Humans and other organisms are in a constant struggle to survive in environments that can, for many reasons, be hostile to their well-being. Apart from threats of accidents, disease, and war, people have become increasingly concerned with the effects of our activities on our environment. Whereas at one time, forty or more years ago, the products and activities of the chemical industry were seen as an unmitigated boon, skepticism has increased to the point where "chemical-free" is seen as a positive description by a large fraction of the populace. The story of how "chemicals" came to be seen as generally harmful is beyond the scope of this discussion, but we can examine some known hazards of chemical exposure and try to evaluate them rationally.

A. Human Health

Acute toxicity. Fear of poisons is an age-old phenomenon. The word toxic comes from a Greek word meaning arrow, and soldiers have used arrow and spear poisons since prehistory. Acutely toxic substances are those that cause rapid death, and include such classic poisons as cyanides, arsenic and lead salts, and strychnine.

The 16th-century German physician Paracelsus recognized that poisonous effects depended on dose. He said "no thing is without poison." Therefore, virtually all substances are potentially toxic, and toxicology becomes the science of determining the relative hazard among them.

To establish a toxic effect, an endpoint needs to be chosen. Traditionally that endpoint is death, which is readily determined, at least for macroscopic organisms such as rats or fish. However, even cursory observations reveal that different animals, even individuals of the same species, are not equally susceptible to poisons. Therefore, a statistical approach is required; a number of (usually) vertebrate animals are exposed to various concentrations of the test substance, and the number who succumb are compared to those in a control group. The data are subjected to statistical analysis, and a value for LD$_{50}$ is reported; this is the mean (or median) dose required to kill 50% of the animals under the conditions of the test. The dose could be expressed in various ways, but often the units are milligrams of toxicant per kg of body weight. Extremely toxic substances, such as the pesticides parathion or aldicarb, may have LD$_{50}$s of less than 10 mg/kg, whereas the practically nontoxic compound, ethanol, would exhibit an LD$_{50}$ in the thousands of mg/kg.
Note that measurements of the type described are for deaths produced by a single dose and occurring within a fixed, and relatively short, time. Far more typical of real environmental or dietary poisons is the situation where sublethal doses are repeated over a large fraction of the lifetime of the animal, and death eventually results. Such effects might be considered to fall into a borderline category between acute and chronic (see below) toxicity. For obvious reasons, this kind of experiment is not subject to easy analysis, and is almost never done. Of course, sublethal doses may induce other harmful effects; ethanol, certainly, has obvious physiological effects when ingested at a few hundred mg/kg, and in some individuals repeated exposure to this level could eventually produce lethal conditions.

**Chronic toxicity.** Although many chronic conditions, including arthritis, blindness, emphysema, reproductive disorders, nerve damage, and kidney or liver failure, can include causes that feature exposure to chemicals, the principal fear-inducing chemical substances are now those that "cause cancer." Unfortunately, cancer is not a well-understood illness, and the mechanisms of carcinogenesis are not usually well enough known to permit us to link exposure to a particular chemical or group of chemicals to the development of a carcinoma or other tumor. Typically, the time period between exposure to a carcinogen and the development of cancer is on the order of decades, which is why lung cancer among heavy smokers is a disease of old age.

There are a few (perhaps 30) known human carcinogens, some of which are constituents of the diet of a particular sub-group, and others that have produced rare cancers in a group of factory workers who have long histories of exposure to high concentrations of the chemical. Examples include aflatoxin, a causative agent in liver cancer, found in moldy peanuts and rice, especially important in parts of Africa; formaldehyde, used in the wood and textile industries and associated with nasal and sinus cancer; some aromatic amines (dye-synthesis intermediates), causes of bladder cancer; and some polycyclic hydrocarbons, constituents of smoke and soot, linked to cancers of the skin, scrotum, and lung.

There is a much larger number of carcinogens that have been shown to be active in animal tests. Rats are the most commonly used test animal, followed by mice. Exposures are by variable routes; oral, injection into the peritoneal cavity, or (rarely) by inhalation. Amounts administered are often very high, in order to see statistically significant
differences between treatment and control groups; extrapolation to reasonable environmental levels is then performed (see Section 3).

All such tests are costly and time-consuming. In addition, when effects are small, much uncertainty results; findings may be disputed, or replication studies conducted by others may give opposite results. Furthermore, not all test species are equally responsive to carcinogens of different classes, and, in fact, some agents even give positive responses in one of the two sexes of the test animal. Accordingly, it is often a question of interpretation as to whether a substance that is an animal carcinogen should be classified as a probable human carcinogen. In practice, it is considered prudent to assume that it is.

In addition to carcinogens, compounds that induce the formation of actual cancers in animals, we find mutagens, compounds that induce mutations (changes in genetic material) that can be detected in short-term, usually microbial, bioassays. A large fraction, but not all, carcinogens are mutagens. For those that are not, different mechanisms of action prevent mutations from occurring in one of the test systems. For example, carcinogenic metal ions are not taken up by the microorganisms used in the short-term tests, and therefore cannot cause changes in their DNA. In addition, many classes of compounds are bacterial mutagens that have not, so far, been implicated as animal carcinogens.

Included among nonmutagenic carcinogens are epigenetic agents, those that interfere with other aspects of cellular activity. Peroxisome proliferators, for example, increase cell division by a still-not-fully explained disturbance of oxidative metabolism in liver and kidney cells. Agents such as some herbicides, aspirin, phthalates, and halogenated solvents (chloroform, trichloroethylene e.g.) appear to act by this mechanism. There are two important features of carcinogenesis by this process; first, it is principally a phenomenon of high doses, unlike genotoxicity, which can often be triggered by low levels of a contaminant. Secondly, there is much species variability; mice, rats, and hamsters are susceptible to these chemicals, but guinea pigs and monkeys are not; and the evidence so far points toward a lack of susceptibility in humans, also. These findings have implications for risk assessment and policy-setting which will be examined in Section 3.

Below is a graph that illustrates chronic toxicity. Fish are harmed by turbid waters and increasing turbidity causes an increase in the effect. Death of these animals occurs only after long-term exposure. Brief exposure to turbid water has virtually no effect on the fish death rates.
B. Ecosystem Health

*Ecotoxicology.* The effects of a chemical substance on organisms living in an ecosystem cannot simply be predicted by extrapolating its toxicity to an individual organism that might be part of that ecosystem. In laboratory animal studies, a precise amount of a test chemical can be administered to a target organism; but in nature, not only do concentration gradients of pollutants exist, but much of the pollutant may be distributed to sinks, such as sediment in a lake, where direct exposure to living organisms of concern may not occur (see Section 2). Furthermore, species in nature may have little or no similarity to laboratory test species. The environment contains a constantly changing mix of species with varying ages and degrees of fitness, and with varying susceptibility to xenobiotic chemicals.

Because humans have a tendency to overmanage their environment, removing "pests" whose offenses may be as trivial as being caterpillars that hang from urban trees, large ecosystems have been exposed to toxic chemicals. In