

3.2: Factors Affecting Toxicity

Factors Influencing Toxicity

In some instances, individuals can have unpredictable reactions, or **idiosyncratic responses**, to a drug or other substance. An idiosyncratic response is uncommon, and it is sometimes impossible to understand whether it is the result of a genetic predisposition or has some other cause such as the status of the immune system. It could result in an abnormally small or short, or abnormally large or long response to the drug or other substance. Or, the response could be qualitatively different than what has been observed in most other individuals.

The toxicity of a substance usually depends on the following factors:

- Form and innate chemical activity
- Dosage, especially dose-time relationship
- Exposure route
- Species
- Life stage, such as infant, young adult, or elderly adult
- Gender
- Ability to be absorbed
- Metabolism
- Distribution within the body
- Excretion
- Health of the individual, including organ function and pregnancy, which involves physiological changes that could influence toxicity
- Nutritional status
- Presence of other chemicals
- Circadian rhythms (the time of day a drug or other substance is administered)

Factors Related to the Substance

Form and Innate Chemical Activity

The **form** of a substance may have a profound impact on its toxicity especially for metallic elements, also termed heavy metals. 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 the enzyme cytochrome oxidase resulting in cellular hypoxia and rapid death.
- Nicotine binds to cholinergic receptors in the central nervous system (CNS) altering nerve conduction and inducing gradual onset of paralysis.

Dosage

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. Examples are:

Toxicant	Acute Toxicity	Chronic Toxic Effects
Ethanol	CNS depression	Liver cirrhosis
Arsenic	Gastrointestinal damage	Skin/liver cancer

Table 3.2.1. Examples of acute and chronic toxicity

Exposure Route

The way an individual comes in contact with a toxic substance, or **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.

Different target organs often are affected by different routes of exposure.

Diagram of toxic substances being ingested

Figure 3.2.1. Ingestion

(Image Source: ORAU, ©)

Diagram of toxic substances being breathed into the lungs

Figure 3.2.2. Inhalation

(Image Source: ORAU, ©)

Absorption

The **ability to be absorbed** is essential to systemic toxicity. Some chemicals are readily absorbed and others are 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 a chemical and the route of exposure to it. 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.

Factors Related to the Organism

Species

Toxic responses can vary substantially depending on the species. Most differences between species 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. For example:

- An insecticide is lethal to insects but relatively nontoxic to animals.
- Antibiotics are selectively toxic to microorganisms while virtually nontoxic to humans.

Life Stage

An individual's age or **life stage** may be important in determining his or her 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.

Illustrated silhouette people of varying ages and sizes standing outdoors under a tree

Figure 3.2.3. An individual's life stage can impact that person's response to toxicants

(Image Source: iStock Photos, ©)

Gender

Gender can play a big role in influencing toxicity. Physiologic differences between men and women, including differences in pharmacokinetics and pharmacodynamics, can affect drug activity.

In comparison with men, pharmacokinetics in women generally can be impacted by their lower body weight, slower gastrointestinal motility, reduced intestinal enzymatic activity, and slower kidney function (glomerular filtration rate). Delayed

gastric emptying in women may result in a need for them to extend the interval between eating and taking medications that require absorption on an empty stomach. Other physiologic differences between men and women also exist. Slower renal clearance in women, for example, may result in a need for dosage adjustment for drugs such as digoxin that are excreted via the kidneys.

In general, pharmacodynamic differences between women and men include greater sensitivity to and enhanced effectiveness, in women, of some drugs, such as beta blockers, opioids, and some antipsychotics.

Studies in animals also have identified gender-related differences. For example:

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



Figure 3.2.4 *Gender symbols for female (left) and male (right)*
(Image Source: iStock Photos, ©)

Metabolism

Metabolism, also known as biotransformation, is the conversion of a chemical from one form to another by a biological organism. Metabolism is a major factor in determining toxicity. The products of metabolism are known as metabolites. There are two types of metabolism:

1. Detoxification
2. Bioactivation

In **detoxification**, a xenobiotic is converted to a less toxic form. This is a natural defense mechanism of the organism. Generally, detoxification converts lipid-soluble compounds to polar compounds.

In **bioactivation**, a xenobiotic may be converted to more reactive or toxic forms. Cytochrome P-450 (CYP450) is an example of an enzyme pathway used to metabolize drugs. In the elderly, CYP450 metabolism of drugs such as phenytoin and carbamazepine may be decreased. Therefore, the effect of those drugs may be less pronounced. CYP450 metabolism also can be inhibited by many drugs. Risk of toxicity may be increased if a CYP450 enzyme-inhibiting drug is given with one that depends on that pathway for metabolism.

There is awareness that the gut microbiota can impact the toxicity of drugs and other chemicals. For example, gut microbes can metabolize some environmental chemicals and bacteria-dependent metabolism of some chemicals can modulate their toxicity. Also, environmental chemicals can alter the composition and/or the metabolic activity of the gastrointestinal bacteria, thus contributing in a meaningful way to shape an individual's microbiome. The study of the consequences of these changes is an emerging area of toxicology.

[Learn more](#) about human exposure to pollutants and their interaction with the GI microbiota.

[Learn more](#) about the microbiome and toxicology.

Distribution Within the Body

The **distribution** of toxicants and toxic metabolites throughout the body ultimately determines the sites where toxicity occurs. A major determinant of whether 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 sites. Blood serves as the main avenue for distribution. Lymph also distributes some materials.

Excretion

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.

Health Status

The health of an individual or organism can play a major role in determining the levels and types of potential toxicity. For example, an individual may have pre-existing kidney or liver disease. Certain conditions, such as pregnancy, also are associated with

physiological changes in kidney function that could influence toxicity.

Nutritional Status

Diet (nutritional status) can be a major factor in determining who does or does not develop toxicity. For example:

- Consumption of fish that have absorbed mercury from contaminated water can result in mercury toxicity; an antagonist for mercury toxicity is the nutrient selenium.
- Some vegetables can accumulate cadmium from contaminated soil; an antagonist for cadmium toxicity is the nutrient zinc.
- Grapefruit contains a substance that inhibits the P450 drug detoxification pathway, making some drugs more toxic.

Find out more about nutrition and chemical toxicity [here](#).

Circadian Rhythms

Circadian rhythms can play a role in toxicity. For example, rats administered an immunosuppressive drug had severe toxicity in their intestines 7 hours after light onset compared to controls and to other times in the day. The rats had changes in their digestive enzyme activity and other physiological indicators at this dosing time.

Find out more about circadian rhythm and gut toxicity [here](#).

Other Factors

Presence of Other Chemicals

The presence of other chemicals, at the same time, earlier, or later may:

- **Decrease toxicity** (antagonism)
- **Add to toxicity** (additivity)
- **Increase toxicity** (synergism or potentiation)

For example:

- Antidotes used to counteract the effects of poisons function through antagonism (atropine counteracts poisoning by organophosphate insecticides).
- Alcohol may enhance the effect of many antihistamines and sedatives.
- A synergistic interaction between the antioxidant butylated hydroxytoluene (BHT) and a certain concentration of oxygen results in lung damage in the form of interstitial pulmonary fibrosis.

Information on additional examples of lung damage from chemical interactions can be found [here](#).

Knowledge Check

1. A target organ is an organ that:

- Absorbs a toxic substance
- Stores an absorbed substance or its metabolite
- Is damaged by a toxic substance

Answer

Is damaged by a toxic substance

A target organ is an organ in which a substance exerts a toxic effect.

2. What are the important factors that influence the degree of toxicity of a substance?

- Innate chemical activity, form, dosage, and exposure route
- The species, life stage, gender, health status, nutritional status, and circadian rhythms of the organism
- Absorption, metabolism, distribution within the body, excretion, and presence of other chemicals
- All of the above

Answer

All of the above

3. Metabolism, or biotransformation, of a xenobiotic:

- Always results in reduced toxicity of the xenobiotic
- May result in detoxification or bioactivation
- Has no influence on the toxicity of the xenobiotic

Answer

May result in detoxification or bioactivation

Metabolism of a xenobiotic results in either detoxification, which converts the xenobiotic to a less toxic form, or bioactivation, which converts the xenobiotic to more reactive or toxic forms. For example, a xenobiotic itself might not be carcinogenic, but a metabolite of the xenobiotic might be.

4. An antibiotic administered to humans kills bacteria in the body but does not harm human tissues. This is an example of:

- Selective toxicity
- Acute toxicity
- Varying absorption of the antibiotic

Answer

Selective Toxicity

Selective toxicity refers to differences in toxicity between two species simultaneously exposed, much like the antibiotic in this example.

5. A major determinant of whether a toxicant will damage cells is its:

- Acidity
- Biotransformation
- Lipid solubility

Answer

Lipid solubility

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.

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