RISK ASSESSMENT BACKGROUND

For most of human history, concern about the toxic effects of chemicals has been focused on poisons which act quickly and result in death. A well known example is hemlock, which was ingested by Socrates to commit suicide. Until recently, exposure to these chemicals was not common and the risks were well known so there was little public concern about these poisons.

In this century, however, people have become increasingly concerned with poisons, including those that cause adverse effects only after long periods of exposure. There are two main reasons for this change. One is that the average human life span has increased tremendously due to cures and treatments for infectious diseases. This longer lifespan has made chronic non-infectious illness more common. The second is that the industrial revolution has led to new and increased uses of known chemicals and the synthesis and widespread use of newly developed compounds. This tremendous increase in both the quantity and variety of chemical use has led to greater awareness of possible health effects of industrial products.

RISK ASSESSMENT

One result of this attention was the establishment of the Environmental Protection Agency in 1970 and the enactment of new legislation during the 1970s to regulate chemicals in the environment. With the passage of these new laws, an important problem was how to evaluate the severity of the threat that each toxic chemical posed under the conditions of use. This evaluation is known as risk assessment, and is based on the capacity of a chemical to cause harm (its toxicity), and the potential for humans to be exposed to that chemical in a particular situation; for example, workplace or home.

Risk assessment was not new in the 1970s. The safety of our food supply has been investigated since early in the 20th century. In addition, scientists in industrial toxicology laboratories had been evaluating the toxic properties of potential products as early as the 1930s. Toxic side effects of drugs had long been of concern and received increased attention in the early 1960s after the discovery that severe birth defects resulted from ingestion of a seemingly safe drug, Thalidomide. During the 1970s risk assessment procedures for all chemicals were reevaluated, improved, and more importantly, formalized. Standardized tests were developed so consistent evaluations could be performed and the scientific basis of regulations could be more easily applied.

During this time of change, the term "risk assessment" took on a variety of meanings. However, its definition is made up of two components: toxicity (dose-response assessment) and exposure assessment. The former is a measure of the extent and type of negative effects associated with a particular level of exposure and the latter is a measure of the extent and duration of exposure to an individual or population. For example, characterizing the risk of a pesticide to applicators requires knowing exactly what dose (amount) of this pesticide causes what effects (dose-response assessment) and what dose workers are exposed to (exposure assessment).

Sometimes, this distinction between an exposure assessment and a dose-response assessment is forgotten and conclusions are drawn without any measures of exposure

having been made. For example, dioxin is often referred to as the most toxic man-made chemical known based on dose-response data and thus, is taken to mean that it poses the greatest risk to society. This is not the case because the potential for exposure is usually very small.

EXPOSURE ASSESSMENT

How can exposure assessment be accomplished? There are three basic approaches: analysis of the source of exposure (i.e., levels in drinking water or workplace air), measurements of the environment (i.e., human blood and urine levels), and laboratory tests; for example, blood or urine of the people thought to be exposed. Analyses of air or water often provide the majority of usable information. These tests reveal the level of contamination in the air or water to which people are exposed. However, they only reflect concentration at the time of testing and generally can not be used to quantify either the type or amount of past contamination. Some estimates of past exposures may be gained from understanding how a chemical moves in the environment.

Some other types of environmental measurements may be helpful in estimating past exposure levels. For example, analyses of fish or lake sediments can provide measures of the amounts of persistent chemicals which are and were present in the water. Past levels of a persistent chemical can be estimated using the age and size of the fish, and information about how rapidly these organisms accumulate the chemical.

Analyses of body fluid levels of possibly exposed people provide the most direct exposure measure. However, they do not provide good estimates of past exposure levels because the body usually reaches a balanced state so there is no longer any change in response to continued exposure; many chemicals are excreted from the body after exposure stops; and basic understanding of what happens to chemicals in the human body is often lacking for those that do persist. Thus, direct examination of a population may provide information as to whether or not exposure has occurred but not the extent, duration or source of the exposure.

Overall, exposure assessments can be performed most reliably for recent events and much less reliably for past exposures. The difficulties in exposure assessment often make it the weak link in trying to determine the connection between an environmental contaminant and adverse effects on human health. Although exposure assessment methods will undoubtedly improve, there remains significant uncertainty in the foreseeable future.

DOSE-RESPONSE ASSESSMENT

Turning to the dose-response assessment, a distinction must be made between acute and chronic effects. Acute effects occur within minutes, hours or days while chronic effects appear only after weeks, months or years. The quality and quantity of scientific evidence gathered is different for each type of effect and, as a result, the confidence placed in the conclusions from the test results are also different.

Acute toxicity is easiest to deal with. Short-term studies with animals provide evidence as to which effects are linked with which chemicals and the levels at which these adverse effects occur. Often, some human experience is available as a result of accidental exposures. When these two types of evidence are available, it is usually

possible to make a good estimate of the levels of a particular toxicant that will lead to a particular acute adverse effect in humans. This approach is the basis for much of the current regulation of toxic substances, especially in occupational situations.

Chronic toxicity is much more difficult to assess. There are a variety of specific tests for adverse effects such as reproductive damage, behavioral effects, cancer, etc. It is not possible to discuss all of these, but a look at cancer assessment will reveal some of the problems inherent in long-term toxicity assessments and also focus on the health effect which seems to be of most public concern.

In cancer assessment, it is not only the chronic nature of the disease but also the low incidence which is of concern, that causes difficulty. Society has decided that no more than one additional cancer in 100,000 or one million people is acceptable, so assessment measures must be able to detect this small increase. Two types of evidence are utilized to determine the dose of chemical that will result in this change. One is based on experiments on animals and the other is based on experience with humans.

Ideally, to detect an increase of one cancer in a million animals, millions of animals would have to be exposed to environmentally relevant amounts of the chemical. However, there are neither the scientific nor the economic resources to carry out this type of study. Thus, investigations are performed on smaller numbers of animals (a few hundred) who have been exposed to very large amounts of a chemical. These large amounts are necessary to produce a high enough incidence of cancer to be detectable in this small population. Thus, the results of such studies indicate the levels of a chemical that will cause cancer in a high percentage of the population.

How can this information be used to assess the level of chemical that will cause one additional cancer in a million animals or, more importantly, in a million humans? Because our basic understanding is limited, mathematical models must be used to predict this level. There are a variety of possible models and the one generally chosen is that which provides the greatest margin of safety; for example, which overestimates rather than underestimates the ability of the chemical to cause cancer.

The other type of evidence utilized in chronic toxicity assessment is human experience, better known as epidemiological evidence. In this type of study, human populations are carefully observed and possible associations between specific chemical exposures and particular health effects are investigated. Considering the previous discussion about exposure assessment, it should be clear that this is not an easy task. It is made even more difficult in cancer assessment by the requirement of detecting very small changes in incidence; for example, one extra cancer in a million people.

As a result, epidemiological assessments have been most useful in only certain situations. One is exposure in the workplace, a place where levels are usually above environmental ones and where the duration of exposure can be determined. Even there, a sizable increase in cancer incidence is needed before a connection can be established. The conclusion that asbestos causes lung cancer is based on this type of situation. An exception to the need for a high cancer incidence is the situation where the effect is unique so that even a few cases are significant. An example of this was the observation that a small number of vinyl chloride workers developed a rare form of liver cancer. However, even with known occupational carcinogens, the question of what

happens at low exposures, for example, common environmental ones, has not been answered.
Thus, the techniques available for assessment of chronic toxicity, especially carcinogenicity, provide rather clear evidence as to whether or not a particular chemical causes a particular effect in animals. However, there is great uncertainty about the amounts needed to produce small changes in cancer incidence in humans. This uncertainty, together with the difficulties in exposure assessment, make it difficult to draw definite conclusions about the relationship between most environmental exposures and chronic health effects.

SUMMARY

Risk assessment is a complex process which depends on the quality of scientific information that is available. It is best for assessing acute risks where effects appear soon after exposure occurs. Uncertainty becomes greater, the longer the period of time between exposure and appearance of symptoms. This is due to greatly increased uncertainties in exposure assessment and also the problems involved in using epidemiological or laboratory animal results in such cases. In many circumstances, these uncertainties make it impossible to come to any firm conclusions about risk. Thus, risk assessment is a process which is often useful but cannot always provide the answers that are needed.

From the EXTOXNET website: http://ace.ace.orst.edu/info/extoxnet/tibs/riskasse.htm