5

Dose and Response for Chemicals

DOSE AND RESPONSE FOR CHEMICALS

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

— Paracelsus, 16th century

THE DOSE IS THE AMOUNT OF CONTAMINANT THAT A TEST ANIMAL IS ADMINISTERED OR AN INDIVIDUAL IS EXPOSED TO. IT IS USUALLY EXPRESSED AS THE WEIGHT OF THE SUBSTANCE (G, MG) PER UNIT OF BODY WEIGHT (E.G., MG/KG).

5.1 DOSE-RESPONSE

Different kinds of hazardous substances can vary widely in their toxicity, or ability to cause adverse health effects. There is no compound that cannot produce a toxic response if the amount is large enough. For example, ordinary table salt can be toxic to humans, but only if a very large amount is eaten all at once (i.e., around 280 g for an adult). If a very small dose causes an effect, a contaminant is said to be more toxic than a substance that causes health effects only when the dose is very large. Botulinum toxin, for example, is extremely toxic even in minute amounts (the lethal dose is about 0.00001 mg/kg body weight) and causes several deaths each year in Canada. Fortunately, only a few substances are very toxic, and choices can be made as to what risk of health effects people want to tolerate.

The relationship between the amount of a contaminant that is given (the dose) and the health effect (the response) is referred to as the **dose-response** relationship. This relationship is key to understanding how contaminants cause adverse health effects. The main factors that influence any dose-response relationship are the host, the amount of a contaminant provided (dose) and its toxicity, the route (inhalation, ingestion, dermal contact) of exposure, and the frequency and duration of exposure. Is exposure short-term (e.g., minutes, hours) or long-term (e.g., years) and was exposure constant or intermittent? Short-term or single exposures are referred to as acute, whereas long-term exposures, up to a lifetime, are called chronic or sub-chronic exposures.

Because individuals react differently to a contaminant, the dose-response relationship cannot be used to predict exactly when a particular health effect will begin in a particular individual. Instead, researchers speak of the probability of a health effect occurring as a result of exposure. As the dose increases, the probability of adverse health effects for any particular individual also increases.

Lethal Dose - 50

The acute toxicity of different substances is often expressed as an LD_{50} (Lethal Dose - 50). This is the amount of a substance that will kill 50 percent of test animals following a single dose. In real life, exposure levels are always much lower and exposure can occur over days, weeks, months or even years (i.e., not a single dose), and may involve different or

even multiple routes of exposure. As well, although there are many similarities between the way rat and human bodies function, they are not identical. Thus, it is always necessary to interpret the results for human health. An LD_{50} is a useful way of judging how acutely toxic one substance is relative to another, but is not very useful when trying to determine the long-term effects of exposure to lower non-lethal doses of chemicals. Other laboratory animal assays (experimental techniques) can be used to assess the effects of chronic exposure.

Storage and Latency

Most of the time, chemical contaminants are excreted in a slightly modified form or as metabolic by-products. If they are not excreted, contaminants or their by-products are stored in the body, where they can bioaccumulate in tissue. Health effects may not become obvious until a certain level is reached. Sometimes contaminants can take many years to cause health effects. The time between the first exposure and the observation of a health effect is called the **latency period**. Many types of cancer can have latency periods of 20 to 30 years.

5.2 Investigating Dose-Response Relationships

The dose-response relationships of chemical contaminants are investigated primarily by toxicological studies using laboratory animals. In some instances, when the data are particularly clear and convincing, human epidemiological studies can be used to provide information on dose-response relationships. Such human studies include occupational health and clinical studies, and those on accidental poisonings. In most other studies on humans, there is not enough information to establish actual dose-response relationships, because of the difficulty in controlling and quantifying the exact exposure and the consequent response.

Toxicological Studies

Toxicological studies provide indirect information about the potential health effects of toxic substances in humans. These studies are carried out on laboratory animals or through the use of other models to approximate the effects on human health. Exposures and doses of the contaminants can be carefully controlled by the experimenter. These are called experimental studies as compared with observational studies.

Some of the more common types of toxicological studies are outlined below.

- **Acute toxicity studies** examine the health effects of a single large dose of a substance given to the test animal. They are used mostly to determine what short-term specific health effects a substance produces in order to compare it with the acute toxicity of other substances, and to help determine lower dosages to be used in long-term studies.
- **Subchronic toxicity studies** examine the health effects of longer exposure to smaller doses of a substance. Periods of 90 days or longer are generally chosen. By using several exposure levels, the exact relationship between dose and the health effect is explored.

- **Chronic toxicity studies** and **carcinogenicity bioassays** look for health effects that occur only after a very long exposure to a substance. Most health effects become evident during the subchronic studies, but certain effects that develop very slowly (e.g., cancer) may appear only after exposures that last most of a lifetime. Chronic toxicity studies are the most important in assessing potential health risks to humans since the experimental conditions are similar to those in which the general population is routinely exposed, i.e., long-term, low-level exposure to chemicals and radioactivity.
- **Multigeneration studies** determine reproductive and developmental effects on test animals (usually rodents) from a given treatment with a contaminant, from one generation to the next. These types of studies are valuable in identifying potential effects of contaminants to fetuses and newborns, especially those conceived by and born to dams (female rats) who have had continuous exposure. Normally, a two generation study will provide sufficient information, however, sometimes it is necessary to proceed to a third generation.
- **Metabolic and pharmacokinetic studies** determine what happens to a substance inside a living organism, i.e., how quickly it is absorbed and metabolized, transported through, and excreted by the organism. The results of such studies are used to help interpret the results of other studies and to compare tests on different kinds of living organisms.
- **Genetic studies** look for inheritable changes in bacteria, fungi, plants, insects, small mammals, or cells of mammals grown in a special culture. Since organisms and cell cultures are used in these studies, exposure to contaminants need not be long-term and results can be produced quickly.
- **Structure-activity analyses** take the chemical structure of a contaminant and attempt to predict toxic or carcinogenic effects based on the chemical and physical properties of the contaminant and its molecular structure. Examples of such properties include the types of chemical bonds or the number of chlorine atoms in organochlorine compounds. Such studies have had some limited success, but they are far from perfect.

Epidemiological Studies

Epidemiology is the study of disease patterns in populations and the factors that influence these diseases. The simplest form of an epidemiological study looks at the patterns of illness (morbidity) or death (mortality) in a defined human population and examines the possible contributing factors. For ethical reasons, people cannot be used in toxicological experiments of most environmental contaminants. Therefore, observational studies are generally used to investigate the distribution of human health effects caused by past or ongoing exposures to environmental contaminants.

The most common types of observational epidemiological studies are summarized below.

- **Ecologic studies** examine the distribution of a particular health effect across areas, regions or groups. They may make use of existing large databases like cancer registries or specific disease reporting databases. In ecologic studies, information about the health and exposure of each individual is not known. Instead, the study compares disease rates in the entire population in each

region and can identify unusual excesses of disease by area or group. Ecologic studies cannot control for confounding factors, such as individual characteristics (e.g., smoking or diet) that can affect outcomes. Therefore they cannot, by themselves, establish a cause and effect relationship. Rather, the studies are useful for identifying differences in disease rates across geographical and temporal strata, which can lead to hypotheses to try to explain the differences. The hypotheses may then be investigated more rigorously in analytical studies.

- **Cross-sectional studies** determine the presence or absence of health problems and the presence or absence of exposure in a sample of the population. Confounding factors, such as lifestyle (e.g., smoking, diet), can be evaluated for each individual, if included in the questionnaire, providing a better understanding of the factors affecting the health outcome or effect. If either the risk factor of interest or the outcome is rare, (i.e., if it has a low prevalence), the number of people required to adequately study the relationship is very large.
- **Case-control studies** look at the relationship between a health outcome and possible causes by comparing a group of individuals who have or have had the disease, with a group who do not or have never had the disease. For each individual in each group, the study obtains information about past exposure to contaminants and other lifestyle factors and then compares the groups to see if there are differences in exposure rates while considering all other factors (i.e., case control studies estimate the likelihood of exposure for a known disease). Case-control studies are among the most common form of epidemiological study.
- **Cohort studies** always follow a healthy population as it develops its illness experience. This follow-up may start concurrently (if it starts now and proceeds into the future — a concurrent prospective study), or examine a population defined in the past (e.g., an occupational cohort) and look at its illness experience up to the present (a historical or non-concurrent study sometimes called "retrospective"). In both situations, the population studied (the cohort) is followed so as to examine its illness experience from the time it is identified to the time of illness or death. Cohort studies differ methodologically from case-control (true retrospective) studies in that case-control studies always examine the exposure experience of people who are already sick whereas cohort studies examine the illness experience of people who start out healthy. Therefore, case-control studies are "retrospective" with respect to exposure.

Epidemiological studies are only one tool in the cascade of determining causality between a given exposure and an outcome (e.g., cancer). Regardless of the rigour of the study (sample size, appropriate statistical methods, and control of confounding factors), a single epidemiological study is rarely enough to determine a definite cause-effect relationship. However, strong epidemiological studies in concert with well conducted toxicological studies can be used together to infer that particular exposures cause particular adverse health effects. From this information, control of the appropriate exposure can then occur.

5.3 Threshold and Non-Threshold Doses

The results of toxicological studies are used to determine the dose-response relationship of individual chemicals. For some substances, no health effects are observed when the exposure dose falls below a certain level. This level is called

the threshold dose. For others, especially substances that cause cancer by directly affecting the genetic material of the cell, it is assumed that there is no threshold dose. In these cases, there is assumed to be a probability, though extremely minute, of developing cancer even at very low doses. Threshold and non-threshold types of dose-response relationships are shown in Figure 5.1.

NOAEL and LOAEL

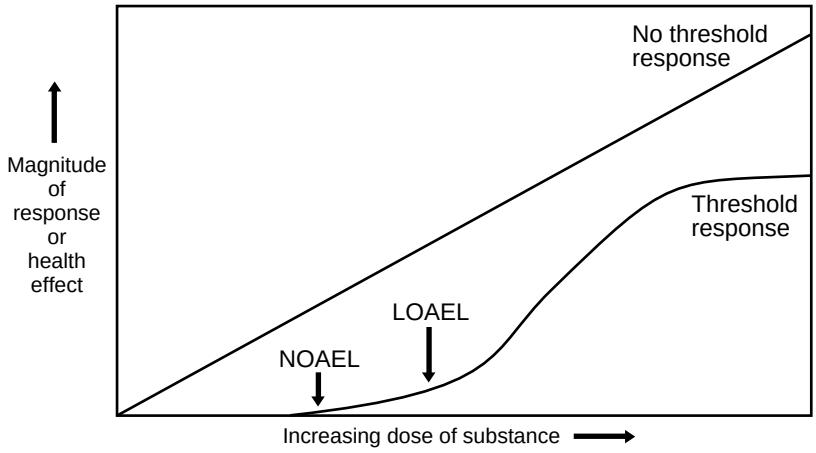
Scientists use test data from laboratory animals and, in some instances, epidemiological data from humans to determine threshold values that are then used numerically in risk assessment. Such values include the no observed adverse effect level (NOAEL), which is the level of exposure to the chemical at which no significant adverse health response is observed. Another value is the lowest observed adverse effect level (LOAEL), which is the lowest dose used in the study that produces any measurable adverse effect.

5.4 Establishing Levels that Protect Health

Once a contaminant has been identified as a hazard to health, it is important to establish levels at which exposure does not to pose a threat to human health or is within a level of risk deemed acceptable by society. In order to develop these levels, two approaches are generally followed, depending on whether a substance is suspected to cause cancer or not. The development of tolerable daily intakes and risk-specific doses are described below.

Figure 5.1

Dose-Response Relationships



NOAEL – no observed adverse affect level – The level of exposure to a chemical at which no adverse effects were observed during studies with animals.

LOAEL – lowest observed adverse affect level – The lowest level of exposure to a chemical at which adverse effects were observed during studies with animals.

Tolerable Daily Intake (TDI)

For substances that do not cause cancer or for the non-carcinogenic effects of carcinogens, a level of exposure can be estimated below which effects on human health are not expected. For these substances, toxicological studies on laboratory animals and epidemiological studies are used to identify the dose threshold, i.e., the no observed adverse effect level (NOAEL) or the lowest observed adverse effect level (LOAEL). This threshold dose is then converted to a dose considered tolerable by the average human population by using an uncertainty factor (UF). The uncertainty factor takes into account the differences between individuals, between test animals and humans and the type of experimental data available.

By dividing the animal NOAEL (or LOAEL) by the uncertainty factor — usually by 10, 100, or sometimes as high as several thousand — a tolerable daily intake (TDI) is calculated. The tolerable daily intake is a standard that implies that exposure over a lifetime above this level may lead to increased risk to health, based on the best existing scientific evidence. The risk from short-term exposures above the TDI is likely to be minimal.

$$\text{TDI} = \frac{\text{NOAEL or LOAEL}}{\text{UF}}$$

The Uncertainty Factor

The uncertainty factor (UF), also known as the safety factor, reflects the uncertainty associated with the variety of scientific data used to estimate the tolerable daily intake (TDI). An uncertainty factor of 10 is used when TDIs are based on epidemiological studies of prolonged exposure of healthy humans or when no serious adverse effects are known to occur. This factor accounts for differences in people's sensitivity to contaminants. If the TDI is not based on studies of prolonged human exposure, this basic UF of 10 is multiplied by another 10 for each of the following conditions that apply:

- When TDIs are based on experimental studies using long-term exposure to laboratory animals. This factor accounts for the uncertainty involved in applying animal data to humans.
- When TDIs are based on scientific studies using shorter exposures of the animals to the contaminants. This factor accounts for the uncertainty in extrapolating from short-term to long-term exposures.
- When TDIs are based on a LOAEL rather than a NOAEL. This factor accounts for the uncertainty in calculating NOAELs from LOAELs.
- Additional uncertainty factor (up to 10, and in some cases greater than 10) may be applied depending on the seriousness of the adverse health effect observed.

Risk-Specific Dose

A different approach than the tolerable daily intake is required for chemicals known to cause cancer. Contaminants, which are known carcinogens, are generally assumed to have a non-threshold dose-response so that there may be no level of exposure to these contaminants that does not present some risk to health. In these cases, zero risk can be achieved only by eliminating all possible human exposure. This may not be possible with persistent contaminants that are widespread in the environment. Therefore, it is desirable to reduce exposure to carcinogens to as low a level as possible. "Zero exposure" may be impossible to achieve but remains the goal for non-threshold toxicants.

For such substances, a decision must be made as to how large a risk of cancer can be accepted in order to set acceptable intake levels. Various acceptable levels of risk are currently being used around the world, depending on specific circumstances. Such levels often vary between one extra cancer death per year per 10,000 people exposed (1×10^{-4}) to the contaminant over their entire lifetime to one extra cancer death per year per million people exposed (1×10^{-6}). The use of these levels is somewhat arbitrary and often takes into account the balance between the risk to the health of the population and the cost to society associated with achieving these risk levels.

Once an acceptable level of risk (R) has been established, it is possible to calculate a dose that people can be exposed to on a daily basis, that will not exceed this chosen risk of cancer. In other words, if people are exposed to an amount of a carcinogen every day of their lives that lies below this calculated dose, then their risk of cancer will lie below the acceptable level of risk. This dose is called the risk-specific dose (RsD). To obtain the risk-specific dose, the level of risk (R) is divided by a factor, known as the slope factor (SF), which has been determined from the results of laboratory and epidemiological studies. In essence, the slope factor states what the cancer risk is for every possible dose of the contaminant. The risk-specific dose is usually expressed in milligrams of chemical per kilogram of body weight per day (mg/kg/day).

$$\text{Risk-specific Dose} = \frac{\text{Level of Risk (R)}}{\text{Slope Factor (SF)}}$$

Estimating Risk

When humans are exposed to chemical amounts that exceed the tolerable daily intake or the risk-specific dose, then there may be an unacceptable level of risk. Calculating and comparing such risk levels is called "risk estimation." In order to evaluate the risk associated with exposure to environmental contaminants, it is important to establish levels, such as the TDI or RsD, and to estimate people's exposure to these contaminants by calculating their estimated daily intakes (EDI). (See Chapter 4. "Exposure" for a description of EDIs.)

Once an EDI has been calculated for a chemical, it is then compared to the TDI or to the RsD, depending on whether it is a non-carcinogen or a carcinogen. As a general rule, if the TDI or RsD is exceeded, exposure to the chemical is a potential health concern. In some instances, additional medical and toxicological information may indicate that exposures exceeding the TDI or RsD are not a health concern. In other instances, exposures below the TDI or RsD could be a health concern because of interactions between chemicals or because certain individuals in the exposed population are more sensitive (e.g., children, the elderly). For example, children are at a greater risk when exposed to lead as compared with the general population. This is because children consume more calories per body weight than adults and have greater gastro-intestinal absorption; also, their respiratory uptake is comparatively greater on a body weight basis. It should therefore be recognized that the TDI and RsD are estimates of exposures at which adverse health effects are not expected to occur for the majority of the population. They do not describe a level at which we are absolutely certain that no risk to health will occur for every individual.

How Does EDI Compare with TDI or RsD?

NON-CARCINOGENS

- If the EDI is well below the TDI, it indicates that exposure to that contaminant likely does not pose a significant risk to human health.
- As the EDI approaches the level of the TDI, the concern regarding the risk to human health increases.
- If the EDI is above the TDI, then exposure and potential risk to human health should be considered important. Action may be necessary to reduce the exposure.

CARCINOGENS

- If the EDI is well below the RsD, it indicates that the risk of cancer from exposure to that contaminant is minimal for that situation.
- As the EDI approaches the RsD, the concern regarding the risk to human health increases.
- If the EDI is above the RsD, then exposure and potential risk to human health should be considered important. Action may be necessary to reduce the exposure.