Principles of Toxicology
Or
A Small Dose of Toxicology

A book chapter of
A Small Dose of Toxicology - The Health Effects of Common Chemicals

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Supporting web sites
web: www.asmalldoseof.org - "A Small Dose of Toxicology"
web: www.toxipedia.org - Connecting Science and People

Introduction

There are three basic and interwoven principles of toxicology: 1) dose-response, 2) hazard X exposure = risk, and 3) individual sensitivity. While these principles may form much of the foundation of toxicology, when it comes to any specific substance there is likely to be controversy. Disagreement may arise on the relative importance of any one of these principles while trying to evaluate implications for public health. Exploring these principles is an essential first step before examining their application to any specific substance. This chapter will explore some of the details and issues surrounding these principles, but first it is appropriate to put them in historical context.

Basic Principles of Toxicology

Dose-Response

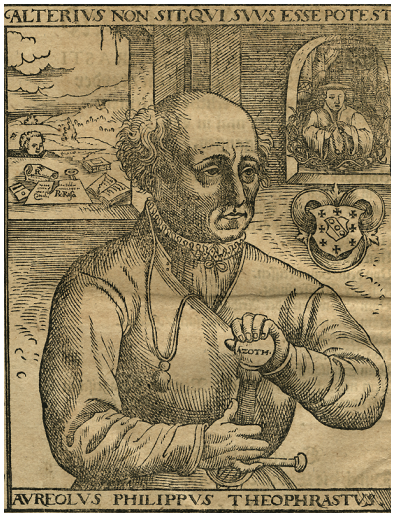
Risk = Hazard X Exposure

Individual Sensitivity

Our ancient ancestors worried about being poisoned ether accidentally or on purpose. The formal study of poisons (and thus toxicology) began 500 years ago during the Renaissance, a period of incredible change and challenge to traditional thought. Phillippus Aureolus was born in Switzerland (Figure 2.1), a year after Columbus sailed in 1493. He took the pseudonym of Theophrastus Bombastus von Hohenheim and still later invented the name Paracelsus (1493-1541). This name may signify his desire to move beyond the Roman philosopher and medical writer Aulus Cornelius Celsus (cAD3-64), who promoted cleanliness and recommend the washing of wounds with an antiseptic such as vinegar. Paracelsus's claim to toxicology is that he elegantly stated the principle of dose-response as "All substances are poisons; there is none, which is not a poison. The right dose differentiates a poison from a remedy." This often-used quote accurately states that too much of anything, even drinking too much water, can be harmful. (It should be noted that too little of some substances can also be harmful.)

What Paracelsus failed to emphasize is the variation in sensitivity of the individual. A bee sting or a peanut can be deadly for some individual while only annoying or even tasty for most people. There are now numerous examples demonstrating that the developing infant is very sensitive to the poisonous effects of a substance that does not harm the adult. For example, alcohol consumption during pregnancy can result in permanent harm to the infant without affecting the mother. The brain of the developing infant is sensitive to low levels of lead exposure, which is not the case for the adult. Another approach to the principle of dose / response might look like this: "The sensitivity of the individual differentiates a poison from a remedy. The fundamental principle of toxicology is the individual's response to a dose." The principle of dose / response is only useful when linked to the sensitivity of the individual.

Figure 2.1: Paracelsus



In this portrait Paracelsus is surrounded by various philosophical symbols. From Paracelsus: *Etliche Tractaten, zum ander Mal in Truck auszgangen. Vom Podagra und seinem Speciebus* (Coln, 1567). Washington University Collection. (from web site http://www.nlm.nih.gov/exhibition/paracelsus/paracelsus_1.html)

Individual sensitivity to a hazardous agent depends on age, genetics, gender, current or prior illness, nutrition, and current or history of exposure to chemical agents. Age is important factor for the very young or the elderly for very different reasons. The developing nervous system of the infant is more susceptible than the mature nervous system to a range of agents. Our metabolism of agents slows as we age and our bodies again become more vulnerable to the effects of an agent. Our gender and genetics dictate our ability to metabolize agents either more quickly or even not at all. For example, some people metabolize alcohol more slowly that other people because of their genetics. All these factors are important as we judge our susceptibility to a particular hazard.

There are many familiar hazards in our lives, some easier to evaluate than others. An agent or situation is hazardous when it can produce an adverse or undesirable effect. Hazard is a property of a particular agent or situation. Early in our lives we learn about the hazards of crossing the street or falling off a ladder or stumbling down the stairs. Learning about the hazards of a chemical agent is not so easy. Defining the hazard of a chemical agent requires experience in human exposures or careful study in experimental models. Through personal experience we gain an understanding of the hazards of some agents like alcohol or caffeine.

We routinely combine our knowledge of hazard, exposure, and individual susceptibility to judge the possibility or risk of harm. A young person judges the speed of the approaching car and decides to run across the street while an elderly person waits for the traffic light to change. This decision is based on a judgment about the risk of being struck by the car. An experienced mountain climber will judge the risk of harm on a difficult climb very differently from someone with no experience. Judging the risk of harm from a

chemical agent is often far more difficult because the adverse effects may not be immediately obvious or may depend on individual sensitivity.

The ability of an agent to damage to the nervous system or of causing cancer 10 years after exposure is clearly not obvious. The formal process of determining the potential of agent to cause harm is called risk assessment. The risk assessment process is in itself complicated and often controversial because needed data may not be available or there is conflicting information. Risk assessment is the process of combining all the known information about the hazard of an agent and making a determination of the potential for harm to people, animals or the environment. The next step is risk management.

Risk management combines the risk assessment with economic, political, public opinion and other consideration to determine a course of action. These judgments seldom satisfy everyone. The principles of toxicology form the foundation for the risk assessment and ultimately for the risk management decisions. Individual and community involvement in the decision-making process is a critical part of developing sound policies to minimize risks to people and the environment.

Dose / Response

The two most important words in toxicology are dose and response; in other words, how much of an agent will produce what reaction. In toxicology the focus is usually on adverse reaction or response, but it is equally useful to consider a full range of responses from desirable to undesirable. Experience teaches us how to moderate the dose to achieve a desired result or avoid an undesirable effect. Eating one apple is beneficial, but eating five apples may produce a stomachache. One cup of coffee in the morning may be just right, but if you drink three cups too quickly you will suffer the consequences. For light-skinned people, acquiring a tan without getting sunburned requires careful management of exposure to the sun. While Paracelsus stated correctly that the "… dose differentiates a poison from a remedy", it is the individual that must constantly be aware of the dose and his or her particular response.

Defining the dose is a critical first step in the effort to predict a response. Dose is the amount of exposure to an agent, a quantitative measure of the exposure related to the subject or individual. For a chemical agent or drug the dose is the amount of the material in relation to body weight. Typically the amount of material is measured in grams or thousandths of a gram (milligrams, mg) and body weight is measured in kilograms (kg), equal to one thousand grams. The dose is the amount of material consumed divided by body weight or mg/kg.

Calculating the dose

Oral dose = amount of material consumed (mg) / body weight (kg)

By knowing just a couple of facts we can turn our everyday exposure of caffeine into a dose. There are approximately 100 mg of caffeine in a cup of coffee. The actual amount of caffeine in a cup of coffee depends on the coffee bean, how the coffee was prepared and the size of the cup. An adult weighing 155 lbs (about 70 kg) consuming this one-cup of coffee would receive a dose of 100 mg divided by 70 kg, or 1.4 mg/kg of caffeine. The importance of including body weight becomes clear if you consider a child that weighs only 5 kg (11 lbs). If this child consumed the same cup of coffee, the dose would be 100 mg / 5 kg or 20 mg/kg, more than ten times higher than the adult.

The difficult part of calculating the dose is often determining the exact amount of exposure to the agent. The amount of caffeine in a cup of coffee varies depending on the bean and brewing method, to say nothing of the size of the cup. Very sensitive instrumentation is now available to analytical chemists to accurately determine the amount of a specific agent in a material. If the agent is pure, it is relatively easy to determine the amount of the substance and then calculate the dose. Some foods, such as table salt or sugar, are relatively pure and the dose easily calculated by weighing the material. Package labeling usually indicates how many milligrams of the drug each pill contains, so the dose can be calculated. An infant formulation contains much less drug per pill, but because of the difference in weight between the infant and the adult the dose is similar.

Calculating the dose following workplace or environmental exposure can be far more difficult. If the agent is in the air, then calculation of the dose must consider not only the concentration in the air but also the duration of the exposure, rate of breathing and body weight. The amount of air inhaled over a period of time is estimated from laboratory data. Given this information, it is possible to estimate the dose according to the following formula:

Inhalation dose (mg/kg) =
Air concentration of agent (mg/ml) X volume of air inhaled per hour (ml/hr) X duration of exposure (hr) / body weight (kg)

For non-chemical exposures, other variables and different units of measurement are required. For example, exposure to sunlight could be measured in hours, but to determine the dose would require knowing the intensity of the light as well as the exposed skin surface area For example, to determine a dose of sunlight requires knowing the number of hours of exposure, the intensity of the light as well as the skin surface area.

Workplace and environmental exposures are often repeated and ongoing over an extended period of time. The health effects of repeated long-term exposures can be very different from one short-term exposure.

Duration of exposure, frequency of exposure and time between exposures are important determinants of dose and response. Four beers in one hour would produce a very different response than four beers over four days. Many years of repeated high levels of alcohol exposure can lead to serious liver damage as well as other health complications quite different from the short term consequences of one exposure to a high level of alcohol. A*cute exposure* is a single or very limited number of exposures over a short period of time. C*hronic exposure* is repeated exposure over a long period of time. The effects of acute or chronic exposure, as in the case of alcohol, are often very different. For many drugs we are looking for the immediate or acute response following exposure. We consume common painkillers with the desire to quickly stop our headache. Long-term repeated use, however, can have undesirable effects on the stomach or liver. Tobacco users desire the acute effect of the nicotine but inevitably suffer the chronic effects of long-term use such as lung cancer and heart disease. It is also possible to have a delayed response to an acute exposure. For example, a laboratory researcher died several months after an acute exposure to a small amount of ethyl mercury. Detailed knowledge about the hazards of a substance is necessary in evaluating exposure and effect or dose/response relationships. This includes information about the consequences of acute or chronic exposure.

There is often a range of responses associated with any particular agent. The response that occurs will vary with the dose, the duration of exposure, and the individual. The acute response to a single dose is often the easiest to characterize, but the response to multiple exposures over a long period of time may be the most important. An emergency response worker that is exposed acutely to a solvent in the air may have her or his judgment impaired, resulting in a serious mistake. However, over the long term this exposure is of no consequence, assuming the worker survives any mistake in judgment. On the other hand, long-term exposure to coal dust can lead to black lung and severe disability. For a long time it was thought that the only serious complication from childhood lead exposure was death resulting from high exposure. Subsequent research demonstrated that even small amounts of lead exposure during childhood could result in brain damage that lasts a lifetime. Determining what responses are most important is a central aspect of many debates in toxicology.

Demonstrating Dose Response

In general, it is true that for any individual, the greater the dose the greater the response. This concept is illustrated in Figure 1 and can be easily demonstrated in the home or classroom with a few simple items (see appendix – Dose-Response Demonstration). Caffeine, which distributes evenly through out total body water, is a good illustration of dose-response. It is important to know if a substance distributes into body water because we made up of approximately 75% water. A can of cola contains approximately 50 mg of caffeine (about 4 mg per once of cola). Consumption of the first can of cola delivers an exposure of 50 mg per total body weight. Assuming a 100 kg person, this would be

50/100 mg/kg or 0.5 mg/kg. Consumption of three cans of cola would result in a dose of 1.5 mg/kg and six cans of cola a dose of 3 mg/kg of caffeine. Because caffeine distributes evenly through out body water you can almost imagine the change in shade depicted in Figure 2.2 as the concentration of the caffeine in the blood. An individual's response to the caffeine varies with the dose and corresponding amount of circulating caffeine.

The right panel (Figure 2.2) illustrates the effect of body size on the dose. When the adult and the child receive the same amount of caffeine, the exposure is the same but the dose is dramatically different. A child that weighs only 10 kg receives a dose of 5 mg/kg after one can of cola. An adult that weights 100 kg must drink 10 cans of cola to receive an equivalent dose. Body size is a critical factor in determining dose and any subsequent response. For the equivalent exposure to any substance such as lead or a pesticide, the child will receive a much greater dose than the adult. As we shall discover, there are other important physiological factors that also make children more susceptible than adults to the effects of an agent.

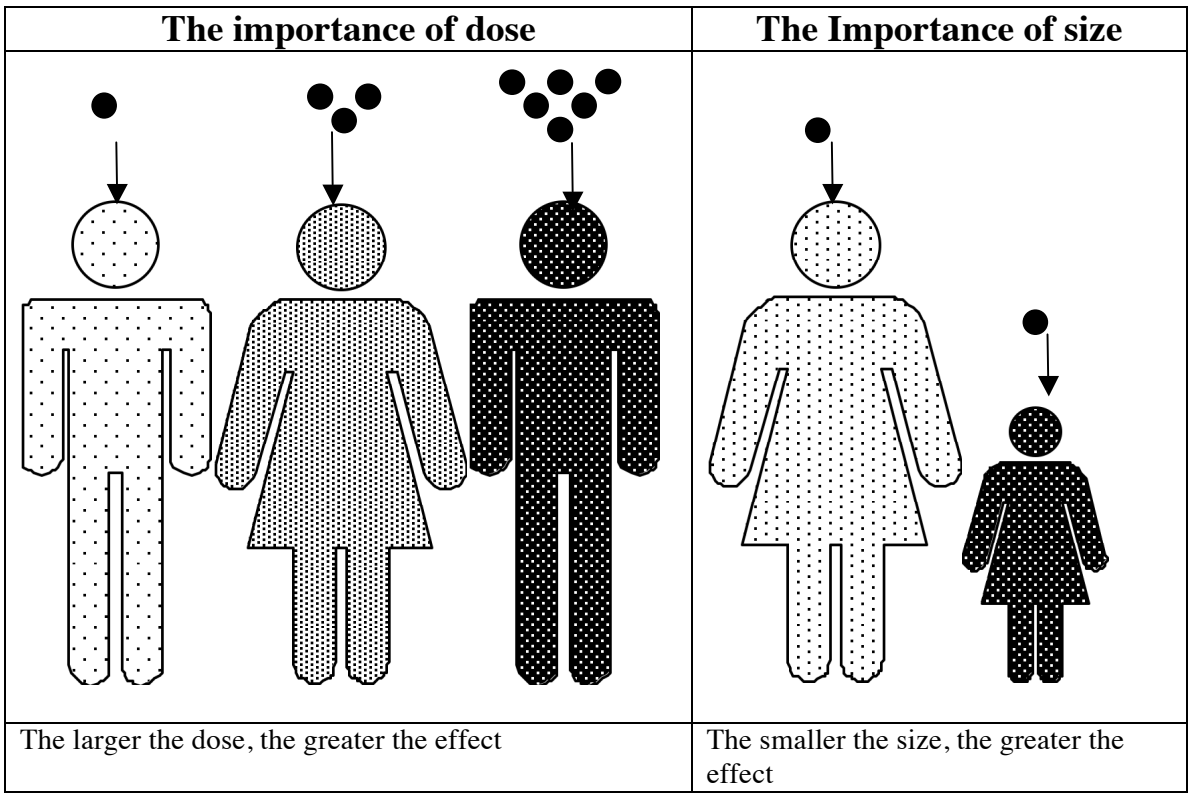


Figure 2.2 The Effect of Dose and Body Size on Response
For a given body size, the larger dose produces a greater effect (left), and for a given exposure, the smaller body size receives a greater effect and larger dose (right).

The next figure (Figure 2.3) graphically illustrates the critical relationship between dose and response. In this case, we define the response as difficulty in walking and the dose of

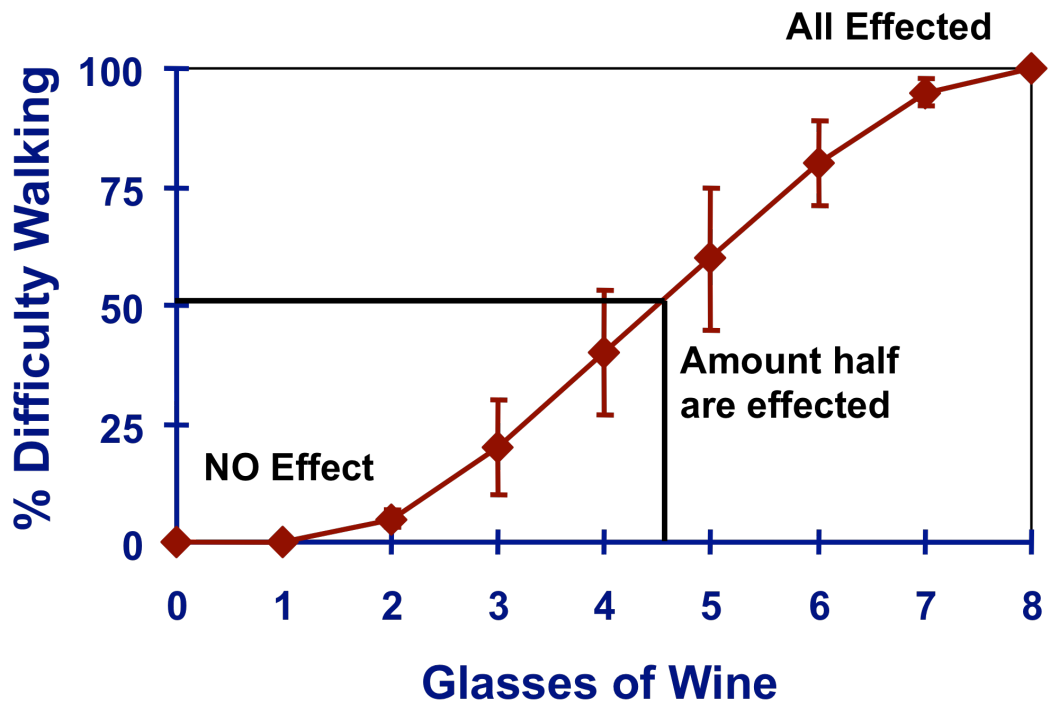


Figure 2.3: Dose Response Graph for Drinking Wine

Dose response function for difficulty in walking and number of glasses of wine consumed. This is an idealized curve, but it illustrates the principle that at low doses (i.e. few glasses) there is little response, then an increasing response to a maximum response. Note that this figure does not take into consideration body weight or any other variables such as gender or frequency of exposure (i.e. time between drinks).

or exposure to alcohol as a glass of wine. To change from exposure to dose we would need to know the body weight and amount of alcohol in the glass of wine. If we selected a group of people at random and offered them wine, no one (most likely) would have difficulty walking after one drink (depending of course on how big the glass was). The number of people responding, or in this case having difficulty walking, is a percentage of the total number of people in our study population. As exposure to wine increases, more and more people would have difficultly walking until finally everyone was affected.

In toxicology, the dose at which one half or 50% of the population is affected is often calculated and used to compare the toxicity of different agents. In this example, 50% of the population is affected after exposure to 4.5 glasses of wine. The vertical bars represent the variability from one test group to the next. If we repeat this experiment with a different group of people, the actual data points could be somewhat different, but should generally fall within the range spanned by the vertical bars or error bars. There are many possible reasons for this variation, including body weight (which changes dose), food consumption prior to drinking, past use of alcohol, genetics, gender, as well as others. Technically this figure is an exposure response graph because the dose is not calculated; the number of glasses of wine represents a measure of exposure not dose.

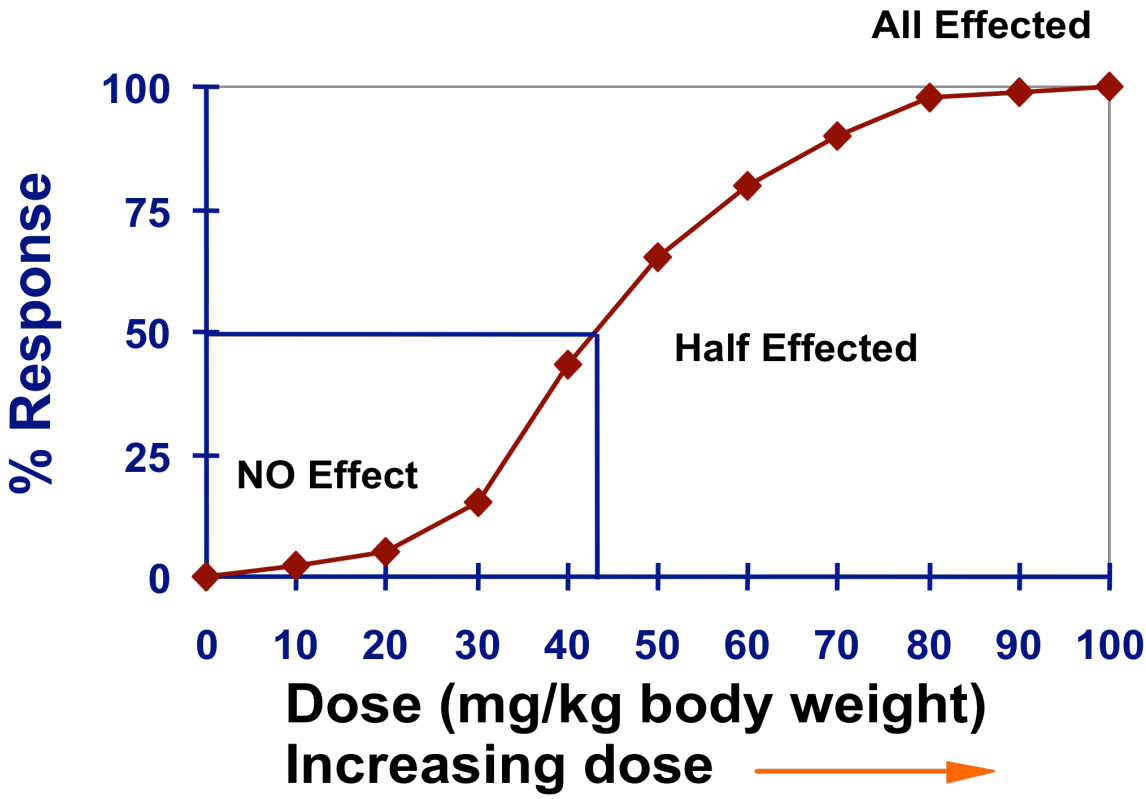


Figure 2.4: An Idealized Dose / Response Graph

The horizontal axis indicates the dose in mg/kg of body weight, while the vertical axis is the percent of maximum response. For very low dose there is no or little response. The response increases with the dose until the maximum response is reached and increasing the dose has no additional effect.

Figure 2.4 demonstrates an "S"-shaped idealized dose / response graph, which is typical of most types of exposure. In this figure the percentage responding is plotted against the dose in mg/kg. This "S" shaped cure illustrates that at low doses there is little or no response while at high doses all individuals respond or demonstrate the effect. The line drawn at 50% responses determines at what dose 50% of the population would demonstrate this response. In this situation, 50% of the subjects respond at a dose of 42 mg/kg, while 99% of the subjects responded at 90 mg/kg. It is important to emphasize that if we repeat this experiment the results would be slightly different. Each individual varies from one time to the next and there is even greater variability between individuals. Variability is a consistent theme in biology, complicating data analysis and interpretation of results. These variations lead to the need for statistical evaluation of data.

Hazard and Risk

The biological effects of an agent often span a broad range from beneficial to harmful, depending on the dose and individual sensitivity. The scientific discipline of toxicology developed in an effort to understand and characterize the potentially harmful or hazardous properties of an agent. *Risk* is the probability of injury, disease, loss of function, or death for an individual or population exposed to a hazardous substance or situation. An agent or situation that can produce or cause a harmful or adverse effect is a *Hazard*. Hazard is an intrinsic property of a substance and any particular substance may have a range of hazards associated with it depending upon specific conditions or circumstances. On a daily basis, we routinely confront a range of potentially hazardous agents, including the fire we cook with, the electricity that lights our homes, the household chemicals used for cleaning, the chemicals that run our cars, drugs in the medicine we take, and the list goes on. We use these potentially hazardous agents but are careful to avoid conditions that will result in the expression of their hazardous properties. Gasoline is a good example of an agent with multiple hazards. We depend on its flammability to make our cars run but that same flammability can be hazardous in an uncontrolled fire. Sniffing gasoline, undertaken by some people for effects on the nervous system, represents a very different hazard. Problems develop when we do not fully appreciate an agent's potential to cause harm or the conditions under which the agent can cause harm. Problems can also occur when products or mechanical systems malfunction.

In the past, the hazard associated with any particular substance was related to immediate or obvious harm. As our knowledge and experience increase, so too does our appreciation of an agent's ability to produce unexpected consequences or harm. Take for example DDT, a very powerful pesticide useful in the eradication of mosquitoes. As Rachel Carson so eloquently pointed out, DDT devastated bird populations not directly but indirectly by thinning eggshells to such an extent that the eggshells failed. This resulted in a devastating decline in bird populations, particularly for birds consuming animals. Still later we learned that DDT was a very persistent chemical and highly soluble in fat. DDT thus accumulated up the food chain and in this case birds at the top of the food

chain were most affected. Humans are also at the top of the food chain, and through a variety of means, DDT ends up in the food supply and becomes stored in body fat. When women are breast-feeding, fat and DDT are mobilized and become the food of nursing infants, which represents a large dose to a small infant. We are still unsure of the consequences of fetal exposure to DDT and its effects on the developing organism. Many other fat-soluble chemicals, such as dioxin and PCBs are known to contaminate breast milk. Lead is another example of a major public health disaster that occurred because the consequences of low-level lead exposure to the developing nervous system were not appreciated.

Recognition of the potential harmful effects of agents from drugs to pesticides resulted in new research efforts as well as the formation of government agencies responsible for regulating hazardous substances. The Food and Drug Administration (FDA) is responsible for ensuring that all drugs and food additives are both efficacious and safe. The Occupational Health and Safety Administration (OSHA) establishes rules to control or limit exposures to a variety of chemicals in the workplace, based upon toxicology data. The Consumer Products Safety Commission (CPSC) works to reduce injury from consumer products. The U.S. Environmental Protection Agency (EPA) governs the release of chemicals into the environment to protect the soil, water and air. It also regulates the cleanup of hazardous chemicals in the environment.

While science plays an important role in characterizing the harmful effects of an agent, society also establishes laws to regulate or limit exposure to known hazards. Tobacco and alcohol consumption are legal despite recognized hazards and considerable cost to society. It was only recently that the government forced the tobacco industry into acknowledging the addictive properties of nicotine and began to recover health costs through litigation. While the adverse effects of excessive alcohol consumption have been recognized for a long time, it was only in the 1970's that birth defects related to alcohol consumption during pregnancy were recognized. In contrast, the U.S. government has declared that marijuana and many other recreational drugs are illegal based upon their known hazard characteristics. Obviously, this is a controversial area, with many people (and even countries) having very different opinions and laws.

Hazard and risk are linked by exposure. Reducing the hazard, the exposure, or both can lower risk. If there is no exposure, then there is no risk or possibility of harm. Knowledge and experience allow one to judge the potential for harm or risk associated with exposure to a substance. In this way we are all toxicologists, always judging the potential for harm against the benefit of exposure. This is often easier said than done, but being knowledgeable about an agent can lead to the development of specific strategies to reduce the potential for harm. Since one cannot necessarily foresee all possible exposures to a hazardous substance, choosing less hazardous substances is also a vital part of risk reduction.

The beneficial use of radiation is one of the best examples of how careful characterization of the hazard is essential for its safe use. A radioactive substance can be safely stored or transported if appropriately contained. Depending on the characteristics of the radioactive material, it can be safely handled by using appropriate shielding and safety precautions. Laboratory workers usually wear special badges that quantify radiation exposure to ensure that predetermined levels of exposure, which are considered safe, are not exceeded. Unfortunately, after more than 50 years, society has not yet been able to design and implement a safe way to dispose of radioactive waste. The hazardous properties of radiation are explored further in a subsequent chapter.

Historically, potentially toxic agents have been ranked by their lethality, or the amount of material that causes death. In this measure, hazard is defined only as death, obviously only the grossest measure of an agent's effect. Because of individual variability or susceptibility, a standardized measure is the dose (in units of mg/kg) that produces death in half of the subjects, a 50% response. This is called an LD50 or lethal dose for 50% of the population. The LD50 is one measure of the *toxicity* of a substance, its capacity for causing illness or death. The LD50 is usually determined on populations of test animals such as rats and mice. Determination of an LD50 is based on a single acute exposure to an agent and the single response of death. Although the LD50 can be useful in comparing the gross hazards of agents, it is not necessarily relevant to a response produced by low-level chronic exposure. For example, the LD50 of lead is not particularly important, given its adverse effects on the developing nervous system even at very low levels of exposure. LD50s are misleading if used as the only characterization of the toxicity of a substance. Aspirin is a commonly used over-the-counter medicine, while DDT is a pesticide that has been banned because of its toxic effects and persistence in the environment. Yet they have similar LD50s.

Table 2.1 lists the LD50s of a variety of common agents. Since the LD50 is the amount of material required to produce death, a higher LD50 implies a lower toxicity and vice versa. Note how high the LD50 is for alcohol, which is fortunate given its widespread consumption. This explains why so few people die as a result of acute alcohol consumption. Generally, people pass out at high blood alcohol levels and die not due directly to alcohol but from suffocating on their own vomit as the body tries to rid itself of this toxicant. Note also the low LD50 (high toxicity) for nicotine, the most active and addictive ingredient in cigarettes.

Table 2.1. Approximate Acute LD50s of Some Common Chemical Agents

Agent	LD-50 (mg/kg)
Ethyl alcohol	10,000
Salt (sodium chloride)	4,000
Iron (Ferrous sulfate)	1,500
Morphine	900
Mothballs (paradichlorobenzene)	500
Aspirin	250
DDT	250
Cyanide	10
Nicotine	1
Tetrodotoxin (from fish)	0.01
Dioxin (TCDD)	0.001 (for some species)
Botulinum Toxin	0.00001

Fortunately, the LD50 is no longer recognized as an adequate or even particularly useful assessment of an agent's ability to cause harm. Toxicologists have developed a wide array of tests to determine if an agent can produce an adverse effect. A variety of tests are performed to evaluate the potential harmful effects across all organ systems. If any hint of adverse effects is observed, further testing is done to carefully characterize and understand the effect. Ultimately, the hazard must be judged on the sensitivity of the individual. Moderate consumption of alcohol can present few hazards for an adult, but this same amount of alcohol can harm the developing fetus. Lead has many beneficial uses and has long been recognized as a hazard, but it is only relatively recently that harmful effects on the developing nervous system have been characterized. At what point does caffeine produce an undesirable effect and another cup of coffee become something to avoid? How much of a hazard is caffeine? To answer these questions, we need to know more about how the body metabolizes or breaks down chemical agents.

Routes of Exposure and Absorption

An agent exerts its effects when it enters or comes into contact with the body, in other words, when an individual has been exposed to it. Although we are primarily concerned with effects on humans, the same principles apply to all living organisms and, indeed, to the entire environment. *Exposure*, like many of the terms in toxicology, has several difference aspects, the most important of which are 1) route of exposure, 2) frequency of exposure, and 3) duration of exposure. Exposure is also affected by *absorption*. Even though we may come in contact with an agent, if little is taken up into the body (or absorbed), there is little effect. For example, the metallic mercury from a broken thermometer, if swallowed, is very poorly absorbed by the gut and will be excreted in the

feces. However, if this same amount of mercury were allowed to evaporate and be inhaled, there would be very serious health consequences. This example shows that metabolism and excretion modify absorption. What is not absorbed (and even some of what is absorbed) may be excreted from the body by various routes, including the urine, feces, and sweat or through exhalation. *Excretion* reduces the effect because it lowers the amount of toxicant in the body, thus reducing exposure to sensitive organs.

There are three main *routes of exposure*: 1) skin (or dermal) exposure, 2) lung (inhalation) exposure, or 3) oral (gastrointestinal) exposure. A fourth route of exposure is by injection, which is used for delivery of drugs or medication that cannot be taken orally. Injections can take several forms. An injection directly into a blood vessel bypasses most of the absorption barriers and the drug will have almost full and immediate access to the most organs of the body. Some medications are injected into the muscle (intramuscularly or IM), which slows absorption as the drug is slowly taken up by the blood supplying the muscle. Finally, injections can be made just under the skin (subcutaneous or SC). This method is commonly used for allergy testing or tuberculin (TB) tests.

Skin is the largest organ of the body and does an amazing job of protecting us from most agents. However, the skin is an important route of exposure to some agents and also a site of highly adverse reactions. For example, the adverse effect of too much exposure to the sun is well known. In many cases, the skin is an excellent barrier to chemical agents, but some solvents can readily penetrate the skin. Solvents such as gasoline or chemical cleaners can readily remove the natural oils of the skin and result in adverse skin reaction, as well as chemical absorption. The labels of many pesticides state that gloves and other skin protection should be worn because of the risk of pesticide absorption through the skin or allergic reaction such as a rash. A number of medications can now be applied through a skin patch, such as nicotine patches to curb the desire to smoke cigarettes. The advantage of a skin patch in that the drug will be absorbed a constant slow rate, thus keeping the drug blood levels relatively constant. This system helps smokers by keeping their blood nicotine levels elevated and constant, curbing the desire to smoke.

Inhalation is an excellent route of exposure to many agents, including the oxygen essential for life. The lungs are very rich in blood to facilitate the absorption of oxygen and thus allow the rapid absorption of other agents directly into the bloodstream, quickly producing an effect. Carbon monoxide is a potentially lethal gas that can be generated in the home by poorly ventilated heaters, faulty furnaces, or a car idling in an attached garage. Carbon monoxide is readily taken up by the blood cells by the same mechanism as oxygen. In fact, carbon monoxide binds to the hemoglobin in the blood cells better than oxygen, so exposure can cause serious injury and even death through lack of oxygen intake. Cigarette smokers become dependent on the nicotine absorbed through the lungs from the tobacco smoke. Marijuana users hold their breaths to allow additional absorption of the active ingredient THC. The lungs can also excrete some agents, although this is usually in very small amounts. The excretion of alcohol forms the basis

for the alcohol Breathalyzer test, which quantifies the amount of alcohol in the body by measuring what is exhaled.

Ingestion of substances orally allows absorption from the stomach and intestines. This is a critical route of exposure for many agents, from essential carbohydrates, proteins, and vitamins, to unwanted pesticides and lead. All that is ingested is not necessarily absorbed, and absorption can be dependent on age. For example, in an adult, only about 10% of the lead ingested is absorbed, but up to 50% may be absorbed by an infant or pregnant women. In this case, unabsorbed lead is passed through the intestine and excreted in the feces. The increased absorption of certain agents at different times of life is related to the body's demand for important elements. In this situation, the intestines are able to absorb increased amounts of calcium and iron but will take lead as a poor substitute (more on this in the lead chapter). Alcohol and caffeine are readily absorbed by the stomach, making for two of the most popular drugs in our culture. Oral exposure also occurs through our food and drinking water, so it is imperative to have unpolluted water and a safe food supply. It is also a good idea to wash your hand before eating or touching food so that what may be on your skin does not ride along on the food you eat.

The other two aspects of exposure are frequency and duration. Frequency can refer not only to the number of times the exposure occurred, but also to the time between exposures. For example, drinking four beers within 15 minutes is quite different from drinking four beers in four days. Frequent exposure of a short duration results in rapidly elevated blood levels of any agent (assuming it's absorbed). Two quick cups of coffee in the morning serve to elevate blood caffeine levels, whereas slowly sipping a cup of coffee will not have the desired stimulator effect. It takes approximately 30 minutes to absorb the caffeine from a cup of coffee and reach your peak blood caffeine levels. The harmful or toxic effects of an agent are often dependent on the frequency of exposure and the time between exposures.

Duration of exposure is a closely related factor. In toxicology, duration is usually divided into three periods: 1) acute exposure (usually just one or two exposures of short duration); 2) sub-chronic exposure (multiple exposures over many days or perhaps months); and 3) chronic exposure (long-term or even lifetime exposure). The terms acute and chronic are also used to characterize the time delay between exposure and the onset of symptoms. Acute effects are those noticed directly following exposure and are usually easily related to the agent. The chronic or long-term effects of an agent may occur years later and are often very difficult to attribute to a particular cause. The acute effects of alcohol consumption or exposure to the solvent in glue are obvious in the drunkenness produced. The effects of chronic exposure to these compounds, as seen by an alcoholic, are very different: specifically, cirrhosis of the liver. The chronic effect of childhood lead exposure can be impaired learning that will be a factor throughout an individual's lifetime. The chronic effects of food additives and pesticides are evaluated in lifetime animal studies to assess the carcinogenic (cancer-causing) potential of these agents.

There are two types of exposure that deserve special attention: fetal exposure during pregnancy and exposure of the brain. For a long time it was thought that the placenta offered the developing fetus significant protection from hazardous agents. We know now that the majority of agents readily cross the placenta and expose the developing fetus to whatever the mother has been exposed to. The fluid surrounding the infant (amniotic fluid) will have the same level of drug as the mother's blood for compounds that readily distribute throughout body water, such as caffeine. Thus the infant is literally swimming in caffeine and its metabolites. Fetal methylmercury can actually be higher than that of the mother, because the developing infant acts as a storage site for maternal mercury. The brain, on the other hand, in the adult but not in the fetus, is afforded some extra protection from hazardous agents. This barrier is known as the blood-brain barrier because of its ability to keep some agents from moving from the blood vessels into the brain tissue. This barrier works primarily on large molecules but does not stop water-soluble agents such as caffeine from entering the brain and producing its stimulatory effect. While there are obviously many good aspects of the blood-brain barrier, it has also proven to be very challenging to move desirable drugs into the brain to treat disease.

From a scientific perspective, we primarily work with single exposures to chemicals to understand how the body reacts to a specific chemical. In real life, however, we are often exposed to a mixture of chemical agents. Multiple agents may interact and effect absorption or how the body reacts to the chemical. The body has a very sophisticated system to metabolize and eliminate chemicals form the body; this system plays an important role in protecting us from hazardous substances.

Metabolism, Distribution and Excretion

Fortunately, living organisms have developed elaborate systems to defend themselves against toxic agents. *Metabolism* refers to an organism's ability to change a substance into different chemical parts or metabolites that are usually less toxic. The body metabolizes the food we consume to recover energy and basic elements necessary for our well-being. In toxicology, metabolism refers to the body's ability to reduce an agent into parts that are either less harmful or more readily excreted, a process called *detoxification*. The most common route of excretion is through urine, although some agents can be excreted in the feces, sweat or even the breath. For toxic agents, metabolism is beneficial, but it can also reduce the benefits of a drug needed to aid in the recovery from an illness. *Distribution* refers to where an agent goes in the body. Some agents such as pesticides and PCBs accumulate in the fat. Other agents such as lead can accumulate in the bone in the place of calcium. Agents stored in the body my never be fully excreted; as we age we continue to accumulate a body burden of these stored agents like PCB or lead. Metabolism, distribution, and excretion are linked aspects that are essential to predicting the adverse effects of an agent and thus determining the risk of exposure to it.

Although most cells in the body are capable of metabolism, the primary organ for detoxification is the liver. The liver has a variety of specialized cells that produce

enzymes to aid in the metabolism of toxic agents. These enzymes can break down toxic agents into smaller elements, making them less toxic. In some cases the compounds are changed so that they are more easily filtered by the kidney and excreted in the urine. Alcohol and caffeine, for example, are metabolized in the liver. The liver is a remarkable organ but can be permanently damaged by diseases such as hepatitis or through long-term alcohol consumption. Liver damage can be detected in the blood by looking for elevated levels of compounds produced by the liver. Insurance companies use liver function tests to evaluate the possibility of chronic drug consumption.

Not all agents can be readily metabolized. The toxic metals lead and mercury are elements that cannot be degraded but must still be removed from the body. Another important mechanism of detoxification is the attachment or binding of another compound to a toxic chemical to make it easier for the kidney to filter the compound out of the blood and excrete in the urine. A primary purpose of the kidney is to screen the blood of waste products and concentrate them in the urine for excretion, as occurs, for example, with mercury. Caffeine is excreted in the urine at approximately the same concentration of the blood because the kidney cannot concentrate caffeine. Vitamins, however, are readily concentrated and excess quickly eliminated in the urine.

Chelators bind metals so that they are more readily excreted in the urine. In the past, chelators were routinely prescribed to people with elevated blood lead levels in an effort to accelerate the excretion of lead in the urine. Unless the blood levels are excessively elevated the current treatment is to determine the source of the lead exposure and take remedial action. The problem with chelators is that they are non-specific and bind useful agents such as calcium.

Half-life is a measure of the length of time an agent stays in the body before being metabolized and eliminated. More precisely, the half-life of an agent refers to the time it takes to reduce the level of the agent by one half. For example, if the amount of caffeine in your blood were measured as 12 units (the particular units are not important), it would take approximately five hours for that level to be reduced to six units. In this case, five hours represents the half-life of caffeine. Another five hours later the amount would be reduced in half to three, and so on until it approaches zero. The half-life of an agent, either toxic or beneficial, is a critical aspect of its ability to produce and maintain an effect. There can be considerable individual variability in the ability to metabolize an agent. This variability is reflected in the half-life for that particular individual. Someone who rapidly metabolizes caffeine (meaning someone for whom caffeine has a short half-life, say three hours) may want to drink more coffee more rapidly to elevate and maintain high caffeine blood levels and achieve the desired effect. Others may find that one-cup of coffee every 3 or 4 hours is adequate. A variety of factors, such as liver disease or even pregnancy, can decrease the metabolism or excretion of an agent and thus increase the half-life. During pregnancy the half-life of caffeine increases to approximately 7 hours, resulting in higher blood caffeine levels for a longer period of time. While the half-life of agents such as caffeine and alcohol are relatively short, many of the most serious

environmental toxicants have much longer half-live values. For example, the half-life of lead is approximately 30 days. Many pesticides and PCBs are also readily stored in the body and have corresponding long half-live values. Careful consideration of the half-life of a drug is an important aspect during medical treatment. The half-life of a hypothetical drug is illustrated in Figure 2.5.

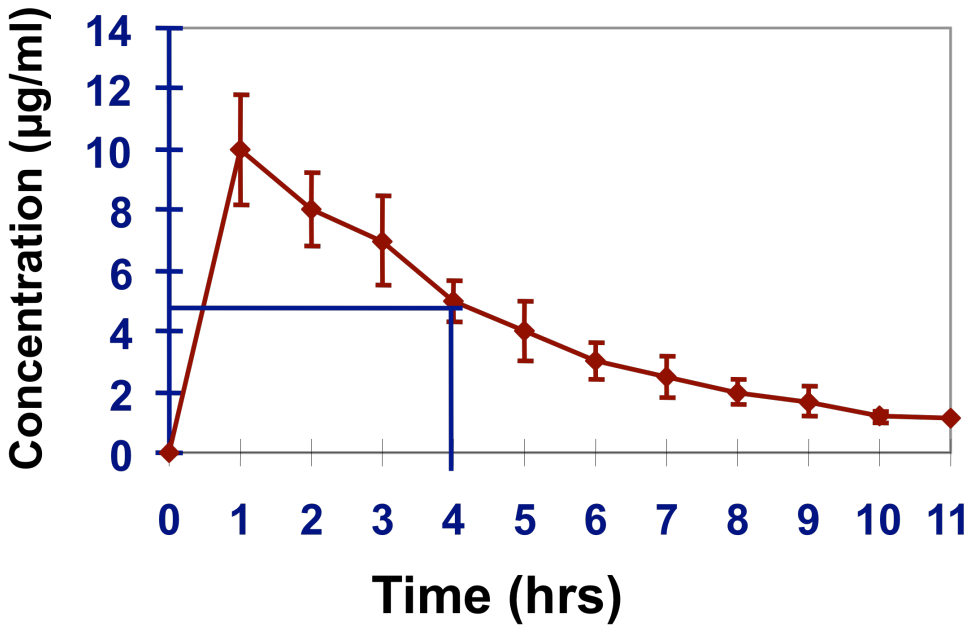


Figure 2.5. A characterization of Half-life
A substance is consumed at time zero (for example, drink a cup of coffee and we could measuring blood caffeine concentrations) and blood samples are collected at every hour. Concentration of the agent is plotted against time. The black line represents the half-life when the blood concentration as dropped by one half its maximum. Thus, in this example, the half-life is 4 hours.

The ability of an agent to get into a specific organ of the body often dictates its effect. For example, alcohol and caffeine would not be consumed were they not readily distributed to the brain, where they produce a considerable effect. As already mentioned, lead can be

exchanged for calcium and accumulate in the bone, while many pesticides and PCBs are stored in fat cells. These patterns of distribution and the storage of compounds in the body can have serious toxicological implications. During rapid weight loss, excess toxicants can be redistributed into the blood supply as fat is metabolized. Lead in the bone can also be mobilized if there is heavy demand for calcium, as occurs during pregnancy. To further complicate matters, each area of the body—in this case the fat and bone—can have its own half-life that can differ from that of blood. The half-life of lead in the blood is measured in days, while that in bone is measured in years.

Sensitivity, Susceptibility and Variability

Susceptibility refers to the differences in sensitivity to toxic agents, causing some people to suffer greater effects than others from the same exposure. This is a key concept in toxicology and risk analysis/management. Susceptibility is primarily related to several factors, including age, sex, health, and genetic background. *Sensitivity* is related to susceptibility but generally refers to special cases of extreme susceptibility to certain agents by some people. Someone who is allergic to bee stings can have a fatal reaction when stung by just one bee, while for most others a sting is of little concern. Enhanced sensitivity to a compound can develop after repeated exposure to it or a similar agent. Allergies to animals such as cats and dogs are examples of specific sensitivities to an agent called animal dander. Other individuals may develop a sensitivity to dust mites.

In general the young and elderly are most susceptible to the adverse effects of an agent. The young, particularly the very young, are more susceptible because the organs are still rapidly developing, and dividing cells are more easily harmed than mature cells. For example, lead affects the developing nervous system to a much greater degree than the adult brain. The brain is rapidly growing during and after birth, particularly throughout the first 7 years of life. The brain is not fully developed until the late teens. During the first year of life the metabolism of agents by the liver is also reduced. This is why the half-life of caffeine can be measured in days for the newborn while it is hours for the adult. The elderly are more sensitive to agents because of decreased ability to metabolize them and decreased ability to compensate for the effects.

Gender can also play an important role in susceptibility to agents, in part due to hormonal influences. The classic example is the female birth control pill. In this case, a very small exposure to specific hormones has a very large influence on fertility. Other agents such as PCBs also appear to affect some of the female hormones. Some athletes use hormones called steroids to increase muscle mass. These agents have different toxic side effects for males and females. Females have additional issues related to pregnancy. Pregnancy causes many changes in physiology that can alter the absorption, distribution, and metabolism of an agent and thus dramatically influence its effects. For example, during pregnancy there is a decrease in liver metabolism that increases the half-life of caffeine. This means that a pregnant woman will maintain higher blood caffeine levels for a longer period of time than when not pregnant, resulting in increased caffeine exposure to the

developing infant. Agents stored in the fat, such as pesticides and PCBs can be mobilized during lactation and thus passed on to a nursing infant. Calcium mobilization during pregnancy can also redistribute lead from the bone if there has been previous lead exposure.

Personal health is another factor that can influence susceptibility to an agent. A compromised liver or immune system can make exposure to even low levels of an agent completely intolerable. Someone who is diabetic may find sugar toxic and may enjoy considerable benefit from artificial sweeteners. On the other hand, someone who cannot metabolize phenylalanine, a naturally occurring and essential substance, may find the common artificial sweetener in some soda toxic. An individual who suffers from asthma may find exposure to wood smoke extremely harmful, whereas many people can tolerate short exposures to it fairly well. (Wood smoke is nevertheless toxic in either case, and chronic exposure can lead to health problems.) The physiological changes of disease or chronic illness are thus are very important considerations in assessing the exposure to an agent.

Finally, our genetic variability may make us more or less prone to disease or the effects of a toxic agent. Some can tolerate caffeine before bed, while for others such exposure would result in a restless night. It is always important to consider the individual and the individual characteristics of a situation.

Applying the Principles

Multiple Chemical Exposure

In the real world we are not exposed to only one chemical at a time. The air we breathe contains many separate chemicals. Indoor air in homes can contain chemicals from smoke, molds, carpet glue, mothballs, and cleaning products, to name only a few. Determining the risk from such multiple exposures is difficult because the body does not necessarily respond to each chemical in the mixture in the same way it would if the others were not present. Sometimes one chemical can cause the body to respond more strongly to another chemical generating a synergistic effect. We know, for example, that exposure to environmental tobacco smoke greatly increases the risk of cancer from asbestos. The increase is not additive—that is, it is not equal to the risk from tobacco plus the risk from asbestos—but is actually much greater than the sum of the two risks.

There are also cases where exposure to two chemicals reduces toxic effects. Methanol (wood alcohol) causes blindness if ingested. Methanol poisoning is treated by administering ethanol (common alcohol), which competes for metabolism in the body, thus slowing the formation of toxic byproducts of methanol and keeping their levels low enough to avoid damage to the optic system. This is sometimes referred to as an antagonistic effect.

When more than two chemicals are involved, the problem of determining risks becomes increasingly complex. Scientific study of chemical mixtures has been relatively limited because of the sheer number of combinations possible. Even if the exact effects of exposure to mixtures are unknown, reducing exposure is still a good strategy to lower risk.

Multiple Chemical Sensitivity

Multiple chemical sensitivity (MCS) is characterized by a variety of adverse effects upon multiple organs that result from exposure to levels of common foods, drugs, and chemicals that do not affect most people. Symptoms include headaches, fatigue, lack of concentration, memory loss, asthma and other often subjective responses following exposure. MCS has remained controversial because standard medical evaluations, such as blood biochemical screens, have failed to identify consistent physical or laboratory test abnormalities that would account for the symptoms.

MCS is thought to develop following sensitization to one chemical, a sensitivity that then is generalized so that chemicals of a similar class and lower concentrations of exposure come to elicit the response. Researchers have been working to develop a mechanism of action for these responses and have focused on the immune system responses and, more recently, on involvement of the nervous system. Others investigators, while respecting the symptomatolgy, postulate that the responses are due to some form of psychological illnesses. Whatever the mechanism of action, it is important to attempt to associate cause and effect relationships and apply the principles of toxicology. Identification of what agents may be causing the symptoms can result in plans to reduce exposure to these agents and thus reduce symptoms and improve the quality of life. In addition, reductions in the exposure to toxic chemicals for all persons may help reduce the incidence of MCS.

Assessing and Managing Risk

As we have seen, risk is closely related to hazard and is defined as the probability of the recognized hazard occurring. *Risk assessment* is the process by which the nature and magnitude of risk are identified, while r*isk management* is the process of determining whether or how much to reduce risk through our actions. Evaluation of the potential adverse effects of some activity or exposure (risk assessment) is something we all do informally on a day-to-day basis. What we decide to do is in part the result of an ongoing risk management decision. It can be as simple as crossing the street against a red light or as complex as spending the extra money for organically grown foods to reduce our exposure to pesticides. Many of the risks associated with chemical exposure are indirect or subtle effects on health; in other words, conditions, situations, or exposures to an agent that affect the quality of life. Table 2.2 lists some of the factors that can influence a person's perceptions and views about health concerns.

Table 2.2. Considerations that influence acceptability of risk.

More-Acceptable Risk	Less-Acceptable Risk
Benefits Understood	Benefits Unclear
No Alternatives	Alternatives Available
Risk Shared	Risk Affects Few
Voluntary	Involuntary
Individual Control	Uncontrollable
Familiar	Unfamiliar
Low Dread	High Dread
Affects Everybody	Affects Children
Naturally Occurring	Human Origin (synthetic)
Little Media Attention	High Media Attention
Understood	Not Understood
High Trust	Low Trust

Risk analysis and risk management play an important role in public policy. These debates range from the development of environmental impact statements for the location of buildings to debates on household lead abatement and what chemicals can be allowed in the food supply. Quality of life issues such as asthma and or loss of mental function are now recognized as important components of risk assessment. For example, childhood exposure to lead can result in reduced IQ, which can affect an individual throughout their lifetime. Similarly, childhood asthma can have a severe impact on an individual's ability to play and socialize.

In the past, much of the formal risk assessment concerned an estimation of the risk of cancer and subsequent death and then deciding what was acceptable. Typically, a risk of death of less than 1 in 100,000 (10^{-5}) or 1 in 1 million (10^{-6}) is considered an "acceptable" level of risk for exposure to a chemical. In comparison, the risk of death in an automobile accident is 1 in 4000 and the risk of death from lightning is 1 in 2 million. Comparisons like those above are sometimes used to argue that the risk of exposure to a chemical agent is negligible. Such comparisons can be misleading, however, if the conditions of the two risks are different. For example, if they affect different populations unequally, say falling disproportionately on those of a particular ethnic background, the risks may be more likely to be judged unacceptable. Or if one risk is the result of voluntary choice (drinking

alcohol) and another is not (eating food contaminated with bacteria), it cannot be assumed that an individual will be equally willing to tolerate them.

Risk assessment is a complex area that requires the application of all the principles of toxicology. It is often divided into four somewhat overlapping areas 1) hazard identification, 2) dose-response assessment, 3) exposure assessment, and 4) risk characterization. Hazard identification is the process of collecting and evaluating information on the effects of an agent on animal or human health and well-being. In most cases, this involves a careful assessment of the adverse effects and what is the most sensitive population. The dose-response assessment involves evaluation of the relationship between dose and adverse effect. Typically, an effort is made to determine the lowest dose or exposure at which an effect is observed. A comparison is often made between animal data and any human data that might be available. Next is exposure assessment, in which an evaluation of the likely exposure to any given population is assessed. Important parameters include the dose, duration, frequency, and route of exposure. The final step is risk characterization, in which all the above information is synthesized and a judgment made on what is an acceptable level of human exposure. In the simplest terms, risk is the product of two factors: hazard and exposure (i.e. hazard x exposure = risk). In real risk assessments, all hazards may not be known and exposure is often difficult to quantify precisely. As a result, the calculated risk may not accurately reflect the real risk. The accuracy of a risk assessment is no better than the data and assumptions upon which it is based.

Risk management is the political or social process of deciding how the benefits balance the associated risks. Risk management is also concerned with how the public perceives risk and how we judge and perform our own risk assessments. An example of risk management was the decision to remove lead from gasoline. After a great deal of research it was demonstrated that low levels of lead exposure are harmful to the developing nervous system. It was then determined that this benefits of removing lead from gasoline was greater than the costs. A program was then developed to gradually phase out lead from gasoline in line with the engines of new cars not requiring lead and the replacement of old cars.

Summary

The principles of toxicology are summarized in as follows: **dose / response**, **risk= hazard X exposure** and **individual sensitivity**. Many of us have an excellent intuitive sense of the principles of toxicology from experience with caffeine, alcohol, or other drug exposures. These experiences form a foundation upon which to build a formal understanding of toxicology that is applicable to many situations. We make many personal decisions based on dose/response and risk consideration. Around our home we must decide which cleaning products to use or whether to apply pesticides to our lawn or garden. As citizens we are also confronted with many broader concerns about environmental exposures. How much do we invest to limit the spread of environmental

contaminants? Should coal-fired power generating facilities be required to invest in more sophisticated smoke stack scrubbers to remove mercury? On what basis do we make this decision? Advances in the toxicological sciences along with general advances in the biological sciences provide new knowledge and understanding upon which to make these and other decisions. And finally, I hope that beyond the principles of toxicology that you will find that toxicology is both fun and informative.

References

See chapter 2 and references from individual chapters.