A Small Dose of Risk Assessment
Or
An Introduction to Risk Assessment

Chapter 3 in Third Edition of
A Small Dose of Toxicology - The Health Effects of Common Chemicals

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Introduction and History

Risk assessment is both old and new. Old in the sense that humans and animals survive by evaluating the risk of harm verses the benefits of action. For early humans, the hunt for food or eating a new plant involved risk of harm but doing nothing risked starvation. In our current society, this kind of informal risk assessment is now more directed towards the risks of eating undercooked hamburger or riding a bicycle without a helmet. More formally, risk assessment now refers to a mathematical calculation of risk based on toxicity and exposure.

> "If someone had evaluated the risk of fire right after it was invented they may well have decided to eat their food raw."
>
> Julian Morris of the Institute of Economic Affairs in London

Concern about the risk of chemical exposures also has a long history. For a period of time, food poisons were a concern for those in power.

> “What is food to one man may be fierce poison to others.”
>
> Lucretius (c. 99 B.C.–c. 55 B.C.)

Percivall Pott made one of the first observations of a health risk related to occupational exposure. In 1775, he noted that chimney sweeps had elevated incidence of cancer of the scrotum. A century later, in 1895, it was observed that workers in the aniline dye industry were more likely to develop bladder cancer.

> "We should remember that risk assessment data can be like the captured spy: If you torture it long enough, it will tell you anything you want to know."
> (William Ruckelshaus -1st administrator of U.S. EPA 1984.)

The number of workers exposed to chemicals grew rapidly with onset of the industrial revolution and advances in chemical engineering. One the first efforts to systematically

evaluate the risk of exposure to chemicals began in 1938 when a group convened in Washington, D.C. that subsequently became the American Conference of Governmental Industrial Hygienists (ACGIH). In 1941, the Chemical Substances Committee of the ACGIH was established and charged with investigating and recommending exposure limits for chemical substances. They established exposure limits or Threshold Limit Values (TLVs) for 148 chemicals. ACGIH now publishes a list of TLVs for 642 chemical substances and physical agents and 38 Biological Exposure Indices for selected chemicals.

In 1958, in response to the increased awareness that chemicals can cause cancer, the U.S. Congress passed the Delaney clause, which prohibited the addition to the food supply of any substance known to cause cancer in animals or humans. Compared to today's standards, the analytical methods to detect a potentially harmful substance were very poor. As the analytical methods improved, it became apparent that the food supply had low levels of substances there were known to cause cancer in either animals or humans. The obvious question was: Is a small amount of a substance "safe" to consume? This question in turn raised many others about how to interpret data or extrapolate data to very low doses. The 1970s saw a flourish of activity to develop and refine risk assessment methodologies.

The initial focus was to develop risk assessment procedures to establish exposure limits for cancer-causing substances, the primary concerns being the food supply and the work place. These efforts were gradually expanded to include non-cancer endpoints such as nervous system development, reproductive effects, and effects on the immune system. Researchers at national and international agencies are developing better approaches to dealing with uncertainty in health effects data and the resulting need to apply judgment in interpreting the results. The area of judgment is a critical aspect of risk assessment. The process of interpreting and communicating risk assessment results requires full understanding and disclosure of the assumptions, data gaps, and possible financial interests that may play a role.

> " In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation."
>
> Principle 15: Rio Declaration 1992

Concerned by the shortcomings of risk assessment, a growing body of scientists is advocating a precautionary approach to risks that are not fully understood. The precautionary principle has been applied to issues related to toxicology, public health and

sustainable development and use of the environment (Cairns (2003; Goldstein (2001) and is an established global principle (Rio Declaration, 1992).

Risk Assessment

Hazard x Exposure x Individual Sensitivity = Risk

Risk assessment is a multi-step process to relate the association of exposure to a chemical or physical agent with adverse outcome. The relationship between hazard, exposure, and individual sensitivity is never exact. For example, understanding the hazard depends on the end point such as cancer or immune system or nervous system effects. Exposure depends on the route and duration. Individual sensitivity could be influenced by genetics, age (young or old), gender or other variables. Initially the focus was human health but now it has broadened to include wider environmental and ecological concerns. Risk management is a more overtly political process directed at determining an action based on relevant public and environmental health goals, cost, societal issues and other related or even unrelated issues. An important part of risk management is balancing the risks, costs, and benefits – never an easy task.

Risk assessment is the process of estimating association between an exposure to a chemical or physical agent and the incidence of some adverse outcome.

Steps in risk assessment

- Hazard Identification
- Exposure Assessment
- Dose-Response Assessment
- Risk Characterization

The first step in risk assessment is to gather health-related information associated with an exposure. Ideally, hazard identification starts before there is significant use of the agent. The structure of the compound is compared to that of compounds with known toxicity

profiles. Cell-based studies are often performed to screen for toxicity. Finally, animal bioassays and human studies are performed to characterize and develop a toxicity profile. Multiple health-related endpoints are evaluated to determine if the compound is associated with adverse effects. Advantages of animal studies include experimental control and accurate knowledge of the dose.

Using knowledge gained from animal studies or observations from human populations, a more formal human epidemiology study may be performed. Human studies have the obvious advantage of being done on the subject of most interest, but they are time consuming and expensive, and often have many variables that are difficult to control.

Common Toxicity Endpoints for Hazard Identification

- Carcinogenicity
- Mutations
- Altered immune function
- Teratogenicity
- Altered reproductive function
- Neuro-behavioral toxicity
- Organ-specific effects
- Ecological effects (wildlife, environmental persistence)

If the hazard assessment indicates that the compound is potentially hazardous, the next step is to evaluate the various possibilities for exposure. What is the most likely route of exposure: oral, inhalation or skin? How much absorption is expected from the different routes of exposure? Information is also needed on amount, duration and frequency of exposure. Is exposure occurring in the home, workplace, school or other areas? This information helps to define the population of concern. Exposure information may also be important for designing appropriate studies on hazard assessment and certainly for the next step of establishing dose / response relationships.

Exposure Assessment

- Route of exposure (skin, oral, inhalation)
- Amount of exposure (dose)
- Duration and frequency of exposure
- To whom (animals, humans, environment)

Next it is important to characterize the dose / response relationship for the agent. Data from the initial hazard assessment, combined with exposure assessment information are used determine the most sensitive endpoint. Available data are used to define dose at which there is no observed effect (NOEL – no observed effect level) and the shape of the

dose / response curve. It may be necessary to perform additional studies to define the dose / response curve. The ED50 is defined as the effective dose at which 50% of the subjects respond.

The final step is to take all the information from hazard assessment, exposure assessment, and dose / response assessment and summarize it in a risk characterization for the chemical substance. Any uncertainties in the data set or missing information must be evaluated. While all efforts are made to minimize professional judgment by having robust data, it is often the case that not enough of the right information is available. Recommendations must still be made as to an acceptable level of exposure for a given population, the goal being to ensure the even the most sensitive individuals are protected from any adverse effects. The dose thought to insure protection is called a reference dose (RfD) or acceptable daily intake (ADI). Note the word safe is NOT used, only the avoidance of adverse effects.

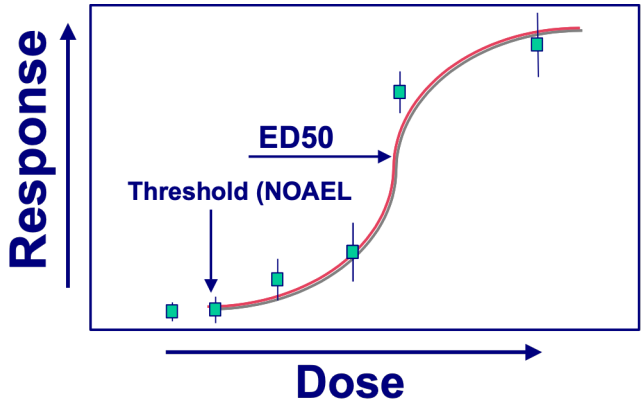

Figure 22.1 Dose Response

Acceptable Daily Intake (ADI)

"The daily intake of a chemical, which during an entire lifetime appears to be without appreciable risk on the basis of all known facts at the time."
WHO (1962)

There are of course many mathematically complex ways to perform a risk assessment but first key questions about the biological data must be resolved. The most sensitive endpoint must be defined along with relevant toxicity and dose / response data. A standard risk assessment approach that is often used is the so-called "divide by 10 rule". Dividing the dose by 10 applies a safety factor to insure the even the most sensitive individuals are protected. Animal studies are typically used to establish a dose response curve and the most sensitive endpoint. From the dose response curve a NOAEL dose or no observed adverse effect level is derived. This the dose at which there appears to be no adverse affects in the animal studies at a particular endpoint which could be cancer, liver damage or a neurobehavioral effect. This dose is then divided by 10 if the animal data is in any way thought to be inadequate. For example, there may be a great deal of variability, or there were adverse effects at the lowest dose, or there were only tests of

short-term exposure to the chemical. An additional factor of 10 is used when extrapolating from animals to humans. Last, a factor of 10 is used to account for variability in the human population or to account for sensitive individual such as children or the elderly. The final number is the reference dose (RfD) or acceptable daily intake (ADI). This process is summarized below.

Safety factors are typically used in a risk assessment to define an acceptable dose for food additive and pesticides. It is obviously very important to ensure that an artificial sweetener such as aspartame, which is commonly used in artificially sweetened sodas, has a large margin of safety. All age groups as well as pregnant women consume artificial sweeteners so it must have a large margin of safety. On the other hand, consider a compound such as lead. The risk of lead exposure to the developing child is well known but there has been no safety factor applied to blood lead level of concern.

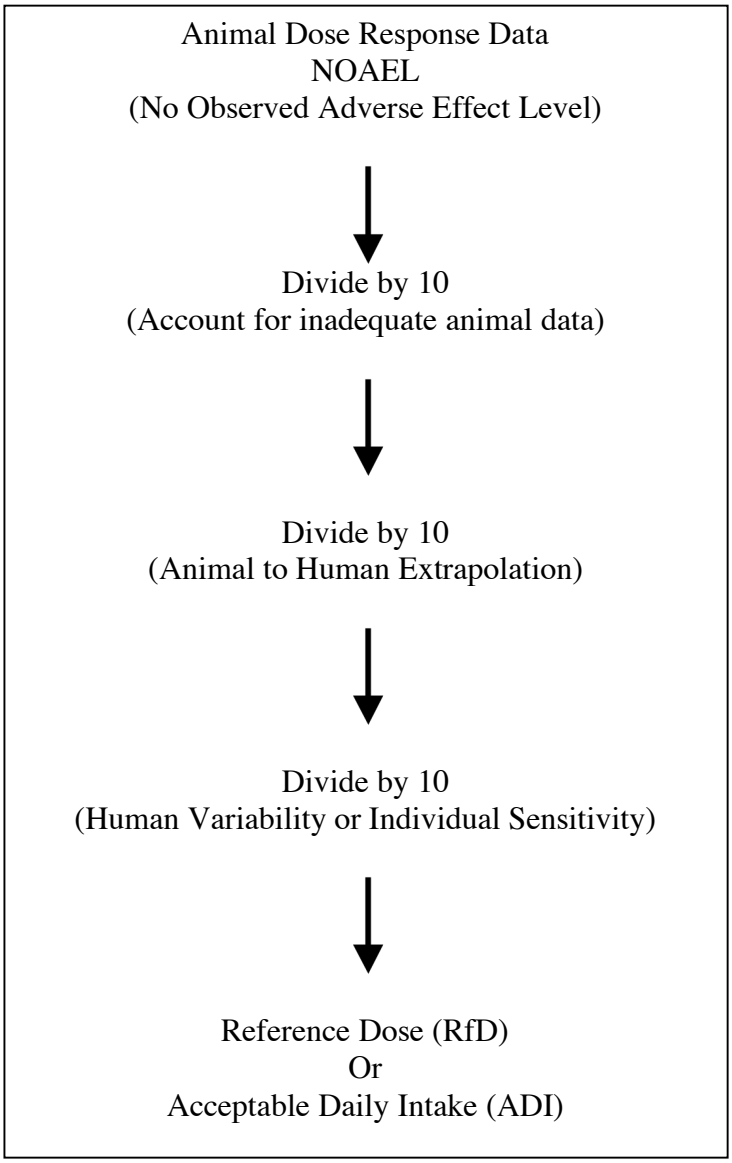

Table 22.1 Factors to consider

Route of exposure	
Ingestion	Concentration of toxicant in ingested material, amount consumed, frequency of ingestion, absorption factor
Skin	Concentration of toxicant in applied material, skin area exposed, absorption factor
Inhalation	Concentration of toxicant in air, breathing rate, exposure time, absorption factor

Risk Management

Risk management is the process of deciding what to do to reduce a known or suspected risk. Risk management balances the various community demands with the scientific information generated from the risk assessment. Public perception of risk is also considered. The following table characterizes some of the factors that influence perception of risk.

Table 22.2 Characteristic of Risk

Characteristic	Level	Examples
Knowledge	Little known	Food additives
	Much known	Alcoholic drinks
Newness	Old	Guns
	New	Space travel
Voluntariness	Not voluntary	Crime
	Voluntary	Rock climbing
Control	Not controllable	Natural disasters
	Controllable	Smoking
Dreadedness	Little dread	Vaccination
	Great dread	Nerve gas
Catastrophic potential	Not likely	Sunbathing
	Likely	War
Equity	Distributed	Skiing
	Undistributed	Hazardous dump

(Adapted from Kraus and Slovic (1988))

An individual's perception of risk is sometimes very different from a risk assessment based on a more objective analysis of the data. For example, individuals often rank nuclear power as a high risk but most experts give it a low risk rank.

Early risk evaluation often just looked at death as the main endpoint, asking if a particular action or exposure lead to increases in death or reduced number of working years. Advances in the biological sciences have required that more complex risk analysis be undertaken to evaluate quality of life issues and not just death as an endpoint. The challenge for both risk assessment and risk management will be to take into consideration quality of life and individual values into the decision-making process.

Precautionary Principle

> "When an activity raises threats of harm to the environment or human health, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically."
> - Wingspread Statement on the Precautionary Principle, Jan. 1998

Another approach to risk-based decision-making is the precautionary principle. The risk assessment and risk management approach used in United States places a heavy reliance on the certainty of the data. The Precautionary Principle emphasizes that there is always some uncertainty and that decisions should be based on recognizing the possibility of harm. When in doubt, be cautious until adequate data are available to show that there is little potential for harm. Action to reduce exposure to hazardous agents should begin even if there is some uncertainty in the data. In other words, some uncertainty in the data should not be used as an excuse for inaction. This approach is being given more consideration in Europe than in the United States. The approach gains credibility when one considers how its application years ago would have prevented the tragic effects of lead in gasoline and paint.

Precautionary Assessment

The goal of precautionary assessment (PA) is to move beyond risk assessment and allow communities and individual to incorporate their knowledge, values and ethics into a more comprehensive evaluation of a hazardous condition. The PA combines the philosophy and ethics of the precautionary principle with the standard scientific evaluation of the hazards. Precautionary assessment contains three basic elements: a) community and social issues, b) exposure, and c) hazard and toxicity. Each element is broken down into a series of questions that are scored numerically and summed to produce a summary score for each element. The PA is designed to help place the knowledge available within the

context of the community. In contrast to the traditional risk assessment, the PA is a more comprehensive approach to evaluating the human and environmental health risks. Overall, the PA can be considered a more reasonable, rational, and responsible approach to evaluating risk of chemicals. A detailed discussion of the PA and spreadsheet are available on line (Gilbert, 2006). Other authors have also discussed alternative decision-making approaches to risk assessment, for example O'Brien (2000).

More Information and References

Slide Presentation

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  "We clarify the environmental risk for human health and ecosystems posed by environmental pollutants and other risk factors, through the cooperation of environmental risk field and environmental health field, to assure environmental safety."

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  "Our mission is to protect and enhance the health of Californians and our state's environment through scientific evaluations that inform, support and guide regulatory and other actions.'

Non-Government Organizations

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  "The ACGIS community of professionals' advances worker health and safety through education and the development and dissemination of scientific and technical knowledge."

- Society for Risk Analysis (SRA). Online: <http://www.sra.org/> (accessed: 30 October 2019).
  "The Society for Risk Analysis is a multidisciplinary, interdisciplinary, scholarly, international society that provides an open forum for all those who are interested in risk analysis."

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