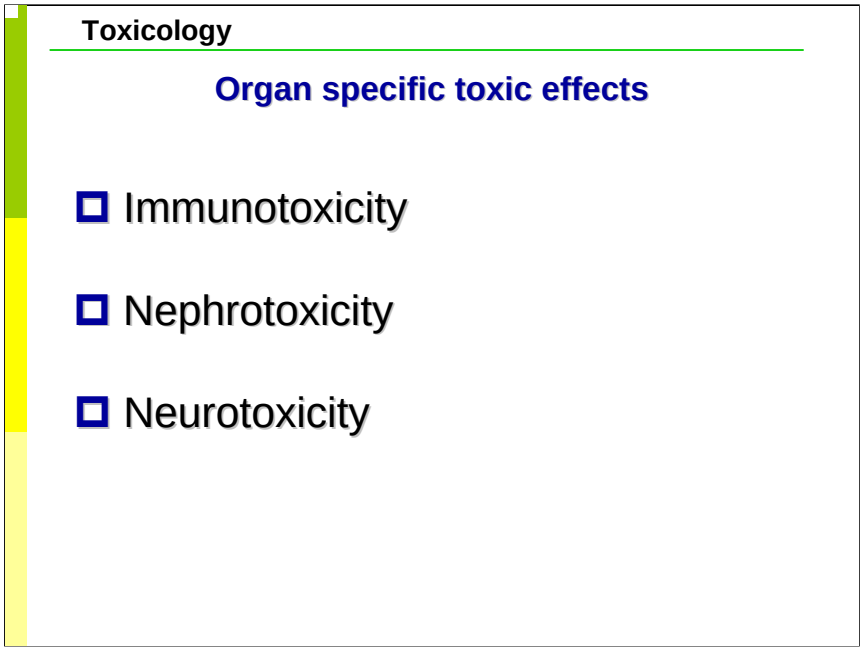
- Hepatotoxicity

Steatosis	lipid accumulation in hepatocytes
Chemical hepatitis	inflammation of the liver
Hepatic necrosis	death of the hepatocytes
Intrahepatic cholestasis	backup of bile salts into the liver cells
Hepatic cancer	cancer of the liver
Cirrhosis	chronic fibrosis, often due to alcohol
Hypersensitivity	immune reaction resulting in hepatic necrosis

continued from previous slide:

Types of organ specific toxic effects are:
Blood/Cardiovascular Toxicity
Dermal/Ocular Toxicity
Genetic Toxicity *(germ cells)*
Hepatotoxicity
Immunotoxicity
Nephrotoxicity
Neurotoxicity
Reproductive Toxicity
Respiratory Toxicity

Hepatotoxicity is toxicity to the liver, bile duct, and gall bladder. The liver is particularly susceptible to xenobiotics due to a large blood supply and its role in metabolism. Thus it is exposed to high doses of the toxicant or its toxic metabolites. The primary forms of hepatotoxicity are mentioned in the table.



continued from previous slide: Types of organ specific toxic effects are:
Immunotoxicity
Nephrotoxicity
Neurotoxicity
Reproductive Toxicity/ Respiratory Toxicity

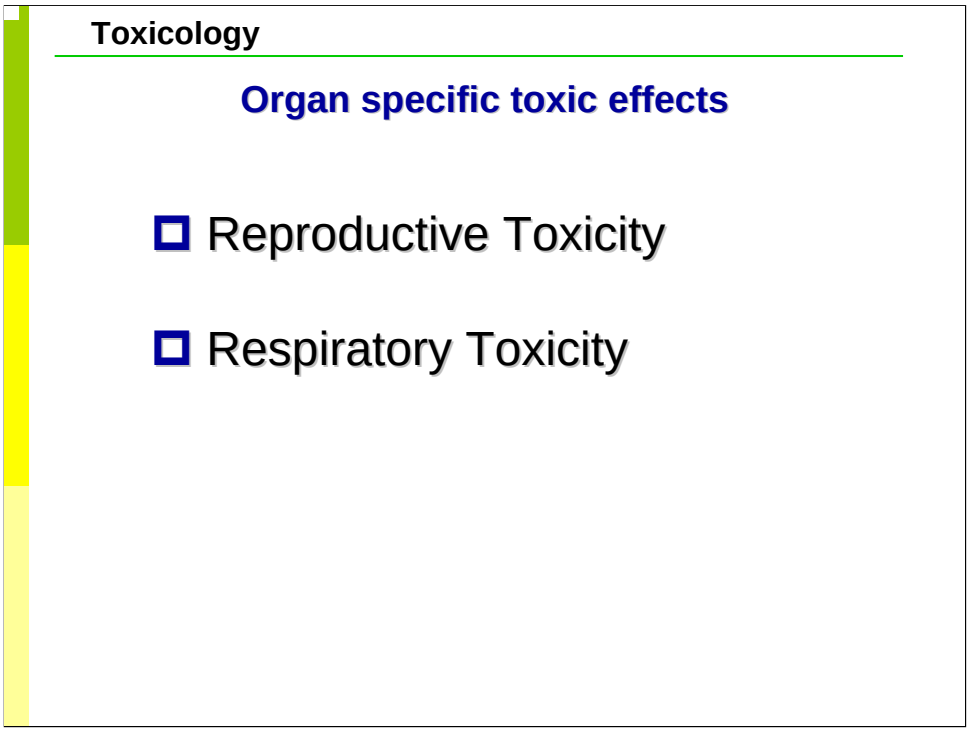
Immunotoxicity realtes to the immune system. It can take several forms: hypersensitivity *(allergy and autoimmunity)*, immunodeficiency, and uncontrolled proliferation *(leukemia and lymphoma)*. The normal function of the immune system is to recognize and defend against foreign invaders. This is accomplished by production of cells that engulf and destroy the invaders or by antibodies that inactivate foreign material. Examples:

- contact dermatitis due to exposure to poison ivy
- systemic lupus erythematosus in workers exposed to hydrazine
- immunosuppression by cocaine
- leukemia induced by benzene

Nephrotoxicity

The kidney is highly susceptible to toxicants for two reasons. A high volume of blood flows through it and it filtrates large amounts of toxins which can concentrate in the kidney tubules. **Nephrotoxicity** is toxicity to the kidneys. It can result in systemic toxicity causing:
- decreased ability to excrete body wastes
- inability to maintain body fluid and electrolyte balance
- decreased synthesis of essential hormones *(e.g., erythropoietin)*

Neurotoxicity represents toxicant damage to cells of the central nervous system *(brain and spinal cord)* and the peripheral nervous system *(nerves outside the CNS)*. The primary types of neurotoxicity are:
- neuronopathies *(neuron injury)*
- axonopathies *(axon injury)*
- demyelination *(loss of axon insulation)*
- interference with neurotransmission



continued from previous slide: Types of organ specific toxic effects are:
Reproductive Toxicity
Respiratory Toxicity

Reproductive Toxicity involves toxicant damage to either the male or female reproductive system. Toxic effects may cause:
- decreased libido and impotence
- infertility
- interrupted pregnancy *(abortion, fetal death, or premature delivery)*
- infant death or childhood morbidity
- altered sex ratio and multiple births
- chromosome abnormalities and birth defects
- childhood cancer

Respiratory Toxicity relates to effects on the upper respiratory system *(nose, pharynx, larynx, and trachea)* and the lower respiratory system *(bronchi, bronchioles, and lung alveoli)*. The primary types of respiratory toxicity are:
- pulmonary irritation
- asthma/bronchitis
- reactive airway disease
- emphysema
- allergic alveolitis
- fibrotic lung disease
- pneumoconiosis
- lung cancer

Frequency & duration

- Acute toxicity (single dose or < 24h)
  - may lead to immediate (“acute”) effects
  - may lead to delayed or persistent (“chronic”) effects
- Chronic toxicity (repeated doses)
  - may lead to sudden (“acute”) effects
  - results from accumulation of toxic agent or from cumulative effects
  - may lead to delayed or persistent (“chronic”) effects

The distinction between acute and chronic effects is not exactly given in hours or days. Some organisations use also the term “intermediate” for effects that occur between 24 hours and 2 weeks.

Mixed exposures

- Additive effects (1+1 = 2)
- Synergistic effects
  - toxicokinetic interactions (1+ 0 = 2)
    - e.g. improved dermal penetration by solvents
  - toxicodynamic interactions (1+1 = 3)
    - e.g. smoking + air pollutants
- Antagonistic effects (1+1 = 1)

There are several approaches to look at mixed exposures. It depends on the compounds in which way the effects are manifesting itself.

Response of host

- Detoxification
- Bioactivation

Metabolism of a xenobiotic may result in either detoxification *(less toxic metabolites)* or bioactivation *(more toxic metabolites)*. In some cases, a xenobiotic itself may not cause cancer but a metabolite of the xenobiotic may have carcinogenic potential. *(This is a form of bioactivation)*.

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