Toxlearn

Module I - Introduction to Toxicology and Dose-Response

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Objectives

Upon successful completion of this module you will be able to:

- Define toxicology
- Identify the six applied areas of toxicology
- Explain ways in which toxicology is relevant to our daily lives
- Outline the basic principles of toxicology
- Define dose and contrast the types of dose measures
- Distinguish how each type of dose is measured
- Explain the concept of dose-response
- Describe the concept of dose-effect

Introduction

News has always had a penchant for the sensational and toxicology often fills the bill. There would likely have been a considerable buzz even in ancient times about events such as the sentencing of Socrates to drink hemlock.

When not bombarded by high impact news stories, we have to contend with personal worries about toxic substances:

- What are the side effects of this **drug**?
- Should I be picking these mushrooms?
- Is it safe to be jogging outside with the ozone level this high?

This is the human part of the story.

Toxicology is the science behind the stories, not always as dramatic, but possibly as fascinating, and certainly necessary in determining how certain chemicals can harm us under particular conditions, and seeking ways to prevent or alleviate the harm.

Toxicology is relatively new as a distinct scientific discipline although many of its basic principles have been known for some time. This section will explore this history, describe how toxicology has changed over time, and offer a broad definition of this discipline. In addition, the six areas of applied toxicology will be described as well as how these areas are relevant to our daily lives.

Following this, the basic principle of toxicology - "the dose makes the **poison**" - will be explicated and the strengths and limitations of this principle will be explored. This exploration will include discussions of the different types of **dose**, how they are

measured and how **dose-response** and **dose-effect curves** are constructed and used, especially in assessing risks to human health.

This module will provide the reader with an overview of toxicology and provide the context for the more detailed materials that follow.

This module includes the following sections:

1. Introduction
2. What Is Toxicology?
3. Toxicology And Our Daily Lives
4. Determining Toxicity

What Is Toxicology?

History: Poisoning Highlights

Poisoning and the knowledge of **poisons** have a long and colorful history although the science of toxicology has only recently come into existence as a distinct discipline.

Even the cave dwellers had some knowledge of the adverse effects of a variety of naturally occurring substances, knowledge that they used in hunting and in warfare.

Famous early victims of plant and animal poisons were the Greek philosopher **Socrates** and the Egyptian Queen **Cleopatra**.

Conium Maculatum
(Poison Hemlock)

As time progressed, toxicological knowledge and its applications expanded. Indeed, poisoning became institutionalized in a number of places, and some governments utilized poisons for state executions, a practice that continues in some jurisdictions, via means such as lethal injections.

Cleopatra committed suicide through the bite of an asp, a poisonous snake.

Socrates was forced to drink Hemlock for corrupting the youth of Athens.

The European Renaissance was a time notorious for poisonings and poisoners. Born in 15th century Italy, Cesare and Lucrezia Borgia used a concoction of chemicals to assassinate their political rivals. Their potion "La Cantarella," may have included arsenic, copper, and phosphorus.

Unintentional poisoning has always been with us. Through the science of toxicology we now better understand these risks and work to avoid harm to human health.

The naturally occurring element lead was used in the Roman era to line vessels and as a pottery glaze, as well as in cosmetics. In the 19th century in the United States paint manufacturers began to use lead as a pigment, although even in 1786, Benjamin Franklin outlined the hazardous effects of lead on the body in a letter to Benjamin Vaughan, a friend. Though banned in paint today, society needs to be ever vigilant in protecting children (who are particularly susceptible to the effects of lead on the brain and nervous system) from exposure to older flaking paint chips.

Peeling Paint, House Exterior

Lead was also used in gasoline to prevent engine knocking. Because of bans of these uses and intensive public health efforts, lead concentration in urban children has decreased in the past several decades. Studies have demonstrated a correlation between minimal lead exposure and higher cognitive function.

Workers, because they tend to be exposed to higher levels of chemicals than the general population, are in danger of being unwittingly poisoned at rates higher than the general population. Asbestos, as an example, was widely known in antiquity but use increased as a result of the industrial revolution. It has been used in textiles, building materials, insulation, and brake linings. Capable of causing severe lung damage, including asbestosis and mesothelioma, asbestos is now strictly regulated. Today, we are not only concerned about workers exposed to traditional industrial chemicals, but also to those used in the electronics industry, as well as bio- and nano-engineered products.

Chemical and biological warfare date to antiquity. The mythological account of Paris slaying Achilles with a poisoned arrow in the heel has a basis in the way some battles were conducted at the time. Fast forward to 1914, when poison gas was used in a more systemized and large-scale fashion by the Germans in World War I. In 1988, Iraqi government troops attacked the Kurdish town of Halabja with chemical bombs involving multiple chemical agents including mustard gas and the neurotoxic agents, sarin, tabun and VX.

Another broad sphere of poisoning relates to toxicological disasters. While some may be natural (e.g., sulfur and other toxic gases emitted from volcanoes), others are related to industrial mishaps. Love Canal is an iconic example. The vicinity of the Canal was used by Hooker Chemicals as a dumping ground for numerous hazardous substances, a large population was put at risk, and hundreds of families living in homes on top of the dumpsite needed to evacuate. And in 1984, in Bhopal, India, a

release of the chemical methyl isocyanate resulted in many thousands of deaths and many more injuries.

A more recent example of political poisoning is the remarkable survival (albeit chloracne scarred) of the Ukranian president Viktor Yushchenko, after alleged poisoning with dioxin, and, possibly **endotoxin**, prior to the 2004 elections.

In 2006, in a case with overtones of espionage, Alexander Litvinenko, a former Russian spy, was fatally poisoned with radioactive polonium-210. The radioactive isotope was allegedly added to tea he drank at a London hotel.

2007 and 2008 have seen increasing incidents of product contamination, often via international trade. Pet foods, for example, have been found to contain melamine, an organic compound used to make a variety of plastic products. Although there is some doubt about the toxicity of melamine to dogs and cats in the doses to which they were exposed, it is an industrial chemical which should not have been added to the food, and its effects may have been exacerbated by other food ingredients. Toys have been discovered with lead and, in one instance, with a glue which, when ingested, metabolizes to GHB, the date rape drug. Recalls followed swiftly.

Thus toxicology, in its scope, casts a broad net, encompassing hazardous effects of chemicals (including drugs, industrial chemicals and pesticides), biological agents, also known as toxins (e.g., poisonous plants and venomous animals) and physical agents (e.g., radiation, noise). It has been newsworthy since ancient times and will continue to be a subject of fear and fascination, as well as the important source of information protecting humans, other animals, and the environment from dangerous exposures

History: Toxicology Research

During periods of intellectual ferment in Europe, scholars began more systematic studies of poisons and their effect. Two noteworthy examples, products of the 15th Century Renaissance, and the 18th Century Age of Enlightenment respectively, were the alchemist Paracelsus (born in Einsiedeln, now a city in Switzerland) and the Spanish physician Orfila.

Paracelsus

Orfila

Paracelsus (1493-1541) identified the specific chemical components of plants and animals that were responsible for their toxic properties. He also was able to show that varying the amount of the poison affected the severity of the effects.

Orfila (1787-1853), who is often referred to as the father of toxicology, was the first to establish a systematic correlation between the chemical properties and biological effects of poisons. Using autopsy results, he was able to link the presence of particular poisons with specific damage to tissues and organs.

During the 19th century, there was a proliferation of textbooks dealing with toxicology in relation to forensic medicine, in which scientific tools and principles are used to investigate crimes and accidents.

In part, this was due to the great advances in chemical analysis, allowing for a more precise determination of the amounts of **toxicants** in body tissues and fluids (from which study analytical toxicology is derived).

Toxicology developed as a modern science during the 20th century, particularly after the Second World War, at least partly in response to the rapid development and production of many new **drugs** and industrial chemicals.

Thus, toxicology, ancient in practice, came to be known simplistically as the science of **poisons**.

As the understanding of the working of living organisms became increasingly sophisticated, and a true scientific basis evolved, it has become clear that this definition is not adequate.

In light of this, the Society of Toxicology uses the following definition:

> "Toxicology is the study of the adverse physicochemical effects of chemical, physical or biological agents on living organisms and the ecosystem, including the prevention and amelioration of such adverse effects."

Examples of such agents include cyanide (chemical), radiation (physical) and snake **venom** (biological).

The effects on organisms can occur at multiple levels, including the molecular and the organ levels.

Research and Application

Toxicological research is an exciting field of study utilizing and integrating principles developed in a variety of disciplines including chemistry, biochemistry, physiology, pathology, biology, genetics and pharmacology. These inputs are reflected in the names of the areas of toxicological research such as biochemical toxicology, pathotoxicology, toxicogenomics, pharmacokinetics, and pharmacodynamics.

Combining the understanding gained through these disciplines, toxicologists are able to characterize the disposition of agents in living organisms, the types of adverse effects that may be produced after exposure, the mechanisms of action behind these effects and the impacts of possible interactions among agents.

Toxicological studies may be carried out by scientists with training in these diverse disciplines. For example:

- Biochemists, who study the fates of agents in living organisms and the mechanisms by which they exert their effects;
- Geneticists, who investigate the effects of agents on genetic material and the impact of genetic variation on responses to toxic insults; and
- Epidemiologists, who study populations exposed to such agents to look for possible connections between exposures and adverse health outcomes.

The ultimate objective of the combined research of such toxicological specialists is to determine how an organism is affected by exposure to an agent.

This includes an understanding of:

- How the agent moves throughout the organism;
- How it may be changed by interacting with living cells and tissues;
- What parts of the organism are affected by its presence; and
- The health outcomes of this exposure.

The more thorough this understanding, the more accurately toxicologists can predict what will happen when different types of organisms, particularly humans, are exposed to agents in the ambient environment, the workplace, or via exposure to food and drugs.

Today, one way of looking at toxicology divides it into six applied areas - clinical, forensic, analytical, environmental, occupational, and regulatory.

Clinical toxicology, the diagnosis and treatment of human poisoning, and forensic toxicology, the medical-legal aspects of clinical poisoning, are discussed further in a later slide. The related discipline of analytical toxicology is concerned with the identification and quantification of toxic chemicals in biological materials.

Environmental and occupational toxicology are self-explanatory in that they deal with toxic hazards in the environment and in the workplace, respectively. Regulatory toxicology focuses on laws and regulations and their enforcement, an important component of toxicology. Risk assessment, covered in a later module, is often considered a part of regulatory toxicology.

All of these branches of toxicology rely on the same basic science to achieve their goals, and are not all mutually exclusive. Thus, poisoning at the workplace would encompass aspects of both clinical and occupational toxicology.

Regulatory toxicology (i.e., the regulation of potentially toxic substances) has recently been a major driving force in toxicological research.

Much of the support for toxicology is predicated on the idea that increased knowledge will lead to better management of potentially toxic agents, actions which, in turn, will result in improved public health.

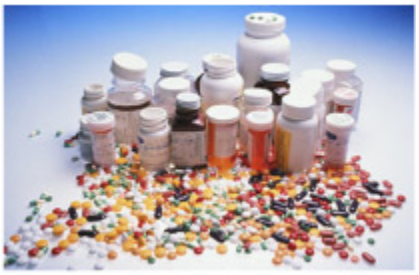
Accurate predictions of effects of chemicals on humans depend upon scientific studies. Most toxicological studies are empirical in nature, and are performed on experimental animals (***in vivo)*** or ***in vitro*** test systems (i.e., cell culture or other systems used to mimic the results in part of a living organism).

Since the results are often used for regulatory purposes, the goal of such studies is to predict effects in humans.

To achieve this goal, scientists need to understand the differences between experimental animals and humans in the way that they process foreign chemicals (**xenobiotics**) and physical agents, as well as the applicability to humans of results obtained in vitro.

Toxicology and Our Daily Lives

Toxicology was relevant historically because knowledge of plant and animal poisons served various ends, some beneficial to society and others not.



In particular, this knowledge could be used for hunting large game, defense against enemies and understanding which plants and animals were safe to eat and which should be avoided.

Toxicology is just as important to us today. Our improved health status and increase in life expectancy are due in part to advances in **pharmacology**. Toxicology research helps ensure that the beneficial effects of therapeutic agents are not outweighed by unwanted side effects. There are about 100,000 chemicals in commercial use and 1,000 new ones added every year.

We have modern toxicology to thank for the safety of our food and drinking water, consumer products, and other industrial chemicals we use or to which we are exposed. Toxicology knowledge helps in the prevention of adverse effects. More specialized branches of toxicology, such as toxicogenomics and nanotoxicology, increasingly have a significant bearing on our daily lives.

Food Toxicology

Despite great advances made by toxicology in assuring that our food is uncontaminated, it is still important to know what products are safe to eat and in what quantities.

In addition to concerns about naturally occurring substances in foods, food toxicologists also investigate the safety of other components of food that have been added deliberately or accidentally.

Deliberate additions include a variety of natural and synthetic additives and artificial substitutes for naturally grown food components. These include sweeteners, color and texture additives, fat substitutes and preservatives.

Accidental contaminants are generally synthetic or natural environmental contaminants in the food chain, such as polychlorinated biphenyls (PCBs) and methyl mercury, found in fish, microbial toxins such as produced by E. coli in

contaminated food, and fungal toxins (like aflatoxins) which may contaminate grains.

Recently scientists have been investigating and debating the safety of Genetically Modified Organisms (GMOs) as food products.

Safety of Pharmaceuticals

Toxicological research is critical in the development and production of pharmaceuticals.

At the beginning of the drug discovery process, toxicity tests help to determine which potential pharmaceuticals are likely to be safe enough for humans and thus warrant further development.

All along the development process, additional testing is performed to ensure that the final product will not only be efficacious but also free of unreasonable side effects. For each and every pharmaceutical, prescription or over-the-counter, safety evaluation studies are performed. Safety evaluation studies often include experimental animals and clinical trials involving humans. This scrutiny includes multi-year studies of possible chronic effects, including cancer.

Toxicology of Industrial Chemicals and Consumer Products

Before new industrial and consumer products can be developed and marketed, toxicological research is needed to ensure that these can be used safely as intended.

This involves investigations of possible **adverse effects** on humans due to exposure to these products in the workplace, home, or in the general environment, and possible dangers to other animals, such as wildlife.

For agents that have been on the market for some time and are already out in the environment, toxicology can help to determine whether or not remediation of sites contaminated by these agents is needed and, if so, how thorough the clean-up must be to protect the local population and the environment.

Clinical and Forensic Toxicology

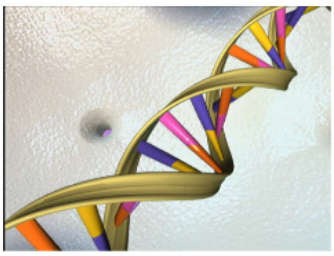
Toxicology continues to be important in the clinical and forensic settings.

In the clinical setting, toxicologists assist in making diagnoses of possible agent-induced harm in individuals exposed occupationally or environmentally.

Clinical toxicologists are also concerned with drug toxicity. Prescription and non-prescription drugs, just like other chemicals, may cause adverse effects dependent upon many factors, including the dose, individual age, hypersensitivity, etc. Drugs of abuse, typically taken for pleasurable effects or sometimes for suicidal purposes, may pose threats ranging from mild to severe.

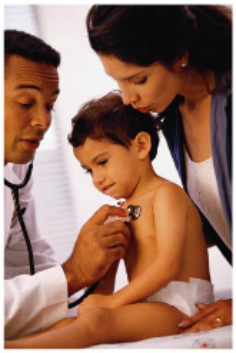
Forensic toxicologists can help to determine the possible effects of agents on behavior (e.g., alcohol on driving ability), and also assist in determining the cause of death in individuals who may have suffered from **intoxication** by chemical or physical agents.

Toxicogenomics



In the new millennium, advances in toxicology are leading to additional and refined uses of toxicology.

Understanding the genetic basis of responses to chemical and physical exposures can help to predict which individuals will respond best, and with the least side effects, to particular pharmaceutical agents and also to predict which individuals will be most at risk from specific occupational and environmental exposures.



This new area of study, known as toxicogenomics, will provide the opportunity for a more customized approach to individual health.

Nanotoxicology

The prefix, “nano,” implying a billionth of an amount, has been appropriated for “nanotechnology,” the science of extremely small materials. An increasing number of consumer and other products are now made of nanoscale substances. The corresponding study of the safety and potential hazards of nanoparticles and nanotubules is known as nanotoxicology.

Many nanomaterials are initially formed from nanoparticles which can produce aerosols and colloidal suspensions. As such they can readily be inhaled, ingested, or potentially absorbed through the skin.

Although our knowledge of the toxic activity of these very small particles is scant, we can, and often do, use ultrafine particles as models of nanoparticulate behavior. Studies to date have indicated that ultrafine particles are more toxic on a mass for mass basis than their larger counterparts. Moreover, ultrafine particles have been

shown to penetrate the skin and translocate from the respiratory system to other locations in the body.

Although nanotechnology promises major advances in the fields of physics, electronics, chemistry, and medicine, workers in nanotechnology industries often face exposure to unknown levels of nanoparticulates with unique sizes, shapes, and activities. Hence, research aimed at defining the potential toxicity of these particulates is needed as are effective monitoring and surveillance techniques and adequate protective equipment.

Determining Toxicity

The Dose Makes the Poison

The basic principle that governs toxicology was first stated by Paracelsus about 500 years ago. In his words:

“All substances are poisons; there are none which is not a poison. The right **dose** differentiates a poison and a remedy.”

This is a very powerful principle since it lays out the fundamental challenge of all toxicological research - to determine the doses at which specific agents cause adverse effects on living things.

It is also important as a counterbalance to the popular idea that agents can be divided into those that are poisons or "**toxic**" agents, and those that are not. All agents are toxic; it is only the degree and type of toxicity that differ from one agent to another.

What is "Dose"?

To understand this principle, it is important to first define dose. The **dose** of a chemical or physical agent is the amount of that agent that comes into contact with a living organism or some part of a living organism. The type of dose most familiar to the average person is that associated with medicines.

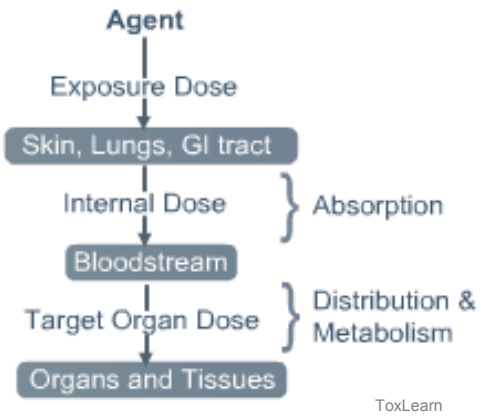
For example, a physician may prescribe a dose of 10 milligrams once each day. However, hidden within this amount is the concept that dose really represents the amount of agent per unit (e.g., kilogram) of body weight. When physicians decide on a prescribed dose, they take into account the

X

weight of the individual receiving the medication. A heavier person, for example, may require a greater dose to achieve the same effect that a lesser dose would have on a lighter person.

In toxicology, it is common for the dose to be explicitly expressed in terms of body weight and, often, in terms of time as well. Thus, the dose may be given as 10 milligrams per kilogram of body weight (10 mg/kg) or even 10 milligrams per kilogram of body weight per day (10 mg/kg/day). This latter dose given to a person weighing 70 kilograms, for example, would result in a total dose of 700 mg (70 x 10) over the course of a day.

One should also keep in mind that medications are chemicals designed for positive effects, but at the right dose. Thus a baby aspirin tablet may not cure an adult of a headache, while two ordinary aspirins are more likely to do the job. One hundred aspirins taken all together will likely result in toxic effects.



In addition to the somewhat different ways of expressing dose, there are different kinds of doses that can be important toxicologically.

For example, dose can refer to the amount of a substance to which an individual or population is exposed. This definition is generally applied in cases of occupational and environmental exposures.

In the experimental situation, the dose to which animals are exposed is known as the **administered** dose. Dose can also be defined as the amount absorbed into the organism, also known as the **internal dose**. This definition reflects the idea that only the amount that is absorbed is available to cause harm at sites in the body distant from the site at which the agent makes contact with the individual.

As toxicological knowledge grew more sophisticated, it became possible to define dose in yet other ways that better reflect the connection between dose and effect. One example is the **target organ dose** or the amount that reaches the site(s) at which the adverse effects occur. This is also known as the **biologically effective dose**.

It is always important to note that the extent and nature of adverse effects, for a given agent, may vary, dependent upon the dose and route of exposure. Major routes of exposure include **ingestion**, **inhalation** or skin contact (**dermal**).

Effects are also dependent upon the age and sex of the exposed individual, as well as other characteristics of this individual, including underlying disease, nutritional status, and history of previous exposures.

In addition, the time course and duration of the dose administration or exposure are important variables. A single large dose given all at once is likely to have quite a different impact than the same total dose given in small amounts over a long period of time.

Also, the spacing between doses given over long periods of time can be critical in determining whether or not adverse effects will occur.

Public interpretation of dose and effect, frequently fueled by media sensationalism, may fail to take into account all the variables affecting dose. Unless this is done, however, reaching conclusions about a chemical's or product's toxicity is purely speculative.

“All substances are poisons; there are none which is not a poison. The right **dose** differentiates a poison and a remedy.”

The original German statement, "Alle Dinge sind Gift und nichts ist ohne Gift; allein die Dosis macht, dass ein Ding kein Gift ist," Is sometimes summarized and translated as "The dose makes the poison." This is a good starting point, but really not as simple as it sounds.

So, while the basic principle expressed so eloquently by Paracelsus governs the practice of toxicology, it is important to understand that applying this principle is difficult and requires an appreciation of all of the factors that influence responses to a given dose and all of the ways that dose may be defined. All too often, conclusions about dose and effect are made without consideration for these issues and such conclusions should be carefully scrutinized before they are accepted.

Thus, dose entails many variables, and the ultimate extent of its effects is closely entwined with the route of exposure. To summarize, the variables which must be taken into account in making a full determination of the consequences of dose include:

- Dose Amount - A measure of the magnitude of the dose.
- Dose Frequency - How often exposure occurs, e.g., daily, weekly, five days out of seven, etc.
- Dose Duration - Over how long a total period of time dose exposure occur, e.g., a week, a month, a year, a lifetime.
- Subject Variability (Natural) - Individual characteristics such as age, sex, body weight, ethnic background, and genetics.
- Subject Variability (Health Status) - Whether any pre-existing health conditions, such as asthma, diabetes, or hypertension, may affect susceptibility to an agent.
- Route of Exposure - The way in which the person is exposed. The three most common routes of exposure are ingestion, inhalation and skin contact.

Later modules will consider how toxicity (of which dose is one attribute) together with extent of exposure determines "risk."

How is Dose Measured?

Depending on the situation, measuring dose can be a straightforward process or a very cumbersome one.

The best setting in which to accurately measure dose is the laboratory, where the conditions can be controlled.

When doing research on experimental animals, it is possible to present them every day with food and/or water containing exactly the same amount of the agent being tested.

Using measures of the amount ingested, it is possible to fairly accurately calculate the total amount of the agent the animal is exposed to each day, and thus the daily dose.

At the other extreme, measuring the doses to which individual humans are exposed in their everyday environment is much more difficult.

The amount of a particular agent ingested is likely to vary from day to day and measures of the concentration of the agent in the media of interest (e.g., air or water), are unlikely to be available on a daily basis.

In this case, it is only possible to estimate the doses to which individuals are exposed using whatever environmental measurements are available and combining them with general information about human behavior (e.g., amount of food or water consumed each day).

Because of the lack of appropriate data, these dose estimates are often quite uncertain; the fewer the data, the greater the degree of uncertainty.

Additional complexity is involved in real world exposures to multiple chemicals, especially at the same time. Consider, for example, the exposure of the population in the vicinity of the 9/11 World Trade Center disaster.

Measuring the **absorbed dose** is more difficult than quantitating the **exposure** dose since it requires information about the way that different animals absorb agents through various routes of exposure (e.g., inhalation, dermal absorption) and under differing conditions. For example, absorption through a young male rat's skin might be very different from the dose delivered through drinking water in an aged female monkey.

Information about absorption is collected through laboratory experiments, generally performed on a limited number of animals. Because of ethical and other considerations, such laboratory studies are typically performed on rodents and rarely on humans. As a result, there is a level of uncertainty in extrapolating the effects of absorbed dose from laboratory animal studies to humans.

The most difficult dose to quantitate is the **target organ dose** or **biologically effective dose** (e.g., the dose that actually reaches the liver) since this generally cannot be directly measured. To make such measurements in animals generally requires invasive procedures that could alter the response of the organism, while to make such measurements in humans would be unethical.

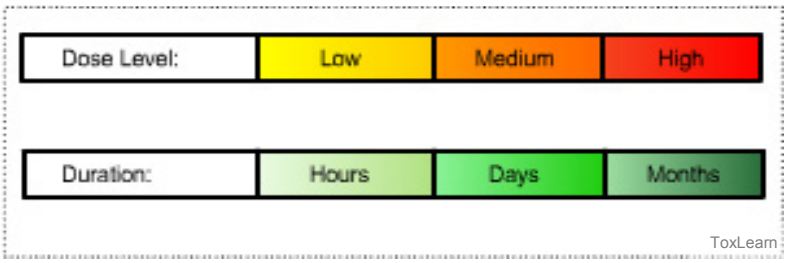
Thus, target organ doses are usually calculated using information about the distribution and fate of the agent in the organism. This information can be gathered from studies on the amounts of an agent that are absorbed, excreted, stored and freely circulating in an orga nism.

Often this type of information is not available or is incomplete so that it is difficult to calculate target organ doses with confidence, even in organisms which have been extensively studied (e.g., rodents). Estimation of the target organ dose is much more difficult in humans since the needed information is generally even less available.

Dose-Effect and Dose-Response

Since the basic question in toxicology is how dose is related to toxicity, most toxicology studies are designed to investigate how living creatures react as doses vary incrementally, from low to high levels. In studies on experimental animals, different groups of animals are **administered**, or **exposed** to, different **daily doses**.

Example increments for toxicity variables



Then, at various intervals, the animals are examined for the presence or absence of effects. These effects may be behavioral changes, alterations in the compositions of body tissues or fluids (e.g., blood, serum, urine), or structural changes in parts of the organism.

Since examination of internal organs requires invasive procedures that can have an impact on the effects observed, examinations of effects on these organs are generally done during autopsy after studies are completed.

Researchers are developing exciting new ways to assess effects in living animals, including techniques such as Magnetic Resonance Imaging (MRI), ultrasound, Positron Emission Tomography (PET), and optical imaging. In the latter, biolumenescing genes

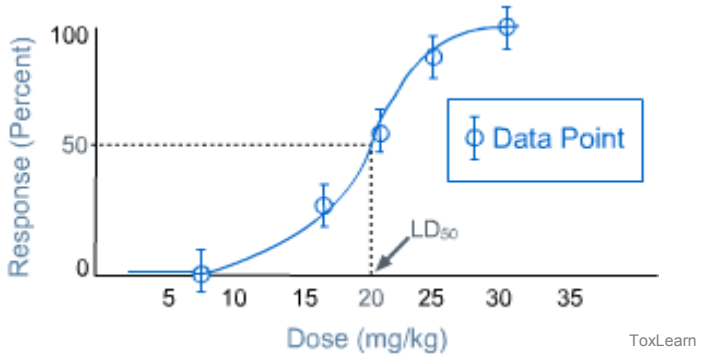
are inserted into the genetic material of animals and detection of light indicates functioning of certain biological pathways.

The data are then plotted on a graph that shows the dose on one axis and the response or effects on the other.

In a typical dose-response graph, the dose is plotted against the number or proportion of animals exhibiting a particular response.

For a long time, death was the response of choice for assessing short term (acute) toxicity, and the toxicology literature contains many citations listing such lethal doses of assorted agents for a variety of laboratory animals.

In most cases, the dose that is lethal to 50% of the exposed animals (LD50) is the value that is published.



Although LD50 values are widespread in the scientific literature and still used and useful, concerns over animal welfare and the development of more technically sophisticated tools have led to other approaches for assessing toxicity.

On the other hand, dose-effect comparisons can be depicted in graphs, charts, or tables which plot dose against the degree of response (i.e., the severity of the effects). Thus, a low dose may cause no effects, a higher dose, limited effects, a still higher dose, serious outcomes, and, at a high enough dose, death.

A common real world scenario that illustrates this type of dose-effect relationship is the sequence of events that can occur as a result of human alcohol consumption.

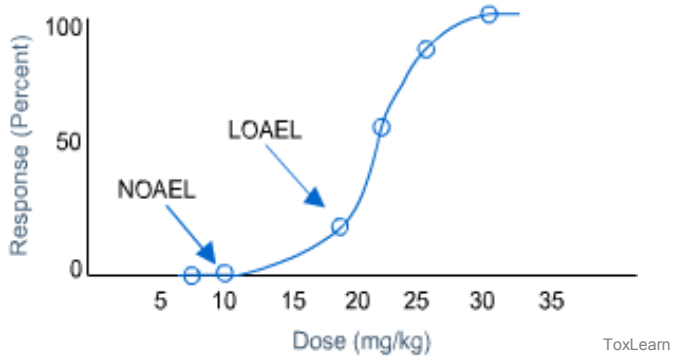
In this case, a low consumption does not result in observable effects but increasing amounts of alcohol lead to increasingly severe symptoms including incoordination and unconsciousness, and sometimes even death.

% Alcohol in Blood	Observed Effect
0.05	Stimulant, social relaxation
>0.1	Incoordination
0.3	Unconsciousness
0.4	Possible lethal level

While the previous alcohol example illustrates the **dose-effect relationship** for a short term (acute) exposure, dose-effect relationships are also commonly used for assessing long term (chronic) effects.

When used to characterize chronic toxicity for chemicals that do not cause cancer, the dose-effect relationship in laboratory animals exposed over long periods of time is examined to determine the highest dose at which no observable adverse effect is seen (NOAEL) or the lowest dose at which an adverse effect is observed (LOAEL).

This single value on the curve is then extrapolated to humans to estimate the maximum exposures that are likely to be without adverse effect. Making this assessment often requires judgment because there may be subtle distinctions between normal variation and an adverse effect.



Note: The Y-axis in dose-response curves does not always measure the same effect. Earlier we saw a curve where lethality was the parameter under consideration as the dose (X-axis) was increased. In this generic graph, though, the response, still measured as a percentage, may represent various effects. Thus, the LOAEL may represent increased blood sugar concentration, say, at just under 20 mg, while kidney damage may begin presenting in some subjects at 25 mg, and at about the 30 mg mark, all the subjects (the 100 percent level) would have contracted one toxic effect (including, possibly death) or another.

Credits

ToxLearn is a free, public domain, modular, online tutorial which updates, and when complete, will expand the former ToxTutor. It is a joint project of the U.S. National Library of Medicine's Toxicology and Environmental Health Information Program and the Society of Toxicology, the world's premiere professional association of toxicologists. ToxLearn was produced by X-Plain.com, using X-Plain, an interactive multimedia software package.

ToxLearn is written at an undergraduate level. It is intended to provide users of NLM's toxicology databases a fundamental understanding of the scientific principles of the subject. It may also be used as an educational adjunct in colleges and for other interested people with a knowledge of basic chemistry and biology.

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