Principles of Health Effects Evaluation and Risk Estimation for Chemicals that May Be Encountered in Forest Vegetation Management

Forest Practices Branch
BC Ministry of Forests

Title
Number

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Abstract

It is possible to measure and predict chemical interactions with biological systems and the environment with sufficient reliability to protect humans and lower species. The scientific fields of toxicology, environmental chemistry and epidemiology provide the foundation for the analysis of potential health impacts of chemicals and predicting whether their uses will cause harm. The biological effects of chemicals follow the natural laws of chemistry, physics and biology and nothing known about chemical effects is found to be outside the orderly structure of nature. All chemical interactions with biological systems depend on the physical and chemical natures of both the chemical and the systems that make up living things. The same order applies to chemical behaviour in the environment. The dose-response relationship or concept is the most important example of the order controlling chemical effects and it is the cornerstone of toxicology and pharmacology; as the dose of a substance increases, so does its effect, and as dose decreases, so does its effect.

To assess risk, we must have two kinds of information. First, it is necessary to know what kind of effect a chemical might produce, along with the dose response for those effects. Most of that information can be learned from experimental animals. The other essential information is the dose acquired by humans or other organisms of concern. The dose is some fraction of the amount of chemical exposed or contacted (e.g., on the skin, digestive tract or airway and lungs).

Other than cancer, the process of assessing risks of effects is relatively simple once the toxicology is understood. For such effects there is a threshold, a dose below which no effect will occur. If the intake of chemical is much lower than the threshold of effect determined in the laboratory, no adverse effect is expected. For pesticides, this margin of safety must be at least 100 fold, which is much greater than that demanded of household chemicals or other consumer products.

Assessment of cancer risk is more complex because (i) the natural background in all species is very high, so small effects are invisible, (ii) cancer cannot be detected until years after it begins, (iii) the effect of the very low doses encountered by workers cannot be measured experimentally and (iv) it is presently assumed that there is no threshold for chemically induced cancer. Cancer risk assessment has become a matter of estimating the probability that such an event will occur. Other irreversible diseases, such as birth defects and miscarriage also have a high natural background in the human population, but when caused by chemical exposure there is a threshold below which no response is expected. The ability of chemicals to cause these effects can be evaluated in the laboratory. Individual perceptions of risk rarely correspond to reality. Some individuals see some minor risks as enormous and unacceptable while others tend to ignore very high risks. Regulatory and administrative decisions about chemical use must be based on valid information about both the utility of the method and its safety.

Acknowledgements

Foreword

Vegetation management is an important reforestation activity for controlling competing vegetation or brush encroachment of young tree seedlings. The activity is necessary to get tree seedlings to free-growing status in most new forest sites established in areas that have been harvested or denuded by wildfire, insects and disease.

There are a number of options for managing forest vegetation. The treatment options include prescribed fire, herbicides, manual removal with hand and power tools (e.g., girdling and slashing tools, chain saws and brush saws), placement of mulch mats, mechanical techniques with heavy machinery, and biological methods. The use of livestock (e.g., sheep) is currently the common biological control technique employed in reforestation areas in British Columbia. Biological methods with insects or specific pathogens is used on forest rangelands for noxious weed control but not commonly used for vegetation control in young forest stands.

The selection of a treatment option involves a decision-making process based on integrated vegetation management concepts that include evaluation of the need for treatment, consideration of all the approved treatment methods and choosing the most appropriate treatment method, monitoring and evaluation. Factors considered in selecting a particular method are the ability of the method to meet the required reforestation objectives, the impact of the treatment at the specific site on human safety and the environment (e.g., recreational resources, fish and wildlife and their habitat, range resources and water supply), as well as the economics of the treatment.

This publication is one of a series of papers that evaluates the potential health effects on forest workers using the commonly employed methods of vegetation control. Other papers in the series are listed at the end of this paper. The emphasis is on risks associated with exposure to chemicals during the use of two most important methods for controlling competing vegetation in regenerated (natural or planted) forest areas. These methods are the use of herbicides and manual removal or control with handheld-motorized (power) equipment.

The herbicides discussed are those that have been commonly used in forestry in Canada. The database on health effects of herbicides is extensive and permits reliable estimates of risk. For components of chain saw exhaust and fuels, there is also voluminous background of toxicological information, but exposure data in forestry is limited. Nonetheless, there is enough information to develop preliminary assessments of potential health effects. While there appears to be a high incidence of physical injury associated with manual methods of brush control, there is virtually no validated data on which to base estimates of risk. The existing data are those of workers compensation boards and insurance companies but such data are generally difficult to obtain or are not specifically enough to characterize the kind of activity that leads to injury.

The information in these reports should provide the basis for important decisions about the way vegetation management in forestry should be carried out, and the use of some forestry activities as a source of assisted employment.

Contents

Introduction

Every activity produces some degree of risk, or probability of harm. Risks may be imposed on individuals who are directly involved in an activity, and as well on those who are quite remote. Real risk may be so small that it cannot be distinguished from zero, or so great that it is nearly a certainty. Estimation of the probability that an activity will cause harm is necessary to the safety of the society, but the process is complicated by individual perceptions of risk that often do not correspond to reality. Some trivial risks are intuitively seen as enormous and unacceptable, other very high risks are ignored. Individual, intuitive assessments of risk are not useful for objective social or regulatory decisions, but nevertheless create great pressure on the regulatory structure, which must depend on valid information.

The information needed for estimation of risk associated with use of pesticides or other chemicals arises from three general fields of scientific study:

Toxicology is the group of scientific disciplines that identifies and studies the adverse effects of chemicals on biological systems. The basis of toxicology lies in laboratory research of the biological effects of chemicals under carefully controlled conditions. Studies may be done with intact animals, or isolated tissues or cells, or even preparations from specific parts of cells. Because of the many similarities in the machinery of life among species, valuable information about chemical effects can be learned even from bacteria or fish. Toxicology study also includes the behaviour of chemicals in the body including their absorption and storage and the way they may be changed and excretion. The limitation of laboratory study lies in the extent to which findings in one species are predictive of effects in others. However, those findings can be coupled with measurements and observations in the environment and in the clinic to enable judgement of effects in the real, more complicated world.

Environmental chemistry studies the physical and chemical processes that govern behaviour of a chemical (such as a pesticide) after it is used. Almost all of the physical and chemical sciences come into play in this area, both in the laboratory and in the field. It is necessary to know how the chemical breaks down, whether by microbial action, sunlight or other environmental influence. Its solubility, ability to vaporize, adsorption (ability to stick) to the various kinds of soil and plant surfaces are also critical. That kind of information eventually makes it possible to estimate how much of a chemical will actually reach the subjects of concern.

Because the physical environment is almost infinitely variable, even within relatively small areas, it is necessary to develop a large number of categories into which, say, a given soil sample may be placed in order to predict its properties. A further problem is that a sample drawn from one location may not represent others nearby.

Epidemiology: In the context of this report, epidemiology is the study of possible associations between environmental and occupational chemicals and occurrence of diseases. The term "associations" is used in its statistical sense, which means that the relationship cannot demonstrate cause and effect. While not required for registration of pesticides, epidemiology is mentioned here because such data may be useful in evaluating risks associated with pesticides that have been in widespread use for a long time. For certain pesticides that are being re-registered, pertinent epidemiology studies are reviewed.

This discussion is an introduction to the basic ideas of toxicology and risk estimation as it relates to chemical exposure. It serves as background for discussions of the safety of herbicides and such other forestry chemicals as chain saw exhaust, components of smoke, and fuels. The details of toxicology and risk assessment are often complex, but the general ideas are straightforward and common in daily

life. Because this report applies only to worker safety, environmental behaviour as it applies to public health is not discussed.

General Concepts

People who have never heard of toxicology or risk assessment should find in these pages that they know more about the basic ideas than they realize. An obvious first principle in toxicology is that every chemical can be toxic. Life is chemical in nature, and even the most necessary substances to life that we produce in our own bodies can cause harm at some level.

It is not quite so obvious that there are no "magic" chemicals. Chemicals do not produce strange and wonderful effects that have no basis in the laws of nature. It is tempting, nevertheless, to attribute adverse events to some chemical when no other explanation is evident. However, chemicals do nothing that defies the fundamental laws of chemistry and physics. Strange as it may sometimes seem, the world is orderly. There is ever more detail to learn, but nothing learned ever lies outside the basic order. If it were not for such order, there would be no science and no real knowledge, and no ability to examine or predict effects of chemicals.

Because the interactions of chemicals with biological systems follow those natural laws, it is possible to systematically evaluate the effects of chemicals and make reasonable predictions of their impact on humans and other species.

The ability of a chemical to cause harm depends on two factors, toxicity and dose. Toxicity is the whole pattern of harmful effects that a chemical can cause. It is a property of the chemical; it does not change. The dose is the amount of the chemical that actually enters the body to be distributed to all of the organs and cells. Distribution to tissues and cells is selective, and depends on the nature of the chemical and characteristics of each kind of cell. The pattern of toxicity includes the dose-response relationship, the changes in intensity or frequency of effects that occur as the dose changes.

Neither toxicity nor dosage information alone is useful in the prediction of potential effects. A highly toxic substance will do no harm if the dose is low enough; a chemical of low toxicity will cause harm if the dose is high enough.

The toxicity of a chemical is quite constant within a species and reasonably similar across species, although dose-responsiveness varies among species. If this were not true, it would be impossible to use experimental data from animal studies to help predict effects in humans. At the same time there are enough differences that extension of information from species to species must be done with care.

To get into the body, a chemical must first reach some body surface that can absorb it. The surfaces from which chemicals can be absorbed are the skin, and the respiratory and digestive tracts. The amount that reaches a surface from which it might be absorbed is the exposure. The dose is some fraction of the exposure. Exposure to a herbicide does not include material that is on the ground or on foliage nearby. It is only the material that reaches some surface of the body by direct deposition, by dislodgement from soil or plants, or through consumption of contaminated water or food. Ordinary clothing intercepts and retains a substantial amount of deposited herbicide. Exposure is discussed in more detail in another paper of this series.

For herbicides (and most other pesticides) the skin is much more important than other routes, even though the rates of absorption through skin are usually slow. This is because materials deposited on the skin arrive there directly, are often concentrated, and may remain in contact for extended periods.

Very little exposure to herbicide sprays is through the respiratory tract even when using devices like mist blowers. The reason is that the herbicide is distributed in an immense volume of air compared to the volume of air inhaled. In addition, spray droplets settle out of the

atmosphere, and they do not move very far into the respiratory system. (Fumigants differ in that they are inherently very toxic and they are gaseous and penetrate into the lung. They are often concentrated in enclosed spaces.)

Oral exposure while working with pesticides is almost always the result of carelessness in eating and smoking.

Although only very small amounts of chemical enter the respiratory tract, absorption from the airways and lungs is usually efficient. Absorption of pesticides from the digestive tract varies depending on the chemical.

Interactions Between Chemicals and the Body

It is important to understand the relations among dose, exposure, toxicity, and the environmental behaviour of a chemical. Figure 1 and the discussion below should be helpful in illustrating the way these factors fit together.

As mentioned earlier, there are no non-toxic chemicals and there are no "magic" chemicals. All interactions of chemicals with biological systems follow the basic laws of nature. Simplistic or not, these statements are correct for a number of reasons. Every substance has chemical and physical properties that do not change. The solubility in water and fats, the vapour pressure, the various factors that govern reactivity of the chemical do not change. The properties of the many and complex individual components of the environment, however you wish to define environment, do not change. The chemical entities that make up the body and govern its functions, even as incredibly complex as they are, have specific properties, and they do not change. So, interactions between chemicals and the environment or between chemicals and the body are more than somewhat predictable if their respective properties are known.

Consider Figure 1. Several things happen when a chemical reaches the body. The effect of the

chemical on the organism is only part of the story; most of the initial interactions have to do with the way the body handles the chemical. First, some amount is absorbed through the skin or other surface. This is the whole-body dose. (In the case of highly reactive substances, such as caustics or some acids, the reaction at the skin may prevent or limit absorption, and may constitute most or all of the toxicity.)

After absorption, a chemical is transported by the blood throughout the body, where it may or may not enter the cells of specific tissues. Some transport into cells depends simply on solubility; as body water moves in and out of the cells, so does the dissolved chemical. The cells of some tissues protect themselves by blocking the entry of many foreign substances (and even some substance normally in the blood). The brain and reproductive organs are examples.

Most chemicals bind temporarily to proteins in the blood, such as albumin, and are then released to enter cells or be excreted. Substances that are soluble in fats, like some old pesticides or materials like polychlorinated biphenyls (PCBs) may be stored in fatty tissues for long periods. The herbicides used in forestry in Canada are relatively soluble. Unless the dose taken in is large, these substances are likely to be excreted by the kidneys before any toxic action takes place.

It has been stated several times that a chemical will not effect an animal or other organism unless the dose is high enough. This idea can be refined to point out that a chemical cannot do harm until it reaches a specific sensitive site in the animal in amounts sufficient to interfere with an important tissue or function. In other words, the dose-response relationship applies at the cellular level even more specifically than at the whole body level. If a pesticide is able to act selectively on some mechanism, as for example the organophosphate insecticides blocking an enzyme at nerve cell junctions, relatively small doses will produce an adverse effect. The herbicides in forestry use have specific actions only in plants, so effects in other organisms are non-specific and require relatively large intakes.
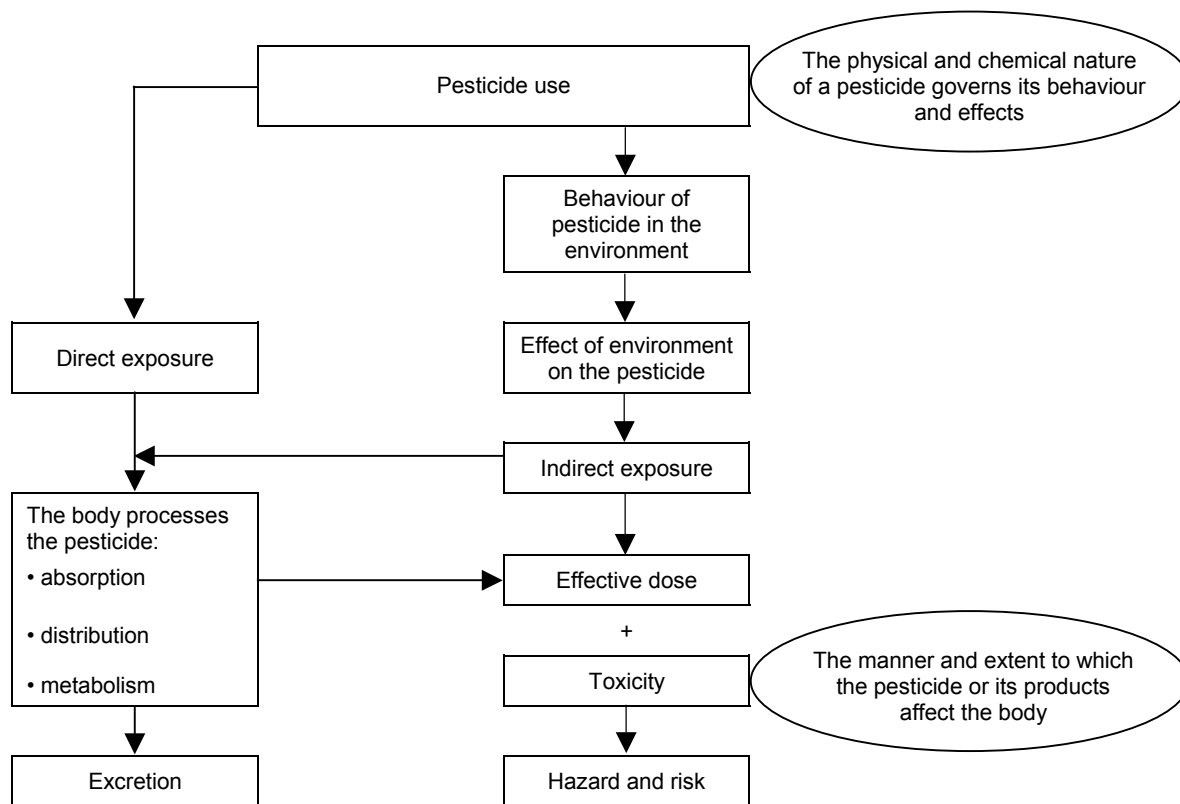
Figure 1. Relation among a pesticide (or any chemical), behaviour in the environment, interaction in the body and potential for harm.

If a chemical is not simply passed through and excreted it must be changed (metabolized) to a more soluble form. (Metabolism is a general term that refers to chemical reactions in the body.) Most of that work is done by the liver. Liver cells are among the most versatile in the body; they have evolved to be able to change (or detoxify) the vast number of substances produced in the body, as well as foreign chemicals. Hormones are produced in the body as needed for regulation of cell activity, but they must be disposed of as the need ceases. The liver has an array of enzymes that can change the hormones to soluble products for disposal. Similarly, foreign chemicals can be managed in the same way.

It is easy to imagine how an organism can develop ways of dealing with its own surpluses or wastes, but synthetic chemicals from the outside are seemingly a completely different problem. Sometimes that is true; PCBs are very difficult to change, some dioxins are almost

impossible. The secret is that while these foreign molecules come in an infinite variety of overall structures, the kinds of specific structural parts have a limit. The variety of molecules lies in the variety of ways the limited number of parts are put together. The situation may be likened to machines. There is an infinite variety of kinds of machines and specific designs within each kind. To take them apart requires only a finite number of tools.

The enzymes of the liver do not take large, complex molecules completely apart. Usually the changes are made in parts on the edges of the molecule. Whether arising from inside the body or outside there are common characteristics of these side groups, which the liver enzymes recognize and act upon, even if they have never "seen" the compound as a whole before. The necessary reactions may take place in a sequence, each step preparing the molecule for the next. Eventually the substance becomes soluble so it can be sent to

the kidneys for disposal in urine, or moved into the bile to enter the intestine. Some chemicals are left unchanged, but a soluble molecule made in the body is fastened on to carry the substance out.

In the degradation of some complex molecules, the reaction sequence produces intermediates that are highly reactive and capable of interacting with large molecules like proteins and deoxyribonucleic acid (DNA). When high intakes of these substances are being processed there is a potential for these intermediate products to move elsewhere in the cell and initiate changes in DNA that could be passed on to daughter cells if not corrected by DNA repair. The only herbicide of interest here that is altered by the liver is hexazinone. Several quite similar derivatives are produced, all of which have similar toxicological properties.

While in most of the interactions the body is doing something to the chemical, at some point the chemical may do something to the organism. Even a chemical that has relatively little ability to exert an effect will find some way to do harm if the concentration in the body or at a given site in the body can be raised high enough. Remember, there are no non-toxic chemicals. Together, the effects of the body on the chemical and the effect of the chemical on the body create the pattern of toxicity.

On the other side of the diagram, the same general relation exists between the chemical and the environment. Here, the field of environmental chemistry comes into play. Interaction in the larger environment governs exposure other than that occurring directly,

such as a spill on the skin or spray drift. Environment can be defined any way one chooses. For an applicator of pesticides, the environment at a given moment may be limited to an area of skin on which a chemical is spilled, where it may be modified by sunlight, bound to soil on the skin, or it may even evaporate.

If the question is broader, such as the potential for movement of a forest herbicide in a watershed, all of the interactions that govern the movement and degradation of the herbicide come into play. It is necessary to learn whether and how fast and how far a substance can move through soil. In part this can be learned by analyzing water in the drainage and sampling soil at various depths after an application, but that data applies only to that soil and the weather conditions over the period. To be able to generalize reliably about the question requires such sampling in a variety of situations, and a great deal of laboratory work observing behaviour under controlled conditions.

The mechanisms that degrade the chemical must be understood. Pesticides usually are broken down by bacteria and fungi, to eventually be reduced to the elements they were made from. How fast this happens, and the influence of environmental conditions must be learned. Much of this kind of information can be obtained in the laboratory, and demonstrated in the field. Almost always a moist, high organic soil will provide the best conditions, and reactions are faster in warm conditions. Some chemicals break apart in sunlight. For example, triclopyr in surface water is vulnerable to sunlight.

The Dose-Response Relationship: Systemic Effects (Effects Other than Cancer)

The dose-response relationship is the central idea in toxicology (and in pharmacology, which is the science dealing with beneficial effects of therapeutic drugs). It may be the simplest major concept in science. As the dose (or concentration) of a chemical increases, the effect increases, and as the dose is lowered, the effect becomes less. This response pattern applies to every interaction between a chemical and a biological system, whether human, fish, bacteria or any other kind of organism or tissue. The dose-response relationship is absolutely essential to judgement of the effect of any chemical.

Almost everyone has experience with the dose-response pattern. The progressive stimulation of too many cups of coffee is a response to increased dosage. So is the depression caused by more and more alcohol. Even the dental anaesthetic that did not quite work on the first injection, but ended the pain when more was added is an example. It is as true with groups of subjects as it is for one individual alone. No exception to the dose response relationship has been shown to be valid.

The dose response relationship for non-cancer (systemic) effects is best illustrated with a graph like Figure 2. This graph is linear on the vertical (response) scale and logarithmic on the horizontal (dose) scale. That means that everything in the range of response (vertical axis) can be described between zero and 100%, or between any other reasonably close numbers. Dosage is on a log scale because it may be necessary to use a very wide range of doses to include all degrees of effect. If the dose range is between 1 and 1,000 units, it can all be fitted by having 1, 10, 100, and 1000 separated by the same distance on the graph.

The horizontal scale is a logarithmic progression; each number in this case is ten times the number before it. The reason for using this arrangement is practical. First, the range of doses can be made to fit on the page. More importantly, in this kind of plot the middle of the curve is almost always a nearly straight line, which makes it easier to interpret.

The responses that would be described in Figure 2 are consistent and graded, and they are reversible unless damage is too severe to repair. Almost all toxic effects fall into this category. Consistent means that every animal in a group at a similar dosage will respond similarly, within the limits of individual variability. The nature of the response is characteristic for the chemical. When the concentration of a chemical in and around the cells of an organ or tissue becomes high enough, most or all of the cells begin to respond and the response increases with concentration. The response is therefore graded. The collective response of the cells means that the affected organ or tissue and therefore the animal as a whole will respond according to the dose. For substances with specific effects on certain cell types the ideal is to determine doses or concentrations at those cells as well as whole body dosage. With the exception of a few research situations this refinement is not practical at present. When the chemical is removed the effect will reverse in each cell unless damage is so great that recovery is impossible.

There is an important point on the graph in Figure 2 where the dose-response curve crosses the zero effect line. This point is the dose below which no effects occur. This no-observed-adverse-effect level (NOAEL) or threshold is very important in judging worker safety with respect to effects other than cancer. If the estimated dose of a herbicide to a worker is very low compared to the NOAEL for the most sensitive effect found in the laboratory, no harmful effect is to be expected.
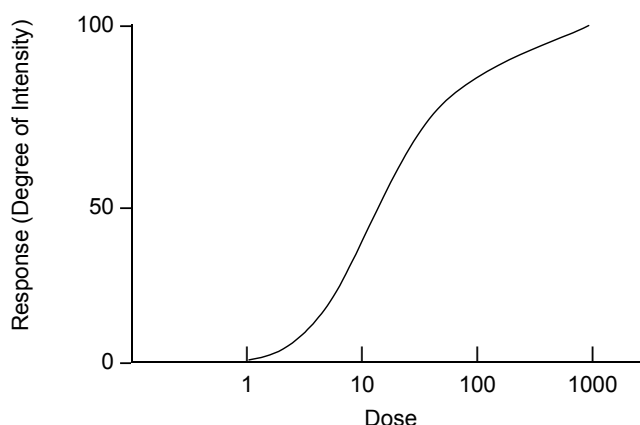
Figure 2.   Typical dose response curve for graded systemic effects (non-cancer effects).

Any point on the curve, including the threshold, has an error range that varies with the nature of the animals, the precision of measurement, the number of samples and so on. To adjust for this potential error when evaluating the safety of herbicide use, the usual practice is to require a 100-fold difference between the dose expected in the field and the NOAEL. If the dose in the field is 100 fold lower than the NOAEL the use is expected to be safe. The basis of the figure lies in the well established convention that differences between species rarely are greater than 10 fold, and differences among individuals fall in a similar range. A multiple of the two factors leads to a standard of 100. Where the available database is less extensive regulatory agencies use a larger uncertainty factor.

The one hundred-fold safety factor is not a legal requirement, but is a generally recognized standard for pesticide use. It is curious that chemicals used for other purposes are not held to this criterion. Over-the-counter drugs, fuels, household cleaning chemicals, solvents and a host of other common toxic chemical classes are given very little attention and are used quite casually by an untrained public. Many will cause harm at doses only a few fold higher than amounts encountered routinely in daily life. Aspirin is an excellent example because it sometimes causes gastrointestinal injury at doses recommended for headache relief. The safety factor in that case is less than one.

A designation called the reference dose (RfD) is now used in regulatory documents in the United States. The RfD is usually based on the most sensitive oral NOAEL, with all appropriate safety factors included. Any oral dose below the RfD is considered unlikely to be associated with an adverse health effect and is therefore acceptable. The RfD does not take into account inefficient absorption from the digestive tract. In the case of the herbicide glyphosate, absorption is poor and the comparison with dosage through the skin takes this difference into account.

Irreversible effects such as birth defects and miscarriage that are caused directly by chemicals are also based on a threshold. (Direct causation refers to effects on the embryo or foetus after conception, as distinguished from genetic effects carried forward from either parent.) The reason for this is that widespread cellular injury is necessary to produce these responses.

Almost all effects of forestry herbicides can be described within the threshold- or NOAEL-based system just described.

The Dose-Response Relationship: Chemically Induced Cancer

The forest vegetation management herbicides of interest in Canada do not cause cancer, but the issue of possible cancer causation must be discussed because it is a natural public concern. In part the concern arises because it is impossible to prove a negative. In the following paragraphs there is a brief general discussion of cancer as a possible consequence of chemical exposure, with attention to the problems associated with defining very low cancer risks.

(The term "cancer" is really a general name that covers a hundred or more diseases, each of which has some characteristics that are different from those of other cancers. In a given species, a carcinogenic chemical in sufficient dosage tends to induce one or only a few tumour types. In this discussion the various kinds of cancer are not separated.)

Cancer is a random or quantal effect. "Quantal" means that an effect either exists or it does not. It does not increase in intensity with dose as a graded response does; rather it increases in frequency or incidence. In other words, rather than a stronger effect, more people or animals or cells will be affected. For a given chemical agent only some fraction of an exposed group of animals will respond or develop a quantal effect. The number of animals responding is related to the dose rate. The same limitation applies at the cellular level; the initial effect is on only one or a few cells. If the process is initiated by a chemical, it does not stop when the chemical is removed; the process is not expected to stop unless the immune system intervenes to destroy the genetically different cells. (Certain chemicals that cannot start the process are able to accelerate it after it has started, and some initiators can also promote the process once it has started.)

For several reasons, it is very difficult to experimentally detect a threshold for a chemical that causes cancer, or to observe the response at the very low doses equivalent to those encountered in the environment. The most obvious reason why very low dose effects cannot be observed directly is statistical. Almost all species, including humans, have a high natural background cancer rate that increases with age, and which hides small increases that might result from chemical exposure or any other specific factor, whether in the laboratory or in human populations.

The other reason why a precise measurement cannot be made lies in the biological nature of cancer. The disease begins with one or a few cells in which genetic control of cell division, growth and other function has been lost or altered. This occurs as a result of unrepaired change in DNA, the genetic plans and working instructions within each cell. With such mutations the cell may still survive and function, although possibly not normally. If the cell divides before the damage is repaired, its descendants may have the same defects. Unless the immune system recognizes the altered cells and attacks them they will divide and divide until they form a large enough mass of cells to eventually be recognized as a tumour.

When a disease has such a small beginning, it is not possible to define just when it begins to exist. When a tumour is large enough to be diagnosed in a human it may have been developing for a long time, possibly decades.

Because of these uncertainties, it is usually assumed for regulatory purposes that there is no carcinogenic threshold or NOAEL for any chemical suspected of being carcinogenic, regardless of its mechanism. In such a situation the curve looks something like Figure 3. The segment of the curve representing very low doses can not be shown because it is not possible to study enough animals to identify very infrequent events. Also, dosage is shown

on a logarithmic scale, which can have no zero.

Later, in the section on risk assessment, the solution to that quandary is discussed, but it is useful at this point to inquire why it should be all that difficult to determine whether a given chemical at very low doses will or will not cause cancer.

Damage to DNA is caused by many factors other than an encounter with some reactive chemical. DNA damage occurs at a very high rate in every normal cell. To convert nutrients to usable energy in the cell, a number of vigorous reactions must take place, which produce as waste large quantities of highly reactive molecules such as peroxides. These substances are normally trapped and neutralized, but if they escape they can cause damage. Along with injurious agents originating inside the cell, our normal environment includes sunlight, radon, wood smoke, food, cosmic radiation, and other destructive factors that cannot be avoided. Much of our external burden of natural cancer-causing factors comes in a typical diet, regardless of source. The contribution of synthetic chemicals is usually trivial except in the cases of a few occupational exposures to industrial chemicals like benzene.

We are protected from the billions of such events that occur in the body every day by a remarkably efficient system in each cell that recognizes and repairs defects in DNA, usually before changes can be reproduced in the next generation of cells. If cells remain genetically damaged and produce similar daughter cells, the immune system traps and destroys most of them.

A third problem, also statistical, is the great difficulty of identifying some specific causation for a clinical cancer. A specific case of cancer can almost never be stated absolutely to be associated with a specific cause, with the exception of a type of cancer, which apparently can only be caused by asbestos. It is rare that some identified cluster or increase of a single kind of cancer in a part of the population can be linked to a given chemical. Almost always such associations occur as a result of very high industrial exposures, and those instances are few. Cancer is not like measles, which can be caused only by a specific organism and no other, and cannot occur without that organism.

The inability to measure low-dose effects, coupled with the very high normal cancer frequency in humans, makes it necessary to resort to indirect estimation, which will be discussed below with other kinds of risk assessment.
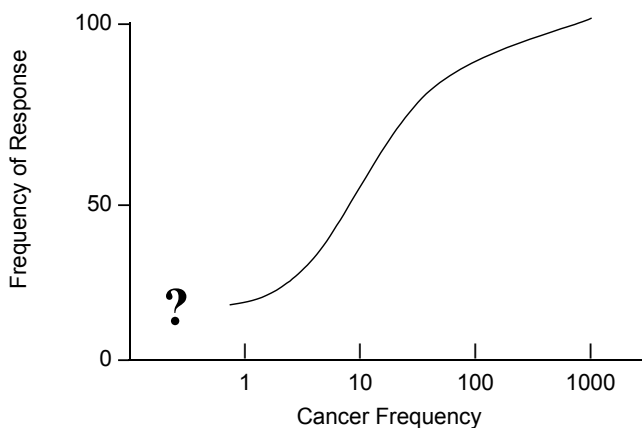
Figure 3.   Typical dose response curve for quantal effects (cancer).

Risk Assessment

General considerations

Risk is defined most broadly as the probability that some adverse or undesirable effect will take place in the future, as a result of some specified activity. Risk assessment is the process of estimating that probability. The concept of risk assessment is familiar to everyone. Crossing a street requires a risk assessment. One gathers information about traffic density and speed, distance to cross, weather, condition of the street, foot speed, urgency and other factors like laws and traffic lights. The information is evaluated in the light of prior data (experience), and a decision is made about the safety of crossing. The risk may be incorrectly perceived; a person may stand terrified beside an empty street or may run headlong into heavy traffic.

Assessing risk from chemical exposure employs the same kinds of concepts but the details are more complex. The analysis is not done reflexly, as it is when we decide whether to cross a street.

Perhaps the most important philosophical difference between a personal evaluation of the safety of crossing a street and assessment of the potential effect of use of a pesticide is that the latter is usually done by others on our behalf. Scientists and governmental regulators examine data, reach conclusions and eventually make decisions about public and worker risk. These decisions imply some degree of public accept-ability as well. The public must either deal with such judgement as a matter of faith (or lack thereof) in governmental process, or become knowledgeable enough to undertake the exercise personally. An intermediate position is perhaps most satisfactory, of understanding the nature of the assessment well enough to assure that the regulatory process is being applied reasonably.

As a general case, risk cannot be estimated without obtaining or specifying several kinds of information. Much of this information is implied in the necessity for learning the details of the toxicology of the chemical and the dosage taken in, as already discussed:

The hazard or kind of effect must be specified. What effect is of concern? Is it cancer, liver disease, skin irritation, reproductive problems, or some other more or less specific response that can be defined and measured? The hazard identification will have arisen either from a suspicion that some specific disease is increasing in incidence or from findings in the laboratory.

The population for whom chemical risk is to be estimated must be specified. The population may be a group of workers in a factory, or children under 15, or herbicide applicators, or residents of the forest. It might even be songbirds or fish. To consider an overly broad population, such as all of the people of the country or a province, would almost certainly be impractical, except when gathering statistics about overall disease incidence without regard to cause, which is done very well by Statistics Canada.

The source of the impact must be identified and measured or estimated. The source of possible impact must be specific enough to work with, like a chemical exposure, or automobile accidents, or exposure to sunlight.

Any one of these factors may be sufficient to institute a risk assessment, but if it is to proceed, it will be necessary to specify all three in some way.

Most people are familiar with a common example of the sequence just described: hazard identification, identification of a population, and evaluation of the dose response. Lung cancer is a hazard associated with smoking. The two obvious populations of concern are smokers and those who live with them. There may be a subset, such as smokers who also drink. The risk to all of these populations is

directly related to the number of cigarettes smoked each day, or the dose.

The great mass of toxicological data from the process of registering a herbicide provides information about the kinds of effects to be evaluated (see Title 2 of the series). In a few cases there may be useful information about effects on human populations. An example might be health histories for workers in the manufacture of a herbicide. There have been several studies of workers in 2,4-D manufacturing to learn whether those personnel have health histories different from the general population or from other similar workers. Even in that case, however, exposure histories are not clear. A much clearer history of exposure to 2,4-D is available for the United States Air Force personnel who handled and applied it as a component of Agent Orange in Vietnam. They were very heavily exposed and are part of a study in which they and an unexposed control population are given very thorough physical examinations every five years.

Systemic, threshold-based effects

Once experimental dose-response and worker exposure information has been obtained, risk estimation for non-cancer (systemic or graded) response becomes relatively simple. One reason is that such effects usually appear relatively soon after exposure and are reversible unless the insult is very heavy. Another reason is that there is a low background incidence of such effects in a normal unexposed population so increases can be recognized and reported. When exposure of workers in the field results in a dose that is 100 or 1000 fold lower than the highest dose that produces no response in the laboratory, it is highly likely that the worker exposure will produce no effect.

In this case the risk assessment process is really a matter of assuring that risk, or probability of effect, is so low as to be negligible.

Irreversible effects

When we begin to deal with major irreversible effects the process becomes more complex. Birth defects and developmental delays, miscarriage, genetic defects and cancer all have a high natural background frequency. Identifying a very few cases of a disease that may result from some specific causation, amidst the substantial natural burden of the same disease is a formidable problem.

Threshold dependent irreversible effects

Birth defects are found in almost 5% of all live births in Canada (See Health Canada, www.hc-sc.gc.ca/hppb/phdd/report/stat.) With the exception of alcohol, tobacco, illegal drug use, and a few medicinal chemicals, very few birth defects are known to be associated with a specific chemical exposure.

Delayed development of organs or structures may occur because of direct foetal toxicity, usually in the latter part of gestation. Normality is often achieved in infancy, but there is also the possibility of permanent impairment.

Miscarriage normally terminates about 15% of all known pregnancies; 50% or more of total conceptions fail. A considerable fraction of miscarriages result from lethal genetic defects. There is no evidence that frequency of any of these kinds of events has changed remarkably in recent years, except for year by year fluctuations.

Chemicals may also affect fertility of either males or females in various ways. The effects may be transitory, but conceptions that might have occurred but did not during a given period are, in a sense, not recoverable.

Despite the inability to see very small increases in incidence of defective reproductive outcomes in the human population, the problem is somewhat simplified by the fact that direct chemical effects are threshold-dependent. The safety factor approach discussed in connection with systemic effects is therefore protective.

Non-threshold dependent irreversible effects

Genetic defects (deleterious mutations) are found in about 1.5% of live births. Many are familial (inherited). Sickle cell anaemia, phenylketonuria, haemophilia and some kinds of diabetes are examples of inherited diseases. Genetic diseases overlap with "birth defects" some of which are clearly genetic in origin.

About 30% or more of the North American population are expected to be diagnosed with cancer at some point in life. As other diseases are pushed back and as life span increases, that percentage will rise. Canadian Cancer Statistics 2001 shows that when correction is applied for the increased age (the term used is "age-adjusted") of the population, the overall incidence of cancer has increased only slightly in the several decades in which records have been kept, and overall mortality is declining. Most of the upward change is in lung cancer related to smoking, and prostate and breast cancer. Colorectal cancer in males is increasing in incidence but decreasing in mortality (death rate). Skin cancer is increasing, but mortality is stable. (National Cancer Institute of Canada: Canadian Cancer Statistics 2001, Toronto, Canada. See www.cancer.ca/stats/currente.htm)

Risk assessment for chemically related cancer and genetic effects is much more complex than it is for the threshold-based effects. The herbicides discussed in this series of reports are not carcinogenic, but it is nonetheless important to discuss the general issue.

For risk assessment purposes, it must be assumed that there is no threshold or no-effect dose for chemically induced cancer. (There are apparently many carcinogens that act by indirect mechanisms; in other words, the genetic alteration that must precede development of cancer is secondary to other change. One example is cancer induced by estrogenic hormones that are caused to increase as a result of some primary intoxication. It is likely that such indirect carcinogens have a threshold below which no response can occur. As yet evidence for specific chemicals is not firm enough for regulatory policy to take this difference into account.) Regardless of mechanism, there is no question that all carcinogenic effects are dose dependent.

The zero threshold idea at its extreme can mean that any minute dose of a carcinogen has some correspondingly small probability of adding to the high normal background incidence. It is generally assumed in regulatory policy that an exposure low enough to confer a theoretical added risk of 10^{-5}-10^{-6} (one case in 100,000 or in 1,000,000 lifetimes) is considered to be virtually equal to zero and is therefore "acceptable." That level or lower is the realm into which the exposures to chemicals in the environment almost always will fall.

The present background cancer incidence is in excess of one case in three lifetimes (more than 300,000 cases per million lifetimes). An added risk of one case in a million lifetimes (10^{-6}) is the difference between 300,000 cases and 300,001 cases per million. That there are many dozens of kinds of cancer, many of which appear in small numbers, does not make the problem much easier. No direct measurement can show very small difference added to such background numbers. There is not necessarily a direct relation between a given cancer type in animals and a specific site or cell type in humans, so we have little choice but consideration of the spectrum of human cancer.

Added to the difficulty of finding very small differences in very large numbers, there are

other complications. It is not possible to see the biological beginning of cancer, and in humans decades may elapse before the disease is diagnosed. Estimation of cancer risk possibly arising from some specific cause, such as chemical exposure, is therefore usually indirect, with all or most of the data coming from animal experiments with the chemical in question. The applicability of the animal data to humans must be evaluated, and while such associations are generally valid, people are not just large rats. Of particular importance are differences among species in the way specific chemicals may be changed in the body, and in specific organs. In some cases, usually with industrial chemicals where exposures in the work place have been measured, epidemiological data may be useful in the estimation of risk.

To visualize the difficulty of predicting cancer risk, compare that exercise with predictions of the risk of automotive head injury. An accurate prediction of risk of head injuries from automobile accidents next year can be made on the basis of statistics from prior years. Each such injury and its cause can be identified at the moment it happens. Furthermore, there is no natural background; the incidence of automotive head injuries not caused by automobiles is zero. If there are changes in such knowable information as increased use of air bags, enforcement of speeding laws and changes in automobile structure, they can be factored into the prediction with high accuracy.

In the face of such uncertainty, how is the risk associated with exposure to a carcinogen estimated? There is no doubt that every carcinogenic effect follows an orderly dose-response relationship. Estimation of the risk of an added burden of human cancer is usually based on the dose-response in groups of experimental animals given the chemical in

question over a lifetime. (Infrequently, data on human populations may be available to contribute to the process.) There is reason to believe that events that may take place in the long life of a human will also take place in the shorter lifespan of a rat or mouse. However, the portion of the dose response curve representing typical very low environmental exposures and dosage cannot be defined experimentally, for reasons discussed earlier. A way of estimating the dose response in that invisible part of the curve must be found.

The current solution has been use of mathematical modelling based on effects at the higher, observable doses in animals. Figure 3 is typical of such data. The result of the mathematical treatment is a projected potency slope or graph that shows the added risk to be expected at the very low doses not visualized in Figure 3.

The model used by regulatory agencies is the most health conservative (produces the highest risk estimate) of several that have been developed. The result is a linear plot as shown in Figure 4, with a straight line to zero dose and zero effect on the graph at the low doses in the range of human exposures. At present, the models are usually based on whole body doses. In reality, distribution and dose to and into specific kinds of cells differ through out the body, and differ to some extent among species. In some cases it is now becoming possible to model these localized differences instead of relying on an overall whole body dose.

The slope in the middle of Figure 4 is called the maximum likelihood estimate, which is the relation between daily dose and risk that has the greatest probability of being correct. The lines on either side are statistical limits that are believed to be 95% certain to include the correct slope. In other words they describe the uncertainty of the estimate.
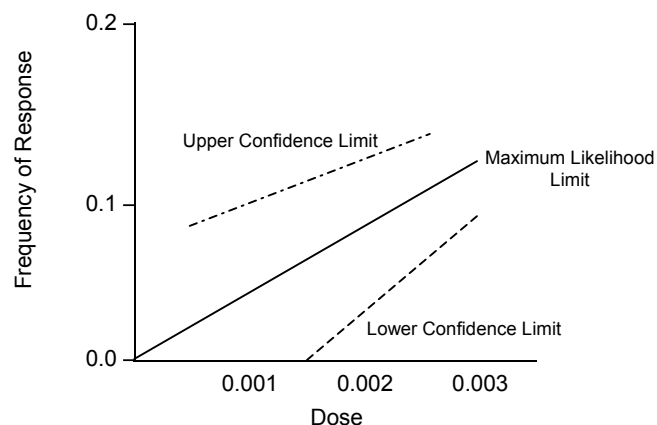
Figure 4.   Idealized linear very low dose-response projection for risk estimation.

Since risk is based on a prediction of future events some uncertainty must always exist, even with very strong data. Reducible uncertainties derive from the quality of individual experiments, the amount of useful information, the divergence or agreement of the various data, understanding of the relation of findings in animals to human effects, and the range of scientific judgement of competent scientists as they evaluate the information.

Statements of risk estimates are usually based on the upper range. That convention helps to assure that uncertainty of the estimate is largely accounted for. It also means that the real risk is likely to be somewhere between the stated value and zero.

With the low dose risk slope estimated from experimental data at high doses, how is the exposure of a human linked to the data? For long-term exposure and its associated risk, usually cancer, the customary approach is to estimate an average lifetime daily dose of the chemical in question, beginning at the time of first exposure. The reason for averaging in this way is that there is evidence indicating that chemical induction of cancer is cumulative. This idea requires an assumption that intermittent exposure has the same impact as continuous exposure, and that an average long

term daily dose represents the same risk as intermittent or irregular intake of the same total dose. There is some basis for this idea, but it is not proven.

Estimates of workday exposure and the number of days exposed per year can be based to an extent on known information. For example, if it is a work exposure, an assumption is made of the number of years an individual is expected to remain in the job under examination. This convention provides an estimate of total lifetime dose. For cancer risk assessment, the total dose is then averaged over the number of days in a lifetime following the beginning of work.

This estimate of average daily dose over a lifetime can be located on the horizontal scale of the linear potency graph (Figure 4) and related to the risk or probability of cancer on the vertical axis.

If the risk is really proportional to dose at low levels, does it not follow that even a single molecule of a carcinogen has some probability of causing cancer? In concept, yes, but practically, no. Chemical reactions would not start unless a sufficient number of molecules are present; it is unlikely that a single molecule can react unless multitudes of other molecules of the same chemical are present.

Consider an example of a hypothetical chemical that is known to have no observable effect at a daily dose of one mg/kg body weight. If the molecular weight is about 300, the daily dose that is without observable systemic effect represents two billion billion (2×10^{18}) molecules/kg. [There are 1.026×10^{23} molecules in one gram molecular weight of any chemical (Avogadro's Number), in this case, in 300 grams.] There are roughly 300 billion cells per kg of tissue. If it is assumed that the chemical is distributed evenly with no excretion, there would be about seven million molecules for each cell, in this case without observable effect.

Furthermore, the chance of an initial interaction either having real carcinogenic potential or going unrepaired is very small amidst the enormous number of damaging events arising from other causes.

If one wishes to assume for the purpose of argument that a single molecule represents a dose-related probability of cancer, it is possible to calculate the probability, or risk, of such an eventuality. Even for a very potent carcinogen, the risk estimate for a single molecule is on the order of about one chance in 20 billion times the earth's population. Another analogy is one chance in 100 times the number of seconds elapsed since the earth was formed. In other words the exercise may be amusing but is of no real value.

The difficulty that it is experimentally impossible to see very low dose effects is offset by other kinds of information applicable to the potential for carcinogenic response. Testing for registration requires evaluation of ability to cause mutations and DNA damage. A chemical with little ability to cause mutation is not likely to initiate the cancer process. It is also necessary to learn how pesticides are changed in the body. Most, if not all, carcinogens, are inactive unless they are converted to active forms in the body. Ironically, these conversions are part of the detoxication process. A chemical that is excreted quickly and unchanged, as most forestry herbicides are, is not likely to be carcinogenic.

What is the meaning of an added cancer risk described with some number like 10^{-6}, or one in a million? Any risk estimate refers to the excess over the normal background of about one case in three lifetimes. The risk may be described in one of two ways. It can be expressed as the expectation that some number of people in an exposed population will acquire the disease in addition to the 30+% already expected to be diagnosed with cancer in their lifetime. Or, it may be the "chance" that a given exposed individual might be affected, over and above the existing risk of 0.30. The numbers are very small. An estimated excess risk of 10^{-4} or one in 10,000 is usually considered to be high and unacceptable, even though the normal background risk is 3000 times greater. Examples of estimated one-in-a-million cancer risks include a transcontinental round trip by air (radiation), living in a masonry house instead of wood for two and one-half months (radiation), or drinking 200 gallons of New Orleans water (chemicals) (apparently not quickly).

Risk has already been defined as a probability, and just above, risks or probabilities of one in 10,000 and one in a million are used as examples. How can sense be made of probability statements like those? Coin tossing can be a good illustration of probability, even with such small numbers as one in a million. When flipping a coin, on any toss there is a 50% probability that the head will come up. Everyone knows that the odds are one in two. Because previous tosses have no influence on the present, the odds for any given toss do not change from 50% (0.5). The chance of getting two heads in a row is one in four, which comes from multiplying $0.5 \times 0.5 = 0.25$. Odds or probability is expressed as a number between zero and one, and may be written as a fraction (1/2), as a decimal (0.5), or as a percentage (50%). Usually a decimal is used.

The odds of three heads in a row is 0.5 x 0.5 x 0.5 = 0.125 or one in eight. The probability of getting ten in a row is one in 1024, and for 20 in a row the odds are one in 1,048,576 (1.05 x 10^{-6}). That is close to the one in a million convention that is considered virtually equal to zero. In other words, it would be necessary to go through more than a million sequences of 20 tosses to expect to see 20 in a row. There is no way of knowing when it might happen. It could happen in the first series, or not until the third million.

Perhaps a different example would be helpful. Let us say that there are 1000 towns, each populated by 1000 people. At an excess risk level of one in a million there may be, in a lifetime, in just one of those towns, one case attributable to the stated risk. In each of the 1000 towns, 300 people would be affected by background factors at some point in their lifetime.

Risk estimates cannot indicate who would be affected, or when. Therein lies a difficulty in perception of cancer risk. If an added risk of one in a million is calculated, and someone says, "What if I am the one"? What is the answer? For someone who is genuinely afraid there may be no satisfactory answer. However, these kinds of numbers are really comparisons for regulatory purposes, and they represent the high side of a range that often includes zero estimated risk.

Glossary

Cancer – A malignant growth of potentially unlimited size that invades local tissues, and may spread to other parts of the body.

Carcinogen – A chemical capable of inducing cancer.

Carcinogenic – Capable of causing cancer.

Deoxyribonucleic Acid – See **DNA.**

Degradation – Breakdown of a compound by physical, chemical or biochemical processes into basic components with properties different from those of the original compound.

Detoxication (Detoxification) – The biochemical process of changing a chemical in the body to a less toxic form or to a form that can be more easily excreted.

Dose – The amount of a chemical that actually enters the body to be distributed to all of the organs and cells. Distribution to tissues and cells is selective, and depends on the nature of the chemical and characteristics of each kind of cell.

Dose-response relationship – The central idea in toxicology and in pharmacology (which is the science dealing with beneficial effects of therapeutic drugs). As the dose (or concentration) of a chemical increases, the effect increases, and as the dose is lowered, the effect becomes less. This response pattern applies to every interaction between a chemical and a biological system, whether human, fish, bacteria or any other kind of organism or tissue. The dose-response relationship is absolutely essential to judgement of the effect of any chemical.

DNA (Deoxyribonucleic Acid) – The genetic library in each cell that contains all of the instructions for building and operating the body. Each kind of cell contains all of the information for the whole body. Only the information needed for each kind of cell is used by that cell; the rest is repressed. Liver cells do not try to be muscles, and muscles do not try to become brain cells, but they contain all of the information.

EC$_{50}$ – Acronym for median effective concentration.

Environmental chemistry – The study of the physical, chemical and biological processes that govern behaviour and fate of a chemical such a pesticide after it is used.

Enzymes – Complex proteins that catalyze (expedite) biochemical reactions. See Metabolism.

Epidemiology – The scientific study of the cause, distribution, and control of epidemics or other disease in a region. In the context of these reports, epidemiology is the study of possible associations between environmental and occupational chemicals and occurrence of diseases. The term "associations" is used in its statistical sense, which means that the relationship cannot demonstrate cause and effect.

Exposure – Amount of a chemical that reaches a surface from which it might be absorbed. The dose is some fraction of the exposure. Exposure does not include material that is on nearby foliage or other surfaces. It is only the material that reaches the skin (by contact), respiratory tract (by inhalation) or digestive tract (by ingestion).

Foetus – The later stage of mammalian development in the womb. In human, this refers to the unborn child during the period of uterine life from the end of the second month until birth.

Foetal toxicity – Direct effects of a toxicant on the foetus, independent of effects on the mother.

Hazard – The kind of effect that a chemical can cause. Cancer, liver disease, skin irritation, reproductive problems, or some other more or less specific response that can be defined and measured. The term is also used non-specifically to signify any dangerous situation.

Herbicide – A chemical substance or cultured biological organism, used to kill or suppress the growth of plants.

Hormone – A substance secreted by specialized endocrine cells and transported by the blood stream throughout the body to regulate biochemical activity of other cells. Insulin and testosterone are hormones.

Immune system – All of the structures and cells and their products that protect against infectious organisms and against cells of the body that have become altered in the very early development of cancer.

LOAEL–Acronym for lowest-observed-adverse-effect level.

Lowest-observed-adverse-effect level (LOAEL) – The lowest measured amount of a chemical that produces significant increases in frequency or severity of adverse effects in exposed subjects. In the general sense it includes all biochemical, pathological, behavioural, reproductive, genetic and other measurable changes. the term may also be applied to any specific parameter under observation.

Malignant – Deadly or very injurious. As applied to cancer, invasive of local tissues and metastatic (migration of cancer cells to other tissues).

Margin of Safety (MOS) – The difference between the estimated dose of a pesticide and the NOAEL. A **MOS** of 100 (estimated dose 100 fold less than the NOAEL) is usually considered to assure that no adverse effects will occur.

Metabolism – The sum total of the biochemical reactions that a chemical undergoes in an organism. The processes include biochemical (enzymatic) reactions in the cells of the body that convert nutrients to energy and structural materials of the body; reactions that change wastes so they can be removed; and reactions that convert foreign substances, such as some pesticides to forms that can be excreted.

MOS – Acronym for margin of safety.

Mutagenic – Capable of producing genetic changes.

Mutagens – Chemicals that are able to induce gene or chromosome damage that is stable and survives cell division to reach the next generation of cells. See **mutation.**

Mutation – Genetic change in DNA of a cell that can be transmitted to the next generation of cells. If in sperm or egg cells, a mutation may be transmitted to offspring. If in somatic (body) cells such as liver, muscle or other organs, a mutation may pass to daughter cells in the organ. The change may have no effect on cell function or it may damage the cell, or even imaginably improve it.

NOAEL – Acronym for **no-observed-adverse-effect level.**

No-observed-adverse-effect level (NOAEL) – The dose rate or concentration at and below which no adverse effects can be detected. (See **threshold; SEE LOAEL)** If the estimated dose of a herbicide to a worker is very low compared to the **NOAEL** for the most sensitive effect found in the laboratory, no harmful effect is to be expected.

Pesticide – Any chemical (or biological product) intended to control or kill pests. Herbicides, insecticides, fungicides are all pesticides. The term is sometimes incorrectly used to mean only insecticide, for example "pesticides and herbicides.".

RfD – Acronym for reference dose.

Reference dose (RfD) – Any oral dose below the RfD is considered unlikely to be associated with an adverse health effect and is therefore acceptable. The RfD is usually based on the most sensitive oral NOAEL, with all appropriate safety factors included.

Registration – The process by which government (e.g., Canadian federal government) authorities determine that a pesticide is suitable for use. Standards of public and worker safety, environmental impact, and usefulness must all be met.

Risk – The probability (likelihood) that some adverse or undesirable effect will take place in the future, as a result of some specified activity. Risk may relate to health, finances or any other kind of undesirable impact. Real risk may be so small that it cannot be distinguished from zero, or so great that it is a certainty. In the context of pesticides, risk is the probability that use of the pesticide will result in some specified harmful effect on workers or the public. Risk assessment is the process of estimating that probability.

Safety Factor – See **Margin of Safety**.

Threshold – The lowest dose that will produce a given effect. As a practical matter, the threshold is little different from the **NOAEL.**

Toxicity – The whole pattern of harmful effects (illness and other undesirable effects) that a chemical can cause. It is a property of the chemical; it does not change.

Toxicology – The group of scientific disciplines that identifies and studies the adverse effects of chemicals on biological systems, whether in the laboratory or in the field.

Tumour – A new growth of cells multiplying progressively and without control. Classically, the term means a swelling.

Titles in this Series

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BRITISH COLUMBIA