August 27, 2003

**Lecture 2: Risk Management & Environmental Toxicology**

## I. Environmental Toxicology Goals & Objectives

A. The overall goal of environmental toxicology is prediction of environmental/health effects at different levels of biological organization.

B. As discussed in lecture 1, a theoretical framework for making predictions has evolved based on principles of thermodynamics and kinetics. This framework is called environmental chemodynamics (EC) and pharmacodynamics (PK) or toxicodynamics.

1. Both EC and PK can tell us what is happening on the lower levels of organization, including the transfer of the chemical from the environment to the organism surface, absorption through the organisms' integument, and interactions within the organism. Thus, at an organismal level we can describe exposure, dose, and likely hazards and even predict the likelihood of an impact (i.e., the risk) based on environmental concentrations.
    a. However, we are still in a "primitive" state in translating effects at lower levels of organization into effects at higher levels.

C. Despite our inability to really predict what happens at the community or ecosystem level, we still want to manage risk.

1. Thus, our desire to manage risk is manifested through our regulatory process.
2. Sometimes, risk management is confused with risk assessment, but although overlapping somewhat, they are different processes.
3. This lecture will differentiate the risk assessment process from risk management, as well as indicate when risk management is actually overlapped with the risk assessment process.
    1. Furthermore, this lecture will demonstrate where environmental toxicology aids the risk management process.

## II. Speaking the Same Language

A. Before proceeding further with a discussion of risk assessment in comparison to risk management, it is important that we agree on the usage of some terms.

B. Definitions relating to the concept of toxicity (from Casarett & Doull 1975)

1. **Toxicity** can be defined as the innate potential of a substance to cause injury, but whether the injury is actually manifested or the degree of injury will be influenced by the context or characteristics of the organism and the dose.
    a. The potential to cause injury under a certain set of circumstances constitutes the definition of **hazard**.
    b. **Safety** can be subjective and is not necessarily definitive, but in the context of risk management it refers to the "practical certainty that injury will not result from use of a substance under specified condition of quantity and manner of use."
2. Duration of exposure terminology: there are two basic "types" of exposure as defined by their duration.
    a. **Acute**: the dose is delivered in a single event (or over a short time interval) and absorption (i.e., movement of the chemical across the

integumental barrier [e.g., skin, exoskeleton, epithelial membranes, etc.]) is rapid.

b. **Chronic**: the dose is delivered over a period of time, usually with some defined frequency, such as daily or weekly.

3. Spectrum of toxic effects terminology: there are two basic types of toxic effects defined by the time to appearance of an effect relative to exposure duration, and there are two basic types defined by the general site of action.
   a. Time to Effect
      1. **Acute effects**: effects that occur or develop rapidly after a single administration of a substance.
      2. **Chronic effects**: effects that occur or develop after the elapse of time.
         a. Note that an acute exposure can result in chronic effects; in other words, the manifestation of injury might occur sometime after a single or short-term exposure.
   b. Site of Action Effects (on the whole organism level)
      1. **Local effects**: effects occur at the site of first contact of the toxicant and the organism
         a. For example, dermal irritations can be local effects if exposure occurs on the organisms' dermis.
      2. **Systemic effects**: effects occur at a site distant to the site of absorption;
         a. For ex., injury to soft tissue organs inside the peritoneal cavity of mammals represent "systemic" sites.
4. Residues of contaminants terminology
   a. Organisms are actually exposed to residues of contaminants in the environment. The term residue refers to contaminant molecules detected in the physical environment and biological tissues.
      1. Historically the term has referred to pesticide molecules after application to the environment. However, it can also refer to the contaminants of any chemical once it is released into the environment. (Discussion of the term and subsequent discussion of residue concentrations taken from Felsot, 1998, "Numbers, Numbers Everywhere—and Not a Drop of Meaning", J. Environ. Law & Litigation 13:91-113.)
         a. Thus, PCBs were used as insulating fluids in electrical transformers. As such they would not be considered residues. If, however, some of the liquid leaked to the soil, the resulting PCB molecules would be considered residues.
   b. Expression of concentrations
      1. The magnitude of residues are expressed as a concentration;
         a. The concentration represents the mass of residue relative to a unit volume, weight, or surface area.
            1. For example, the concentration of contaminant **X** in water might be expressed as micrograms per liter ($\mu$g/L) or milligrams per liter (mg/L).

(a) If the contaminant was in soil, it could be expressed as micrograms per kilogram of soil ($\mu$g/kg) or milligram per kilogram (mg/kg).
(b) If the contaminant landed on a known surface, it could be expressed as micrograms per square centimeter ($\mu g/cm^2$) or milligrams per square meter ($mg/m^2$)
(c) If the contaminant was detected in air, its concentration could be expressed as micrograms per cubic meter ($\mu g/m^3$) or some variation of weight and volume.

b. Often, residues are expressed as proportions, usually in units of parts per million (ppm) or parts per billion (ppb), and occasionally parts per trillion (ppt).
   1. When using proportions like ppm, ppb, or ppt, then be careful to distinguish whether the proportion is given on a weight per weight (w/w) or weight per volume (w/v) basis.
      (a) Only when the medium is water, would the concentration 1 ppm be the same when expressed as w/w or w/v (because the density of water is 1 gram per cubic centimeter (1 $g/cm^3$; 1 $cm^3$ of water = 1 mL).
         (1) Note that 1 ppb = 1 $\mu$g/mL;
         (2) Because a ppb (or ppm) is a proportion, in the same manner that one percent represents one part per 100, than a residue present in water at a concentration of 1 ppb represents a purity of 99.9999999%!!!

c. Residues in the body and body doses are usually expressed as milligrams per kilogram of tissue or body weight (mg/kg). For dosage, the interval of exposure is normalized to one day (d), so that it would be expressed as mg/kg/d.
   1. In biochemical toxicology experiments, residues may be expressed on a molar basis, especially when the experiment involves interactions with enzymes or receptors.
      (a) To translate from weight per volume concentration units, keep in mind that the formula weight (i.e., the molecular weight in grams) is equivalent to one mole and a molar concentration is based on the number of moles in a liter of water, which is equivalent to a kilogram.
         (1) Example: the molecular weight of DDT is 354.5; thus one micromolar concentration of DDT (is 354.5 $\mu$g/L or 354.5 $\mu$g/kg).

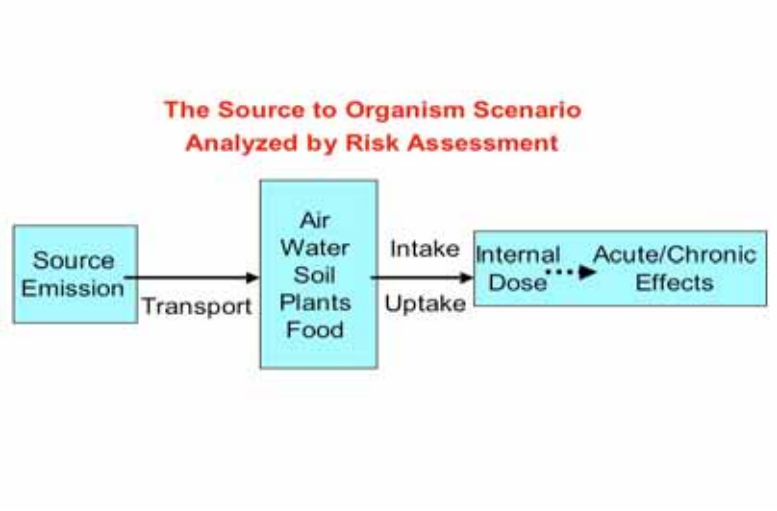
## III. Risk Assessment (RA): A Process Evolved for Determining the Likelihood (Predicting) the Adverse Human Health or Environmental Effects

A. The term "risk assessment" has been defined in several different ways;
   1. For example, the National Research Council (NRC; note that the NRC is the research arm of the National Academy of Sciences, NAS) report, "Improving Risk Communication" (1989) defines risk assessment as "the term generally

used to refer to the characterization of the potential adverse effects of exposures to hazards." The NRC report then gives an operational definition to risk assessment (RA) by describing the questions that it addresses:

a. What are the hazards of concern as a consequence of a substance or activity?
b. What is the probable exposure to each hazard in total number of people or valued things?
c. What is the probability of each type of harm from a given exposure to each hazard?
d. What is the distribution of exposure?
e. What are the sensitivities of different populations of individuals to each hazard?
f. How do exposures interact with exposures to other hazards?
g. What are the qualities of the hazard?
h. What is the total population risk, taking into account all of the above questions?

2. In the 1994 NRC report, "Science & Judgment in Risk Assessment", risk assessment is defined (from a human health perspective) as "the evaluation of scientific information on the hazardous properties of environmental agents and on the extent of human exposure to those agents. The product of the evaluation is a statement regarding the probability that populations so exposed will be harmed, and to what degree." Note that the NRC described RA as being either qualitative or quantitative, and the probability of harm could be expressed either qualitatively or quantitatively.
   a. The 1994 NRC report was a further explication of concepts engendered through an examination of case studies in the 1983 NRC report, "Risk Assessment in the Federal Government: Managing the Process."
   b. The NRC boiled RA down to **four essential analytical steps** applied to a scenario involving release (emission) of a toxicant from a source, transport in environmental media to organisms (thus, creating exposure and consequently a dose), and the hierarchy of responses.

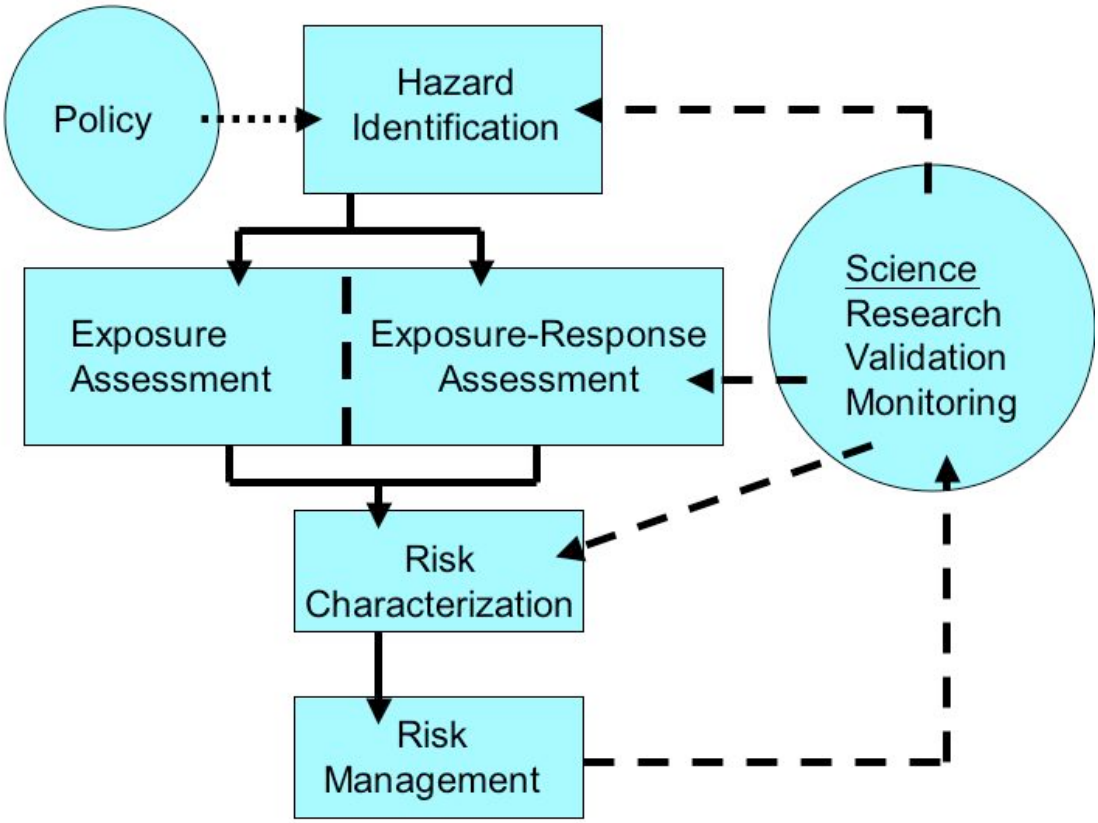


1. Hazard Identification
   a. Identification of contaminants suspected of causing adverse effects;
   b. Quantification of the concentrations at which they are present in the environment;
      1. **Note**: In this class (ES/RP 531), we will consider environmental residue concentrations as part of exposure assessment, especially considering that there are a plethora of factors important to modifying, attenuating, and reducing the bioavailability of these residues.
   c. Description of the specific forms of toxicity (e.g., neurotoxicity, cancer, endocrine disruption, etc.) that can be cuased by the contaminants of concern, and an evaluation of the conditions under which these forms of toxicity might be expressed in exposed organisms.
   d. Information for hazard identification is mostly obtained from experimental studies and to a lesser extent epidemiological research (for human health assessments).
2. Dose-Response Assessment
   a. An evaluation of the conditions under which the toxic properties of a chemical might be manifested in exposed organisms;
   b. Elucidation of the quantitative relationship between the dose and the toxic response;
   c. Assessment of variations in response, for ex., differences in susceptibility between young and old organisms; also, quantification of the differences in response from acute and chronic exposures with respect to dose;
   d. **Note** that this step relies on both empirical observation as well as on mathematical modeling.
3. Exposure Assessment
   a. Specification of the population that might be exposed to the xenobiotic;
   b. Identification of the routes by which exposure can occur;
   c. Estimating the timing of the magnitude, duration, and timing of the doses that an organism might receive as a result of its exposure.
4. Risk Characterization
   a. Integration of information from steps 1-3 to develo9p a qualitative or quantitative estimate of the likelihood that any of the hazards associated with the agent of concern will be realized in exposed organisms;
   b. Expression of risk assessment results;
   c. Discussion of the uncertainties associated with the estimates of risk.

3. In 1993, the NRC issued the summary report of a workshop that considered whether the original 1983 paradigm for risk assessment (which was human

centric) was applicable to ecological risk assessment ("Issues in Risk Assessment", National Academy Press, 1993).

a. For the most part, the workshop participants found the paradigm applicable with several exceptions. The following diagram illustrates how ecological risk assessment as a process would work.
    1. Note that an important point is the risk characterization flows into risk management
        a. In my opinion, part of the risk characterization process is risk management, because the policies dictate what kinds of benchmarks are used to determine the magnitude of risk;
        b. However, under the ecological risk assessment paradigm, risk management decisions are subject to further scientific testing that can feed back into the risk assessment.




An Ecological Risk Assessment Paradigm

## IV. Risk Management

A. Today much activity in risk assessment stems from regulatory requirements, i.e, statutory law that is then interpreted into policy and regulations by various agencies at all levels of government.
    1. The "risk assessors" range from industry scientists to university faculty to consulting scientists to government-employed scientists.
    2. Regardless of who is doing the assessing, the purpose is to develop information that is used to manage the risk.

B. Although sometimes confused with risk assessment, risk management is a separate activity, implemented voluntarily or more often by regulatory fiat.
   1. Risk management has been defined simply as "a term used to describe processes surrounding choices about risky alternatives. In common usage, assessments of the risks and benefits of various options are seen as technical activities that yield information for decision makers, whose decisions are called risk management decisions" (NRC 1989).
      a. Under the NRC (1989) report perspective, risk management entails risk control assessment, which is the activity of characterizing alternative interventions to reduce or eliminate hazard. Response are sought to the following questions:
         1. What are the alternatives that would prevent the hazard in question?
         2. What are the risks of alternative actions and of a decision not to act?
         3. What is the effectiveness of each alternative
         4. What are the costs of each alternative?
      b. Note that under the NRC (1989) paradigm about risk management, risk communication falls under management.
         1. Risk communication can be defined as "an interactive process of exchange of information and opinion among individuals, goups, and institutions, It involves multiple messages about the nature of risk and other messages, not strictly about risk, that express concerns, opinions, or reactions to risk messages or to legal and institutional arrangements for risk management."
            a. "Risk communication is successful only to the extent that it raises the level of understanding of relevant issues or actions and satisfies those involved that they are adequately informed within the limits of available knowledge."
      c. The bottom line for the study of environmental toxicology from a social perspective is that the greatest and most detailed risk assessment report represents only part of the process for protecting sensitive populations and environments. Decisions must be made on how to implement risk reduction measures, and perhaps more importantly, the process and decisions must be communicated to the public in a transparent manner.
      d. Note that risk assessment can be an exercise that helps an agency <u>develop priorities for management and regulation (i.e., strategic planning and priority setting)</u>. In other words, it is not just a tool or exercise for implementing regulatory requirements.

## V. Manifestations of Risk Management—Statutory Laws

A. What we know today about environmental chemistry and toxicology of contaminants has been pushed forward by specific statutory Federal Laws that have evolved over the years. These laws in essence proscribe chemical use and set environmental criteria for protection of human and ecological health

B. The oldest laws regulating chemicals are those pertaining to pesticides, namely the Federal Insecticide Fungicide and Rodenticide Act (FIFRA, originally passed in 1947; evolved from the Insecticide Act of 1910) and the Federal Food, Drug,

and Cosmetic Act (FFDCA, originally passed in 1938; evolved from the Pure Drug & Food Act)

1. The 1972 amendment to FIFRA, known as FEPCA (Federal Environmental Pesticide Control Act), for the first time focused the pesticide registration decision making process to consider as a standard the reasonable certainty of no harm to the environment.
2. As a result of FEPCA, the need for ecological risk assessment gained importance.
3. Risk assessment of pesticides, and therefore environmental toxicological studies, has probably received more attention (as well as development of science policy related to ecological risk) then any other type of chemical technology or contamination.

C. Two laws regulate contaminants in water, the Safe Drinking Water Act (SDWA, recently amended, 1996), which pertains to potable water supplies, and the Clean Water Act (CWA, amended about two years ago), which affects navigable waters (i.e., not potable waters, but water used for fishing, swimming, navigation, etc.)

D. The Toxic Substances Control Act (TSCA) pertains to all chemical manufacturing (originally passed in 1976)

1. Section 5 provision of TSCA mandates that any manufacture of a new substance or any manufacture or process of a substance for a significant new use requires notification of the EPA at least 90 days prior to manufacture or processing;
   a. Data must be submitted to show that manufacture, processing, distribution in commerce, use, and disposal of the chemical substance or any combination of such activities will not present an unreasonable risk of injury to health or the environment.
2. Section 8 of TSCA mandates submission of lists of health and safety studies; a manufacturer must submit any information about the substance to the EPA that indicates a substantial risk of injury to health or the environment

E. Clean Air Act (amended 1990)

1. The original passage of the Clean Air Act in 1963 and amendments that followed addressed deteriorating air quality from all perspectives: particulates, gaseous emissions, and hazardous substances
2. The 1990 amendments were the most stringent; specific standards were set for nearly 200 “air toxics” with the goal of substantial emission reductions

F. Under the provisions of the Emergency Planning and Community Right to Know Act (EPCRA), the Toxics Release Inventory (TRI) requires businesses to report an inventory of chemical releases (only certain chemicals are listed as reportable); however, the TRI allows the creation of an emission database that serves to not only track potentially hazardous substances released into the environment, but also to monitor changes over the years in compliance and pollution prevention.

G. The Superfund (SARA) program, designed to clean up priority hazardous waste sites has provisions for doing human and environmental risk assessment.

## VI. Standards as Risk Management

A. The various regulations, especially regarding pesticides under the mandate of FIFRA as well as other contaminants in addition to pesticides under the Clean Water Act, the Safe Drinking Water Act, and the Clean Air Act often work by promulgating standards that are to either be met or not exceeded.

B. Two types of standards
   1. Narrative: goal or objective desired to achieve
      a. For example,
         1. "Do Not Drift" statement on pesticide product labels;
         2. Do not degrade a potential ground water resource so it is not potable at some future date.
   2. Numerical: a specific target concentration not to be exceeded
      a. Numerical standards usually rely on Margins of Safety, which are uncertainty factors applied to toxicological endpoints to ensure a reasonable certainty of no harm.
      b. For example;
         1. Maximum Contaminant Levels (MCL)
         2. Pesticide Tolerances
         3. Reference Doses

C. One of the objectives of environmental toxicology studies, especially the studies involved in hazard identification and dose-response assessment is to develop toxicological endpoints that become the basis for standard setting.
   1. Using the dose-response studies, the most sensitive endpoint can be deduced, and the dose or concentration not causing any effect (known as the NOAEL, No Observable Adverse Effect Level) can be empirically determined or modeled.
   2. The margin of safety is then applied to the NOAEL to derive the standard.