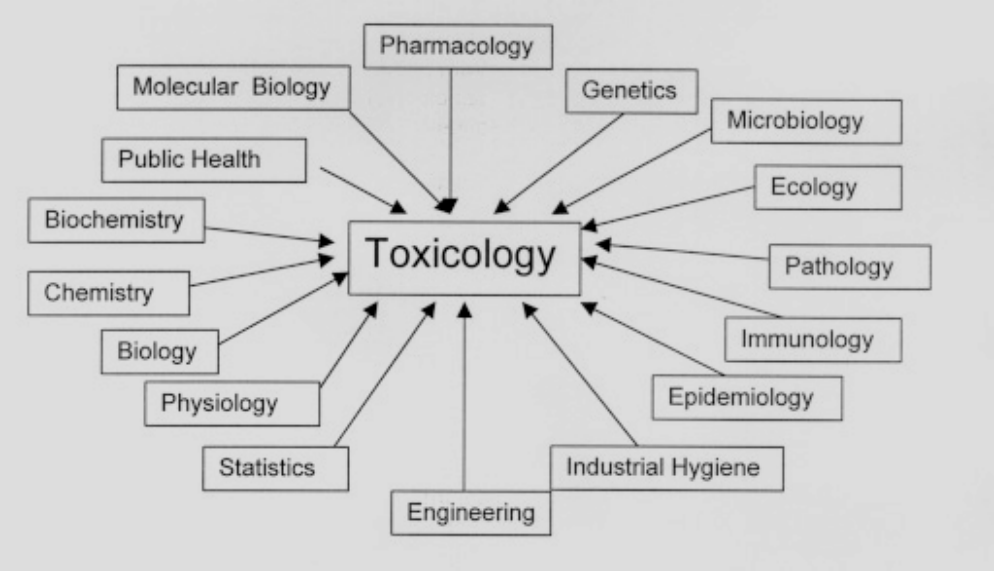
August 25, 2003

Lecture 1: Introduction to Environmental Toxicology; History; Overview of Concepts

I. Environmental Toxicology vs. Toxicology

A. Toxicology is popularly known as the "science of poisons", but such a simplistic definition defies what toxicology has evolved into today.

1. In the classic 1975 text, "The Science of Poisons" by L. J. Casarett and J. Doull, the authors started by posing the question "What Is Toxicology", and concluded that there was no simple answer.
2. Toxicology has evolved from a diversity of fields, and definitions often reflect the area of study from which the definition originates.
   a. In other words, pharmacologists, chemists, and ecologist might be interested in the principles of toxicology as applied to their particular area of interest, but they might define toxicology from their perspective.
   b. The following graphic illustrates that toxicology itself relies on the principles and practices of all disciplines; thus it can best be described as a multidisciplinary study of the nature of adverse effects associated with exposure to natural and synthetic chemicals.



   1. Note that adverse effects, exposure, and all chemicals are key elements
   2. Toxicology is not limited to just defining the magnitude of toxicity of synthetic compounds, like drugs or classical poisons, but it seeks also to predict health (human or environmental) effects (Casarett and Doull 1975).
3. In volume 1 of the second edition of the three volume tome, "General and Applied Toxicology (edited by B. Ballantyne, T. Marrs, and T. Syversen; published by Grove's Dictionaries, Inc., NY in 1999), toxicology was defined as:
   a. "Toxicology is a study of the interaction between chemicals and biological systems in order to quantitatively determine the potential for chemical(s)

to produce injury which results in adverse effects in living organisms, and to investigate the nature, incidence, mechanism of production, factors influencing their development, and reversibility of such effects". (p. 4)

b. The key issues in toxicology include:
    1. The potential to cause injury is predicated on chemicals and/or their conversion products to come into close structural and/or functional contact with tissues(s) or organ(s).
    2. The observed toxicity should be related quantitatively to the degree of exposure to the chemical.
        a. The influence of differing exposure doses on the magnitude and/or incidence of the toxic effects should be investigated.
        b. Dose-response relationships are of prime importance in confirming a causal relationship between chemical exposure and toxic effect, in assessing relevance of the observed toxicity to practical exposure conditions, and to allow hazard evaluations and risk assessment.
        c. The primary aim of most toxicology studies is to determine the potential for harmful effects in the intact living organism.
            1. Results with non-human organisms, for example rodents or wildlife, have a tendency to always be extrapolated to humans.
        d. Toxicological investigations ideally allow evaluation of the following characteristics of toxicity;
            1. The basic structural, functional, or biochemical injury produced;
            2. Dose response relationships;
            3. The mechanisms of toxicity (a.k.a. mode of action)
                (a) Defined as the fundamental chemical and biological interactions and resultant aberrations that are responsible for the genesis and longevity of the toxic response;
            4. Factors that influence toxic response, including:
                (a) Route of exposure
                (b) Species
                (c) Sex
                (d) Formulation of test chemical
                (e) Environmental (or ambient) conditions
            5. Development of approaches for recognition of specific toxic responses (i.e., diagnosis of symptomology)
            6. The reversibility of effects, either spontaneously or with antidotal treatment

B. Toxicology is considered a comparatively recent science, but over the last 30 years it has greatly developed and expanded in its scope. The reasons listed by Ballantyne et al. 1999 include:
    1. Exponential increase in the number of synthetically produced industrial chemicals
    2. Major increase in the number and nature of new drugs, pharmaceutical preparation, tissue-implantable materials and medical devices;

3. Increase in the numbe rand types of pesticides and other substances used in agriculture and the food industry;
4. Mandatory testing and regulation of chemicals used commercially, domestically and medically;
5. Enhanced public awareness of ptential adverse effects from xenobiotics (i.e., non-naturally occurring substances) to man, animals and the environment;
6. Litigation, princiapply as a consequence of occupational-related illness, unrecognized or poorly documented product safety concerns (including drugs) and environmental harm.

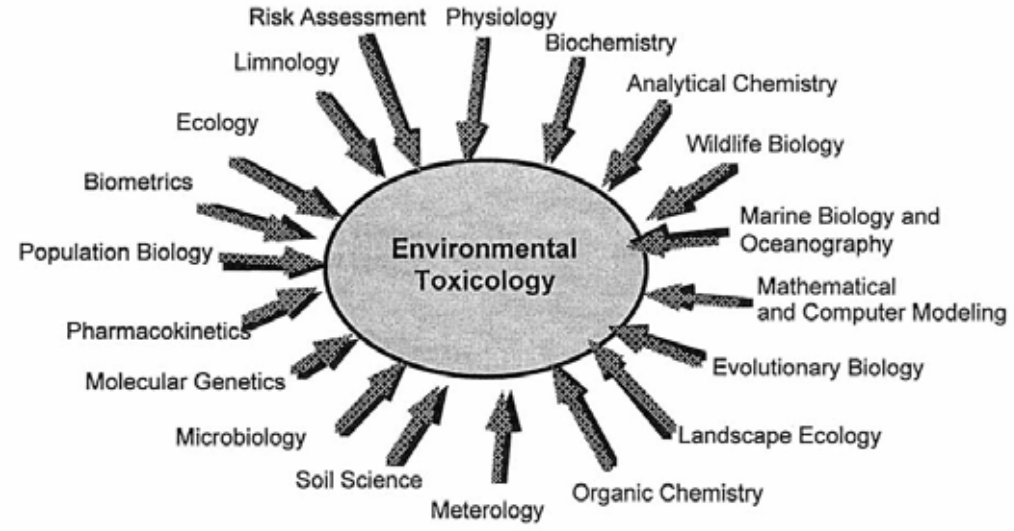
C. Environmental Toxicology itself is one of many subspecialties of toxicology
   1. The subspecialties are listed by Ballantyne et al (1999):
      a. Clinical
         1. Causation, diagnosis and management of established poisoning in humans
      b. Veterinary
         1. Causation, diagnosis and management of established poisoning in domestic and wild animals
      c. Forensic
         1. Establishing the cause of death or intoxication in humans, by analytical procedures, and with particular reference to legal processes
      d. Occupational
         1. Assessing the potential of adverse effects from chemicals in the occupational environment and the recommendation of appropriate protective and precautionary measures
      e. Pharmacological
         1. Assessing the toxicity of therapleutic agents
      f. Toxinology
         1. Assessing the toxicity of substances of plant and animal origin and produced by pathogenic bacteria
         2. The study of naturally occurring toxins in food usually fall under the rubric of “food toxicology”
      g. Regulatory
         1. Administrative function concerned with the development and interpretations of mandatory toxicology testing programs, and with particular reference to controlling the use, distribution, handling and availability of chemicals used commercially, domestically, and therapeutically
      h. Laboratory
         1. Design and conduct of *in vivo* and *in vitro* toxicology testing programs
      i. Environmental
         1. Assessing the effects of toxic pollutants, usually at low concentrations, released from commercial and domestic sites into their immediate environment and subsequently widely distributed by air and water currents and by diffusion through soil
         2. Although environmental toxicology uses the principles of toxicology common to all subspecialties, the term toxicology often refers

specifically to mammalian toxicology and is often oriented toward human safety issues.

3. Environmental toxicology could also be applicable to human safety issues, but often its focus is on environmental effects.
   a. Environmental effects include the effects on organisms inhabiting terrestrial and aquatic habitats.
4. In addition to effects on individuals (the main focus of mammalian toxicology), environmental toxicology has an objective of focusing on higher levels of ecological organization;
   a. Individual→Population→Community→Ecosystem

D. Tools of Toxicology
   1. As previously mentioned, toxicology is an extraordinary interdisciplinary study; however, to properly assess the toxicity of compounds, and extend this knowledge in conjunction with information about exposure to hazards and risk, requires a background in analytical chemistry inorganic chemistry, physical chemistry, organic chemistry, and biochemistry.
      a. Biochemical toxicology focuses on adverse reactions (or effects) at the molecular and cellular levels, and thus determines the cascade of events that is initiated by exposure to a toxicant leading to a toxic end point (Hodgson and Smart 2001; Introduction to Biochemical Toxicology, John Wiley & Sons, p. 1).
   2. Within the context of environmental toxicology, ecological toxicology (which is often contracted to ecotoxicology) is at the other end of the spectrum of toxicology "tools" in that ecological principles are used to interpret adverse effects at levels of organization higher than the organism.

E. Environmental toxicology, like all subspecialties of toxicology, relies on the tools of chemistry and biochemistry, but in addition, it requires functional inputs from a diversity of other disciplines as shown in the following graphic (Landis and Yu, 1999, Introduction to Environmental Toxicology, p. 2) :



II. Historical Roots of Toxicology (source: Casarett and Doull 1975, Toxicology: The Basic Science of Poisons)

A. Prehistoric "culture" hypothesized to be familiar with toxic effects of animal venoms and poisonous plants

B. The Ebers papyrus, probably the earliest written medical document, dates to 1500 BC contains recipes containing recognized poisons

C. Hippocrates, circa 400 BC wrote about controlling absorption of toxic materials in therapy and consequences of over dosing

D. The mythology and classic Greek (and later Roman) history contains many references to poisonous plants
   1. Theophrastus (370 – 286 BC) included numerous references to poisonous plants in *De Historia Plantarum*
   2. Dioscorides (Greek physician in court of Roman emperor Nero, circa 50 AD) attempted classification of poisons with description and drawings
   3. Evidence for concerns about antidotes to poisons ("protective mixtures") during Roman times
   4. Many poisons were extracts from plants, but metals, e.g., arsenic, were also used as poisons.

E. During the Middle Ages, purposeful poisoning became common as a political weapon, especially in Italy
   1. However, social poisoning, for example, knocking off a husband or someone wealthy to gain inheritance was also known
   2. "Experimental" toxicology may have been born in the activities of Catherine de Medici in France.
      a. Cahterine used direct evidence to arrive at the most effective compounds. She tested concoctions under the guise of delivering palliatives to the sick and poor.
         1. Noted rapidity of toxic response ("onset of action")
         2. Noted the effectiveness of a compound ("potency")
         3. Noted the degree of response of specific parts of body ("specificity"; "site of action")
         4. Noted the complaints of the victim ("clinical signs and symptoms")

F. The recognized creator of the scientific discipline of toxicology was Paracelsus (Philippus Aureolus Thiophrastus Bombastus von Hohenheim, 1493-1541), who lived in the late Middle Ages. Three important concepts are attributed to Parcelsus:
   1. The "toxicon" or toxic agent is a chemical entity
      a. This concept persists today in the study of the relationship between chemical structure and toxicity (aka quantitative structure activity relationships or QSAR).
      b. Articulation of the concept that response to a substance is related to dose (dose-response relationship). The corollaries of this concept are:
         1. Experimentation is essential in examining responses to chemicals;
         2. A distinction must be made between therapeutic and toxic properties of chemicals;

3. therapeutic and toxic properties are sometimes but not always indistinguishable except by dose;
4. There is a degree of specificity of chemicals and their therapeutic or toxic effects.

c. Toxicology covers a wide area;
1. Paracelsus' interests extended from detection of accidental or intentional poisonings through a gamut of environmental factors affecting populations and occupational diseases.

G. The recognized father (or founder) of modern toxicology is Matthieu Joseph Bonaventura Orfila (1787-1853).
1. Orfila was a Spanish physician who attended the medial needs of Louis XVIII and was a faculty member of the University of Paris.
2. He was the first to attempt a systematic correlation between the chemical and biological information of known poisons.
3. He studied the effects of poisons in several thousand dogs.
4. He singled out toxicology as a discipline distinct from others.
5. He published the treatise, "Traitie Des Poisons; ou Toxicologie Generale" in 1814.
6. Orfila pointed out the necessity of chemical analysis for legal proof of lethal intoxication and he devised methods for detection poisons. Thus, Orfila developed an analytical approach that has become the basis of forensic toxicology.

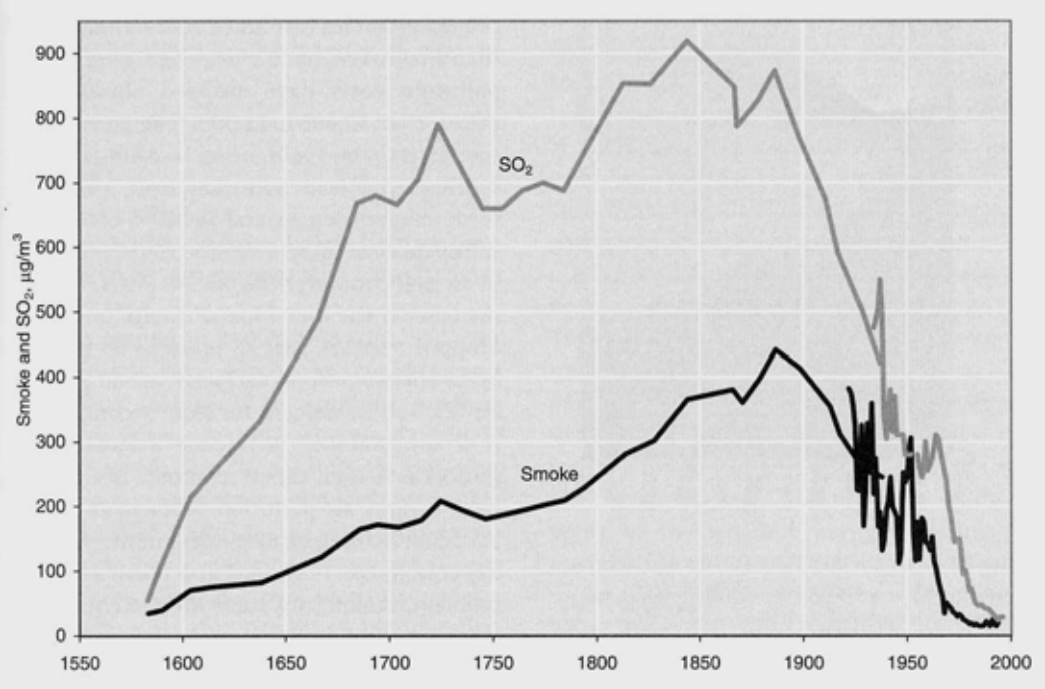
H. Claude Bernard (1813-1878) studied arrow poisons used by natives in undeveloped countries.
1. He studied the mechanism of action of curare;
2. As a result of his studies, he realized that "the physiological analysis of organic systems…can be done with the aid of toxic agents."
a. He noted that carbon monoxide bound to hemoglobin.

I. Paul Muller discovered and studied the insecticidal properties of DDT (a compound that had been synthesized with unknown properties in the late 1800's).
1. Muller was recognized in 1949 with the Nobel prize for discovering the insecticidal properties of DDT.
a. DDT was used extensively during WWII for control of insect vectored diseases, such as louse borne epidemic typhus, and thus was credited with saving millions of lives.
2. Although Muller is not credited with development of any general toxicological principals, his discovery of the insecticidal properties of DDT is ironically the forerunner of what would become the discipline of environmental toxicology.
a. However, the rudiments of the merging of environmental aspects of biology and toxicology can be seen much earlier than the mid 20th century.

III. Historical Roots of Environmental Toxicology

A. Concern over environmental contaminants and effects on wildlife and human health is popularly attributed to the publication of Rachel Carson's Silent Spring in 1962.

1. However, impacts on human health from environmental contamination dates to hundreds of years previously with concerns over pollution in Rome and England (references cited in Lomborg 2001 on page 163).
   a. For example, the politician Seneca in ancient Rome complained about the "the stink, soot and heavy air" in the city.
   b. King Edward I established the world's first air pollution commission in 1284 and 22 years later banned coal burning (not successful).
   c. During the 1300's, attempts were made to avoid throwing refuse in the Thames River of England and avoiding the foul smell (not successful).
   d. Overall, London prior to the 20th century was heaped with refuse, excrement, and smoke.
   e. London had a reputation for centuries as having a thick smog.
      1. An estimated 4000 people died in London during a severe smog of December 1952.
   f. Not until air pollution laws were passed after the 1950's did London's air show improvement, illustrating that one type of pollution was worse from an historical perspective than consumers commonly think it is today. (Graph from p. 165 in Lomborg 2001).



B. Although air pollution (and water pollution, largely owing to fecal waste and refuse) were historically very bad, environmental toxicology only developed after the publication of Silent Spring.
   1. The focus of Silent Spring was on pesticides, most notably DDT.
   2. Rachel Carson essentially hypothesized that avian (and other wildlife) population losses were unacceptably high, leading to the metaphor of a Silent Spring.
      1. Furthermore, human health was threatened from DDT by an impending cancer epidemic.

3. While Carson's hypotheses were arguable in their day, evidence that her perspective had come true on a scale greater than the level of thee individual was weak.
   a. One possible exception, again highly arguable, were declines in certain raptorial species. This topic will be discussed near the end of the course under the aegis of ecoepidemiology (the application of chemical epidemiological studies to wildlife populations).
4. As revered as Rachel Carson was and remains today, her ideas were only assembled after reading an already burgeoning literature that could today be described as studies in environmental toxicology.
   a. The evidence for the source of Carson's knowledge can be viewed by examining the bibliographic citations in the back of her book.
   b. For example, consider these papers published years before Silent Spring and cited by Carson. All represent early themes that continue to occupy modern environmental toxicology.
      1. Case, R. A. M. 1945. Toxic effects of DDT in man. British Medical Journal 2:842l-845.
      2. Pielow, D. P. 1946. Lethal effects of DDT on young fish. Nature 158:378.
      3. Fitzhugh, O. G., and A. A. Nelson. 1947. The chronic oral toxicity of DDT (2,2-bis p-chlorophenyl-1,1,1-trichloroethane). J. Pharmacology and Experimental Therapeutics 89(1):18-30.
      4. Smith, r. F. et al. 1948. Secretion of DDT in milk of dairy cows fed low residue alfalfa. J. Econ. Entom. 41:759-763.
      5. Kostoff, D. 1949. Induction of cytogenic changes and atypical growth by hexachlorocyclohexane. Science 109:467-468.
      6. Cullinan, F. P. 1949. Some new insecticides—their effect on plants and soils. J. Econ. Entomol. 42:387-391.
      7. Young, L. A., and H. P. Nicholson. 1951. Stream pollution resulting from the use of organic insecticides. Progressive Fish culturist 13(4):193-198.
      8. Editorial. 1951. Insecticide storage in adipose tissue. J. American Medical Association 145:735-736.
      9. Laug, E. P. et al. 1951. Occurrence of DDT in human fat and milk. A. M. A. Archives Industrial Hygiene and Occupational Medicine 3:245-246.
      10. Ginsburg, J. M., and J. P. Reed. 1954. A survey on DDT accumulation in soils in relation to different crops. J. Econ. Entomol. 47(3):467-473.
      11. Walker, K. et al. 1954. Pesticide residues in foods. Dichlorodiphenyltrichloroethane and dichlorodiphenydichloroethylene content of prepared meals. J. Agric. and Food Chem. 2(20):1034-1037.
      12. Genelly, R. E., and R. L. Rudd. 1956. Effects of DDT, toxaphene, and dieldrin on pheasant reproduction. Auk 73:529-259.
      13. DeWitt, J. B. 1956. Chronic toxicity to quail and pheasants of some chlorinated insecticides. J. Agric. Food Chem. 4(10:863.

14. Ide, F. P. 1957. Effect of forest spraying with DDT on aquatic insects of salmon streams. Trans. American Fisheries Society 86:208-219.
15. Barker, R. J. 1958. Notes on some ecological effects of DDT sprayed on elms. J. Wildlife Management 22(3):269-274.
16. Harrington, R. W., and W. L. Bidlingmayer. 1958. Effects of dieldrin on fishes and invertebrates of a salt marsh. J. Wildlife Management 22:76-82.
17. Alderdice, D. F., and M. E. Worthington. 1959. Toxicity of a DDT forest spray to young salmon. Canadian Fish Culturist 24:41-l48.
18. Scott, T. G. et al. 1959. Some effects of a field application of dieldrin on wildlife. J. Wildlife Management 23:409-427.

c. The selection of papers cited by Carson also show that the common perception that chemical technologies were not studied very much was not true.
    1. DDT was released for commercial use after WWII, but studies had been conducted on rudimentary safety to humans. After release studies oriented on "environmental effects" began to be published, but these came out within 5 – 10 years, not 20 years later as some have argued.

C. The theme of Silent Spring gave impetus to the development of modern environmental toxicology, but the studies on DDT and other chlorinated hydrocarbon insecticides may have evolved from the conduct of even earlier studies and a need to answer questions about the interaction of chemicals in the environment and organisms.
    1. In the mid-1980's I hypothesized that environmental toxicology may have evolved from a discipline known as insect toxicology that originated in the early 1900's as a result of the need to know how pesticide worked to achieve maximum efficacy.
        a. To test this hypothesis I examined all issues of the Journal of Economic Entomology (JEE), the flagship journal for publication of entomological findings as well as studies related to insect control technology.
            1. As shown in the bibliographic list above, JEE was cited numerous times by Carson
        b. The first issue of JEE was published in 1908. I noted a number of papers published since 1908 had themes that are consistent with the objectives of modern environmental toxicology (Felsot, A. S. 1985. Early contributions of insect toxicology to the evolution of environmental toxicology). These themes were delineated as follows:
            1. Measurement of toxicity
            2. Symptomology, Mode of Action, and Metabolism
            3. Insecticide Resistance
            4. Pesticide Selectivity and Comparative Toxicology
            5. Insecticide Residues and Development of Analytical Methods
            6. Hazard Evaluation
            7. Environmental Chemodynamics

c. The sensitivity of entomologists to the potential nontarget effects of insecticides, as well as disruptions to predators and parasitoids, was aptly expressed by Harold Sheppard, an early insect toxicologist.
    1. Writing in the introduction to his 1939 book "The Chemistry and Toxicology of Insecticides", Sheppard stated the following:
        a. "Chemical control has the advantage that it brings prompt relief from the depredations of insects. On the other hand it is frequently only a palliative and should be accompanied by steps taken to eliminate the sources of infestation. The relation of permanent measures to the economy of other forms of natural life, however, needs full consideration. This was shown recently in the conflicting methods required for mosquito control and for wild gave conservation."

D. Besides the Journal of Economic Entomology, early outlets for publication of studies in environmental toxicology (prior to coining the terminology for this branch of toxicology) included:
    1. Journal of Agricultural and Food Chemistry (first issue 1953)
    2. Environmental Science and Technology (first issue 1967)
    3. Pesticide Monitoring Journal (first issue 1967; publication stopped 1980)
    4. Pesticide Science (first issue 1970) (now called Pest Management Science)
E. By the 1970's, the first journal suggesting environmental toxicology was born as the Bulletin of Environmental Contamination and Toxicology.
F. No doubt that the major factor influencing the evolution of environmental toxicology were the problems associated with pesticide use.
    1. The EPA was born in 1970 under the hand of the Nixon administration.
    2. In 1972, the statutory law regulating pesticides was amended to consider a new standard of a reasonable certainty of no harm to the environment.
    3. Other laws of the time, mainly the Federal Water Pollution Control Act caused us to pay more attention to issues of water pollution that could not only effect humans but also fish and wildlife.
G. By 1979, the Society of Environmental Toxicology and Chemistry (SETAC) was chartered, and the first issue of its flagship journal, Environmental Toxicology and Chemistry was published. SETAC remains the main professional scientific society focusing on all aspect of environmental toxicology.

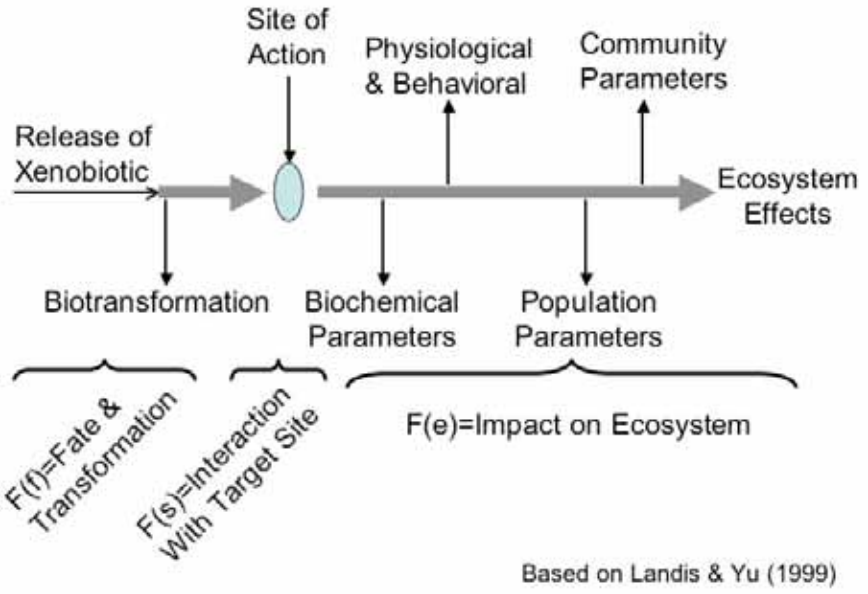
IV. Overview of Main Concepts in Environmental Toxicology

A. According to Landis and Yu, environmental toxicology can be simplified as three functions, and these functions would satisfy the goal of environmental toxicology—prediction of environmental/health impacts. (Note that the term function here is used in the mathematical sense as the relationship of a set of independent variables with a set of dependent variables, and the function is the rule that describes this relationship.)
    1. Interaction of a contaminant or xenobiotic (introduced or otherwise) with the environment
        a. This interaction controls exposure, which is a prerequisite for a dose received by an organism.

2. Interaction of the xenobiotic with its site of action within the organism
   a. Think of the site of action as a biochemical receptor (often a protein), whether it be an enzyme or a hormone receptor or a specific space on the cell membrane.
3. Impact of the molecular interactions at site of action upon the function of the ecosystem.
   a. The interaction of the xenobiotic with the biochemical receptor causes a cascade of events at the molecular scale that translates to effects at increasingly higher levels of biological organization.

B. If a mathematical function could be written that accurately describes how one function interacts with another and influences or transfers its effect to higher levels, then hypothetically one could predict effects in the environment.

C. The main parameters within each hierarchy of organization that must be studied are shown in the following diagram and selected examples are given below:



1. Selected Biotransformation Parameters:
   a. Enzyme induction
   b. Glutathione S Transferases
   c. Mixed function oxidases
   d. Hydrolases
   e. DNA Repair Enzymes
2. Selected Site of Action Parameters
   a. DNA & RNA interactions
   b. Membrane receptors
   c. Key enzymes
   d. Biochemical integrity
3. Selected Biochemical Parameters Indicating Effects
   a. Stress proteins
   b. Metabolic indicators
   c. Enzyme inhibition

   d. Adenylate energy change
   e. Metallothionen production
   f. Immunological suppression
4. Selected Physiological and Behavioral Indicators of Effect
   a. Chromosomal damage
   b. Lesions and necrosis
   c. Tumors and teratogenesis
   d. Reproductive success
   e. Behavioral alterations
   f. Mortality
   g. Compensatory behaviors
5. Selected Population Parameters
   a. Population density
   b. Productivity
   c. Mating success
   d. Alterations in genetic stsructure
   e. Competitive alternations
6. Selected Community Parameters
   a. Structure
   b. Diversity
   c. Energy transfer efficiency
   d. Stability
   e. Successional state
   f. Chemical parameters

D. As shown in the diagram, the three functions are depicted somewhat linearly;
   1. In other words, once the xenobiotic is taken up, then a linear progression of event occurs stemming from the molecular/genetic level through progressively higher levels, with the xenobiotic effects culminating in some ecosystem level effect.

E. Landis and coworkers have argued that the traditional view of an ecosystem in equilibrium that is perturbed by a stressor (or xenobiotic) and that then regains its original state when the stressor is removed or alleviated is far from the reality of ecosystem functioning.
   1. While the effect of a xenobiotic must first be understand at the molecular/genetic level (i.e., organismal level), the ecosystem itself has non-organismal properties the confer a historical "memory" that interacts (provides feedback) on the organisms. In other words, "ecological communities retain information about events in their history." This hypothesis has been called the community conditioning hypothesis (Matthews, R. A., W. G. Landis, and G. B. Matthews. 1996. The community conditiong hypothesis and its application ot environmental toxicology. Environ. Toxicol. Chem. 15(4):597-603. & Landis, W. G., R. A. Matthews, and G. B Matthews. 1996. The layered and historical nature of ecological systems and the risk assessment of pesticides. Environ. Toxicol. Chem. 15(4):432-440.)
      a. An example of this ecological history affecting the organisms and thus the ecosystem is the evolution of resistant organisms due to artificial selection with the xenobiotic. The functioning of the ecosystem in effect contains

the history of prior exposures to the xenobiotic and is manifested in a growing population of organisms resistant to the effects of any further xenobiotic insult.

b. The evidence for the historical "memory" of the ecosystem is seen in microcosm studies ("artificial mini-ecosystem simulators") wherein the trajectory of effects in the microcosm are unpredictable even long after the xenobiotic has dissipated.
    1. In other words, the structure of the microcosm (which simulates an ecosystem) does not return to some ideal pre-exposure state long after the xenobiotic has dissipated. Rather the structure (or other measurable parameters) continues along a trajectory of change or to a new state that is as much influenced by the history of the ecosystem as by the response of the organisms within the ecosystem.

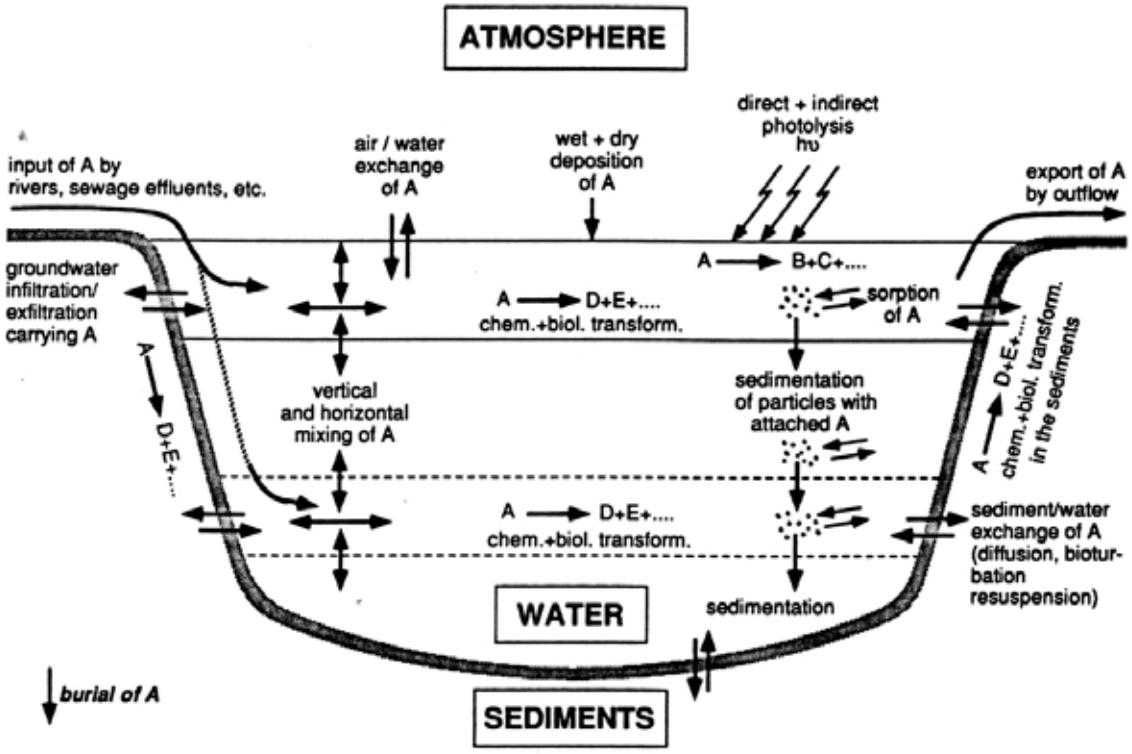
c. Although Landis et al. argue that ecological risk assessment would benefit by considering the community conditioning hypothesis, in practice any risk assessment would not proceed if it waited for a full understanding of community level or higher effects, mainly because our understanding of the historical "memory" in the ecosystem is poorly understand, not to mention that our understanding of what is happening at the organismal level is very far from complete for any one xenobiotic, yet the plethora of them (both natural and synthetic) introduced into the environment all the time.

F. Although we should not expect that a perturbed ecosystem will revert to some ideal equilibrium condition once a xenobiotic has dissipated, given the limitations in resources to measure "everything" and our limited understanding of feedback mechanisms, we are "stuck" with measuring lower levels of organization in order to predict effects and carry out risk assessments for old and new chemical technologies (or any technology for that matter). Thus, within the context of understanding the fundamentals of environmental toxicology so that we can predict higher levels of effect, we have to understand the fundamentals of how xenobiotics function at lower levels of organization, and just as importantly, how the environmental interactions affect organismal exposure, and how exposure is translated to a dose.
    1. Thus, we will focus on the three functions that are needed for effects prediction (which were described above) using a toxicokinetic (pharmacodynamics) and environmental chemodynamic approach. The "dynamic" approach provides a theoretical framework for predicting both the fate and effects of chemicals in the environment.

V. Theoretical Framework for Understanding (Predicting) Fate and Effects of Chemicals in the Environment

A. Complexity of Chemical Behavior in the Environment
    1. To acquire the capability of predicting the fate and effects of environmental contaminants, one must understand literally all possible interactions between the chemical, the environment, and the biota. As shown on the next page for

just an aquatic system, the processes to study are quite numerous (figure from Schwarzenbach et al. 1993).



Processes that determine the distribution, residence time, and sinks of an anthropogenic organic compound in a lake (Schwarzenbach et al. 1993, p. 4).

a. The task, however, has been made somewhat more approachable by a realization of how thermodynamics and kinetics controls chemical fate; thus, a new theoretical paradigm has evolved to help us understand environmental behavior of chemicals.
   1. Note that thermodynamics deals with systems at equilibrium;
      a. The driving force is the free energy state
   2. Note that kinetics deals with the reactivity of the components in a system;
      a. Interested in whether molecules are reactive (i.e., will change their form, usually via environmental degradation or metabolism) and what the rate of change is.

2. With the new paradigm, we can dispel the myth of a difference between natural and synthetic, for all chemicals behave in accordance with the "laws" of thermodynamics (direction and extent of change or reaction); changes in a system or reactions, however, could be fast or slow (kinetics).

B. Our goal is prediction of the potential for adverse effects; risk assessment is the process that allows predictions and can be thought of as the information gathering phase involving direct experimentation or modeling based on tested observations and principles.

1. Predicting of adverse effects partly rests on the toxicological maxim--"Dose Makes the Poison"
   a. Thus, biological effects are dependent on dose and exposure
2. Environmental distribution determines potential for exposure
3. Toxicological studies determine potential effects
4. In summary, risk assessment includes four processes:
   a. Hazard identification (what are the significant toxicological endpoints)
   b. Dose-response characterization (at what dose do the endpoints appear)
   c. Exposure assessment (environmental chemistry)
   d. Risk characterization (probability of hazard occurring under certain set of circumstances; need benchmark or standard of what is acceptable).

C. Environmental Chemodynamics has developed as an interdisciplinary study of the relationship between physicochemical properties and environmental behavior, and has brought us one step closer to adequate predictions of chemical behavior and biological exposure.
   1. A holistic perspective
      a. Viewing the biosphere as compartments with interfaces between all compartments
         1. Exception: sediment at bottom of aquatic system does not interface directly with the atmosphere
      b. The compartments are thought of as phases; knowing the magnitude of each phase would allow a "back-of-the-envelope" calculation of concentrations of contaminants if one knew their total emissions (from Haque and Freed 1974)
         1. air (atmosphere) [5.3×10^{18} kg]
         2. water (lithosphere) [1.3×10^{21} kg]
         3. soil (lithosphere) [to 6 inches = 1.1×10^{17} kg]
         4. biota
         5. plants [1.1×10^{15} kg]
         6. animals [2×10^{13} kg]
   2. Focus areas
      a. Physicochemical properties
         1. vapor pressure
         2. water solubility
      b. Partitioning (phase transfer)
         1. air:water
         2. soil:water
         3. organic solvent:water
         4. organism:environmental phase
      c. Attenuation (reactions: degradation, transformation)
         1. abiotic degradation/transformation
         2. biotic degradation/transformation
      d. Transport (mass transfer)
         1. volatilization
         2. leaching

3. runoff

e. Modeling
   1. deterministic (based on empiricism; i.e., observations)
   2. stochastic (inductive; based on mechanistic understanding and probability)

VI. Toxicodynamics (Pharmacodynamics) & Toxicokinetics (pharmacokinetics)

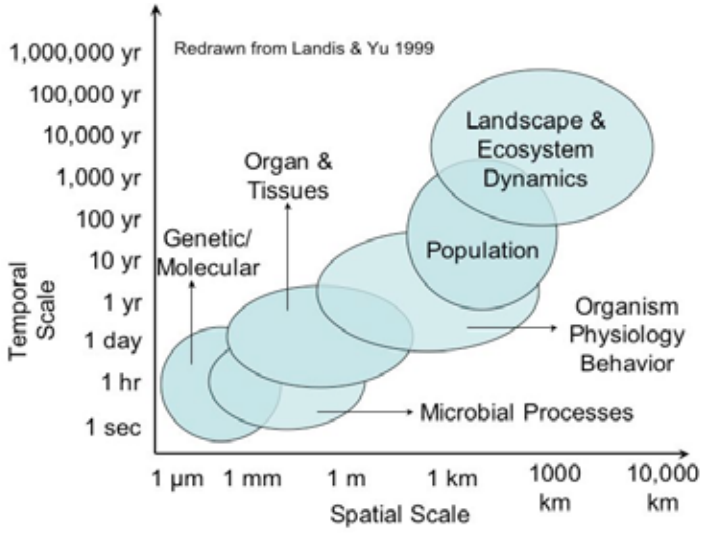
A. Use of bioassays to measure toxicity defines the relationship between dose and response. Thus, we can determine what dose might be safe, but as different chemicals have unique behaviors owing to thermodynamic & kinetic relationships, different species have different susceptibilities to toxicological effects.

B. A theoretical framework is needed to predict toxicity (or at least the likely outcome of an exposure). Toxicodynamics serves in an analogous sense to environmental chemodynamics to help us approach the objective of toxicity prediction or understand the potential biological responses following exposure;
   1. Organisms can be considered interfaced compartments that an absorbed chemical must partition across. In any one compartment (usually considering a cell), transformation reactions occur. Input and output is through the organ system.

C. Important Processes to Consider
   1. Absorption rate/amount
   2. Distribution
   3. Metabolism
   4. Excretion
   5. Target site interactions

VII. The Temporal/Spatial Scale of Effect

A. Effects or environmental impacts, whatever the level of organization (for example, environment-organism partitioning or molecular/genetic interactions) take place over different overlapping temporal and spatial scales.



1. Note that the temporal and spatial scale increase in size as the level of organization being considered increases.
   a. For example, interaction at the genetic and molecular level takes place quickly (thus the scale ranges from about 1 sec or less to about 1 day) and affects single organisms (with the spatial scale accounting for microbes and larger vertebrates).
   b. On the other hand, an impact at an ecosystem or landscape level, may encompass many kilometers of space and take last a long time.
      1. The speed with which a ecosystem level effect takes place may occur quickly if exposure to the xenobiotic is extremely high, but for low level exposures the impact could develop slowly but be long lasting.

B. Any particular xenobiotic release or exposure also has a characteristic temporal and spatial scale over which the effects are manifested.