Environmental Risk Assessment (ERA)

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- Environmental Risk Assessment is a process for estimating the likelihood or probability of an adverse outcome or event due to pressures or changes in environmental conditions resulting from human activities.

Risk Assessment and management

- Risk assessment is gathering of data that are used to relate response to dose
- Such dose-response data can then be combined with estimates of likely human exposure to produce overall assessments of risk
- Risk management is the process of deciding what to do. It is the decision making, **under extreme uncertainty**, about how to allocate national resources to protect public health and the environment
- Difficult decision making in risk management:
  - Is a one-in-a-million lifetime risk of getting cancer acceptable?
  - how do we go for it?
  - Zero risk achievement would cost infinite amount of money

Perspectives on Risks

Leading Causes of Death in the United States, 1992

Cause	Annual Deaths (thousands)	Percent
Cardiovascular (heart) disease	720	33
Cancer (malignant neoplasms)	521	24
Cerebrovascular diseases (strokes)	144	7
Pulmonary diseases (bronchitis, emphysema, asthma)	91	4
Pneumonia and influenza	76	3
Diabetes mellitus	50	2
Nonmotor vehicle accidents	48	2
Motor vehicle accidents	42	2
HIV/AIDS	34	1.6
Suicides	30	1.4
Homicides	27	1.2
All other causes	394	18
Total annual deaths (rounded)	2,177	100

Source: Kolluru et al., 1996.

Annual Risks of Death Associated with Certain Activities

Activity/Exposure	Annual Risk (Deaths per 100,000 Persons
Motorcycling	2,000
Smoking, all causes	300
Smoking (cancer)	120
Hang gliding	80
Coal mining	63
Farming	36
Motor vehicles	24
Chlorinated drinking water (chloroform)	0.8
4 tbsp peanut butter per day (aflatoxin)	0.8
3 oz charcoal broiled steak per day (PAHs)	0.5

TABLE 4.5

Activities That Increase Mortality Risk by One in a Million

Activity	Type of Risk
Smoking 1.4 cigarettes	Cancer, heart disease
Drinking 1/2 liter of wine	Cirrhosis of the liver
Spending 1 hour in a coal mine	Black lung disease
Living 2 days in New York or Boston	Air pollution
Traveling 300 miles by car	Accident
Flying 1,000 miles by jet	Accident
Flying 6,000 miles by jet	Cancer by cosmic radiation
Traveling 10 miles by bicycle	Accident
Traveling 6 minutes by canoe	Accident
Living 2 summer months in Denver (vs. sea level)	Cancer by cosmic radiation
Living 2 months with a cigarette smoker	Cancer, heart disease
Eating 40 tablespoons of peanut butter	Liver cancer caused by aflatoxin
Eating 100 charcoal-broiled steaks	Cancer from benzopyrene
Living 50 years within 5 miles of a nuclear reactor	Accident releasing radiation

Source: Wilson, 1979.

Cigarette Smoking - In the US, 627 billion cigarettes were made in 1975 which is equivalent to 3,000 per person (including children).

It is estimated that in the US, 15% of all Americans (30% of all smokers) die from lung cancer or heart diseases due to smoking.

Average life time risk = 0.15

Annual risk = 0.15/70 = 0.002 (life expectancy in U.S. = 70 years)

Risk per cigarette = 0.02/3000 = 0.7×10^{-6}

Increased mortality risk per million = 1.4 cigarettes

Estimated Expenditures per Life-Year Saved for Selected Programs

Program	1990 U.S.$
Childhood immunizations	Direct savings
Eliminating lead in gasoline	Direct savings
Safety rules at underground construction sites	52,000
Hemodialysis at a dialysis center	56,000
Coronary artery bypass surgery	68,000
Front seat air bags in new cars	109,000
Dioxin effluent controls at paper mills	5,570,000

Source: Kolluru et al., 1996, based on data from the Harvard School of Public Health.

Perception of Risk

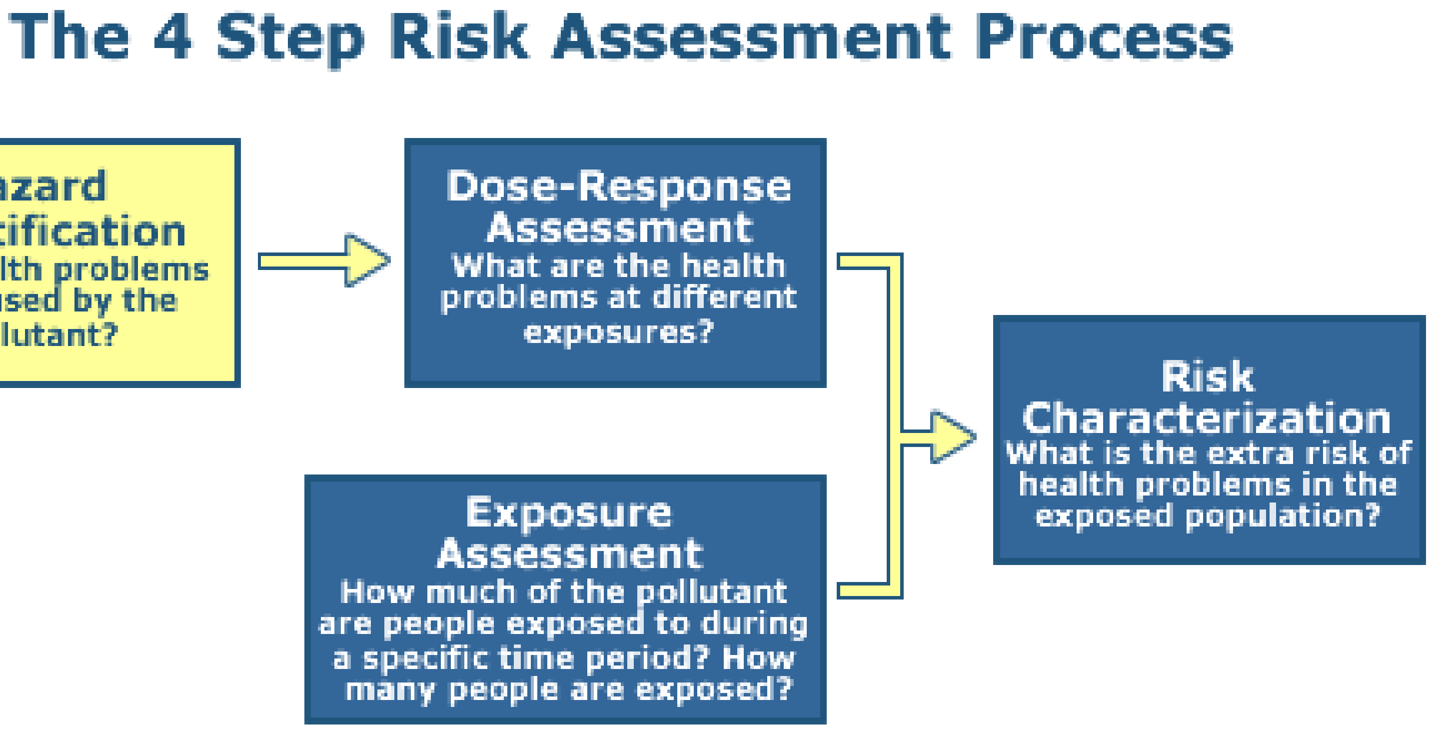
- Perception of risk as seen by an engineer/scientist familiar with the numbers are very different from those of an individual who lives next to a toxic waste site.

Some Characteristics That Change Our Perception of Risk

Attributes That Elevate the Perception	Attributes That Lower the Pe
Involuntary	Voluntary
Exotic	Familiar
Uncontrollable	Controllable
Controlled by others	Controlled by self
Dread	Accept
Catastrophic	Chronic
Caused by humans	Natural
Inequitable	Equitable
Permanent effect	Temporary effect
No apparent benefits	Visible benefits
Unknown	Known
Uncertainty	Certainty
Untrusted source	Trusted source

Source: Based on Slovic, 1987, and Slovic et al., 1980.

Risk Assessment



http://www.epa.gov/risk_assessment/hazardous-identification.htm

Step 1 - Hazard Identification

- Hazard Identification is the process of determining whether exposure to a stressor can cause an increase in the incidence of specific adverse health effects (e.g., cancer, birth defects) and whether the adverse health effect is likely to occur in humans.

- In the case of chemical stressors, the process examines the available scientific data for a given chemical (or group of chemicals) and develops a weight of evidence to characterize the link between the negative effects and the chemical agent.

Step 1 - Hazard Identification

Sources of Data

- Epidemiological studies involve a statistical evaluation of human populations to examine whether there is an association between exposure to a stressor and a human health effect. The advantage of these studies is that they involve humans while their weakness results from generally not having accurate exposure information and the difficulty of teasing out the effects of multiple stressors.
- When data from human studies are unavailable, data from animal studies (rats, mice, rabbits, monkeys, dogs, etc) are relied on to draw inference about the potential hazard to humans. Animal studies can be designed, controlled, and conducted to address specific gaps in knowledge, but there are uncertainties associated with extrapolating results from animal subjects to humans.
- Statistically controlled clinical studies on humans provide the best evidence linking a stressor, often a chemical, to a resulting effect. However, such studies are frequently not available since there are significant ethical concerns associated with human testing of environmental hazards.

Toxic Effects

- Acute Toxicity happen very rapidly after a single exposure has occurred (food poisoning, breathing fumes from a chlorine spill). Sweating, nausea, paralysis, and death are examples of acute effects.
- Chronic Toxicity happen only after repeated long-term exposure (cigarette smoking, eating foods with low levels of contaminants, breathing polluted air). Cancer, organ damage, reproductive difficulties, and nervous system impairment are examples of chronic effects.
- These chronic effects fall into two categories: carcinogenic effects and non-carcinogenic effects.
- **Examples of non-carcinogenic chronic effects:**
  - **Organ damage:** cirrhosis of the liver from long-term alcohol consumption; emphysema from long-term tobacco smoking.
  - **Reproductive difficulty:** decreased fertility from the pesticide DBCP (di bromo chloro propane).
  - **Nervous system impairment:** mental retardation in people exposed to high levels of lead during early childhood.

Assessing Toxicity-Acute

- Most information about acute toxicity of chemicals to humans comes from accidental poisonings or exposures, such as drug overdoses or chemical spills. Physicians/researchers know or estimate the level of exposure and observe and document the effects.
- Scientists also use animal tests called LD_{50} (L-D-fifty) studies to assess acute toxicity. These studies determine the amount of a substance that will kill half the test animals in 14 days. This amount is called the LD50--Lethal Dose for 50% of the animals.
- LD50 is stated in milligrams per kilogram (mg/kg): milligram of chemical per kilogram of body weight.
- Lower the LD50-the lower the lethal dose-the more toxic the substance.

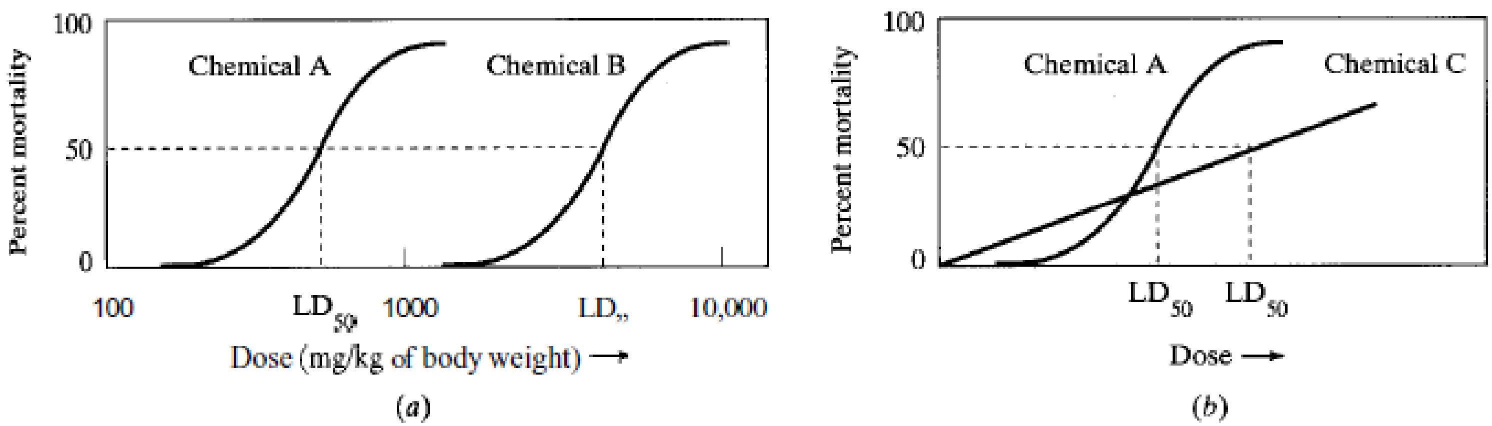


FIGURE 4.4 Dose-response mortality curves for acute toxicity: (a) Chemical **A** is always more toxic than B; (b) but Chemical **A** is less toxic than *C* at low doses even though it has a lower LD_{50}.

LD_{50} Comparison

Chemical	LD_{50} (mg/kg)
Ethyl Alcohol	10,000
Sodium Chloride	4,000
Ferrous Sulfate	1,500
Morphine Sulfate	900
Strychnine Sulfate	150
Nicotine	1
Black Widow	0.55
Curare	0.50
Rattle Snake	0.24
Dioxin (TCDD)	0.001
Botulinum toxin	0.0001

A conventional rating system for the acute toxicity of chemicals in humans

	Probable lethal oral dose for humans	
Toxicity rating	Dose (mg/kg of body weight)	For average adult
1. Practically nontoxic	more than 15,000	More than 1 quart
2. Slightly toxic	5,000–15,000	1 pint to 1 quart
3. Moderately toxic	500–5,000	1 ounce to 1 pint
4. Very toxic	50–500	1 teaspoon to 1 ounce
5. Extremely toxic	5–50	7 drops to 1 teaspoon
6. Supertoxic	Less than 5	Less than 7 drops

Assessing Chronic Toxicity

Non-Carcinogenic Assessment

- Scientists assess non-carcinogenic chronic toxicity by administering varying amounts of a substance (dose) to laboratory animals and noting the effects (responses), if any, at each dose.
- Essentially, the scientists look for the smallest dose that causes any detectable effect. This smallest dose is called the ***Lowest Observable Effect Level (LOEL)***.
- **To conduct these dose-response studies, scientists:**

  Administer different small doses of a substance to several groups of test animals every day over a lifetime.

  Periodically examine and finally autopsy the animals to determine if any effects have occurred. The effects may be:

  - damage to an organ,
  - behavioral modifications,
  - change in the level of an essential body chemical.

  Determine the smallest dose at which an effect occurs--**the Lowest Observable Effect Level (LOEL).**

  LOEL is measured in milligrams (mg) of substance per kilogram (kg) of body weight, or in parts per million (ppm) of substance in food.

Assessing Chronic Toxicity

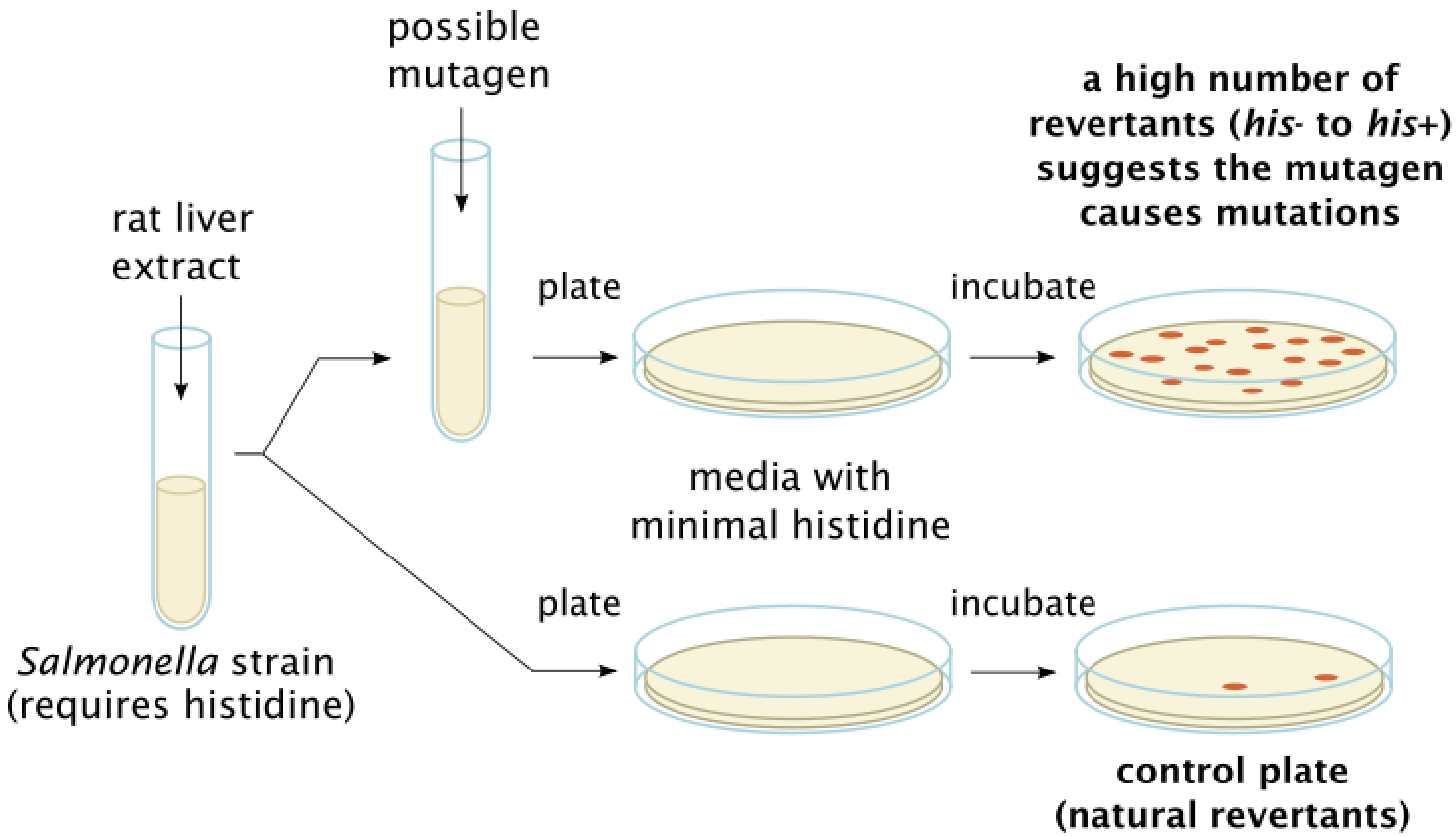
Carcinogenic Assessment

- The prevailing carcinogenesis theory, that human cancers are initiated by gene mutations, has led to the development of short-term, in vitro (in glassware) screening procedures, which are one of the first steps taken to determine whether a chemical is carcinogenic.
- If a chemical can be shown to be mutagenic, then it ***may*** be carcinogenic, and further testing may be called for **Ames mutagencity test**

Ames mutagencity test

- subjects special tester strains of bacteria to the chemical in question.
- These tester strains have previously been rendered incapable of normal bacterial division so, unless they mutate back to a form that is capable of division, they will die. Bacteria that survive and form colonies do so through mutation; therefore, the greater the survival rate of these special bacteria, the more mutagenic is the chemical.
- **Intermediate testing procedures** involve relatively short-term (several months duration) carcinogenesis bioassays in which specific organs in mice and rats are subjected to known mutagens to determine whether tumors develop.

Ames mutagencity test



https://en.wikipedia.org/wiki/Ames_test

Chronic Carcinogenesis bioassay

- Involves hundreds or thousands of animals over a time period of several years.
- National Toxicology Program in the United States has established minimum test requirements for an acceptable chronic bioassay, which includes:
  - Two species of rodents must be tested. Mice and rats, using specially inbred strains for consistency, are most often used. They have relatively short lifetimes, and their small size makes them easier to test in large numbers.
  - At least 50 males and 50 females of each species for each dose must be tested.
  - At least two doses must be administered (plus a no-dose control). One dose is traditionally set at the maximum tolerated dose (MTD),a level that can be administered for a major portion of an animal’s lifetime without significantly impairing growth or shortening the lifetime. The second dose is usually one-half or fourth the MTD.

Chronic Carcinogenesis bioassay

- Exposure begins at **6 weeks of age and ends when the animal reaches 24 months** of age. At the end of the test, all animals are killed and their remains are subjected to detailed pathological examinations.
- These tests are expensive as well as time consuming.
- Testing a typical new chemical costs between $0.5-1.5 million, takes **up to** two or three years, and may entail the sacrifice of thousands of animals (Goldberg and Frazier, 1989).
- The minimum number of animals required for a bioassay is 600 (2 species 100 animals X 3 doses), and at that number it is still only relatively high risks that can be detected.
- With this number of animals, for the test to show a statistically significant effect, the exposed animals must have at least *5 or 10 percent more tumors than the controls in order to conclude that* the extra tumors were caused by the chemical being tested.
- That is, the risk associated with this chemical can be measured only down to roughly 0.05 or 0.10 unless we test a lot more animals.

Epidemiologic studies

2X2 matrix for an epidemiologic rate comparison

	With disease	Without disease
Exposed	**a**	**b**
Not Exposed	c	d

Relative risk = (a/(a+b))/(c/(c+d)) For

Attributable risk = (a/(a+b))-(c/(c+d))

Odd ratio= ad/bc

2X2 matrix for an epidemiologic rate comparison

- An evaluation of personnel records for employees of a plant that manufactures vinyl chloride finds out that of 200 works, 15 developed liver cancer. A control group consisting of individuals with smoking histories similar to the exposed workers, and who were unlikely to have encountered vinyl chloride, had 24 with liver cancer and 450 did not develop liver cancer. Find the relative risk, attributable risk, and odds ratio for these data

- RR= 1.48
- AR=0.024
- OR= 1.52

Weight-of-Evidence Categories for Human Carcinogenicity

Human Evidence	Animal Evidence: Sufficient	Limited	Inadequate	No Data	No Evidence
Sufficient	A	A	A	A	A
Limited	B1	B1	B1	B1	B1
Inadequate	B2	C	D	D	D
No data	B2	C	D	D	E
No evidence	B2	C	D	D	E

Source: U.S. EPA, 1986a.

Only 50 compounds

Group A: Human carcinogen. A substance is put into this category only when sufficient epidemiologic evidence supports a causal association between exposure to the agent and cancer.

Several hundred compounds

Group B: Probable human carcinogen. This group is actually made up of two subgroups. An agent is categorized as B1 if there is limited epidemiologic evidence; and an agent is put into B2 if there is inadequate human data but sufficient evidence of carcinogenicity in animals.

Group C: Possible human carcinogen. This group is used for agents with limited evidence of carcinogenicity in animals and an absence of human data.

Group D: Not classified. This group is for agents with inadequate human and animal evidence or for which no data are available.

Group E: Evidence of noncarcinogenicity. This group is used for agents that show no evidence for carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

Step 2 - Dose-Response Assessment

Step 2 - Dose-Response Assessment:

- A dose-response assessment is to obtain a mathematical relationship between the amount of a toxicant that a human is exposed to and the risk that there will be an unhealthy response to that dose.

- Dose is normalized as milligrams of substance or pathogen ingested, inhaled, or absorbed (in the case of chemicals) through the skin per kilogram of body weight per day (mg kg^{-1} day^{-1})

- To apply dose-response data obtained from animal bioassays to humans, a *scaling factor must be introduced. Sometimes the scaling factor is based on the assumption* that doses are equivalent if the dose per unit of body weight in the animal and human is the same.
- For example, if prolonged exposure to some chemical would be expected to produce 700 cancers in a population of 1 million, the response could be expressed as 0.07 percent. The annual risk would be obtained by spreading that risk over an assumed 70-year lifetime, giving a risk of 0.00001 or $1X10^{-5}$

Dose-response for acute toxicity

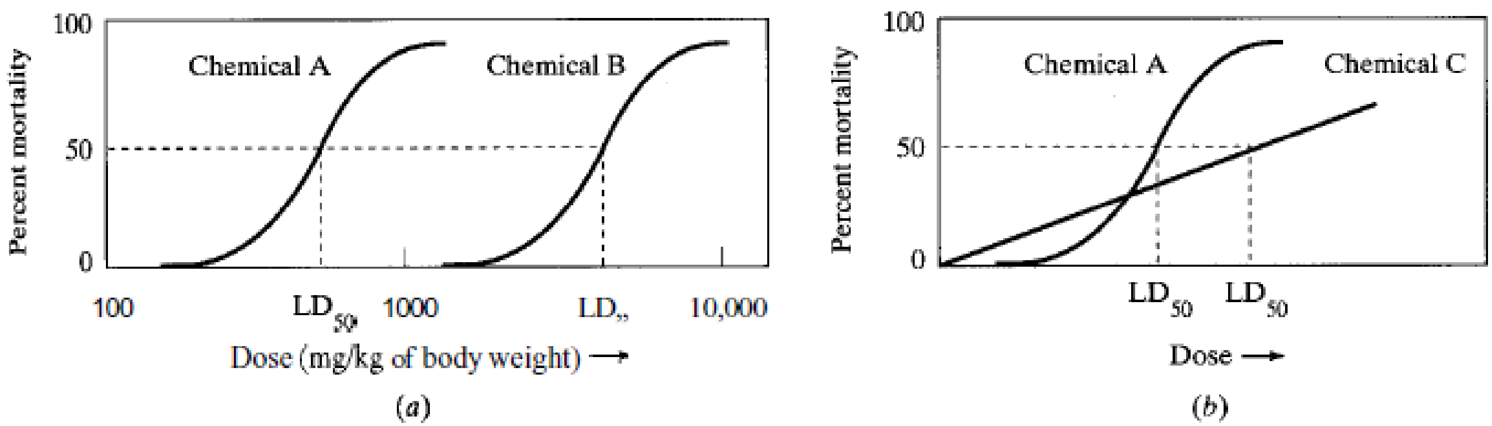
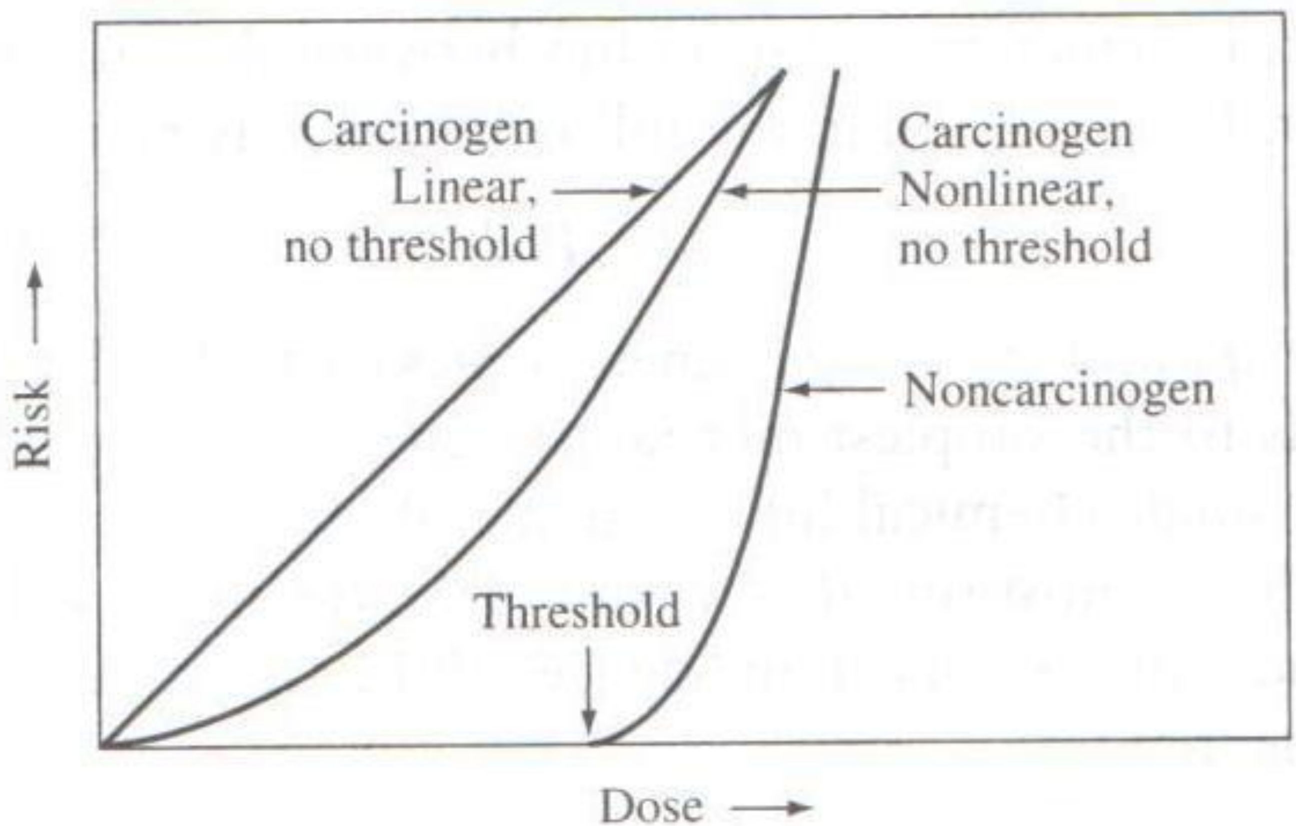


FIGURE 4.4 Dose-response mortality curves for acute toxicity: (a) Chemical **A** is always more toxic than B; (b) but Chemical **A** is less toxic than *C* at low doses even though it has a lower LD_{50}.

Step 2 - Dose-Response Assessment:



Step 2 - Dose-Response Assessment:

- The Reference Dose for Noncarcinogenic Effects
- The key assumption for noncarcinogens **is that there is an exposure threshold; that is,** any exposure less than the threshold would be expected to show no increase in adverse effects above natural background rates.
- Suppose there exists a precise threshold for some particular toxicant for some particular animal species. To determine the threshold experimentally, we might imagine a testing program in which animals would be exposed to a range of doses.
- Doses below the threshold would elicit no response; doses above the threshold would produce responses.
- The lowest dose administered that results in a response is given a special name: the ***lowest-observed-effect level (LOEL)***
- *Conversely, the highest dose* administered that does not create a response is called the ***no-observed-effect level*** **(NOEL)**
- And are often further refined by noting a distinction between effects that are *adverse to health and effects that are not*

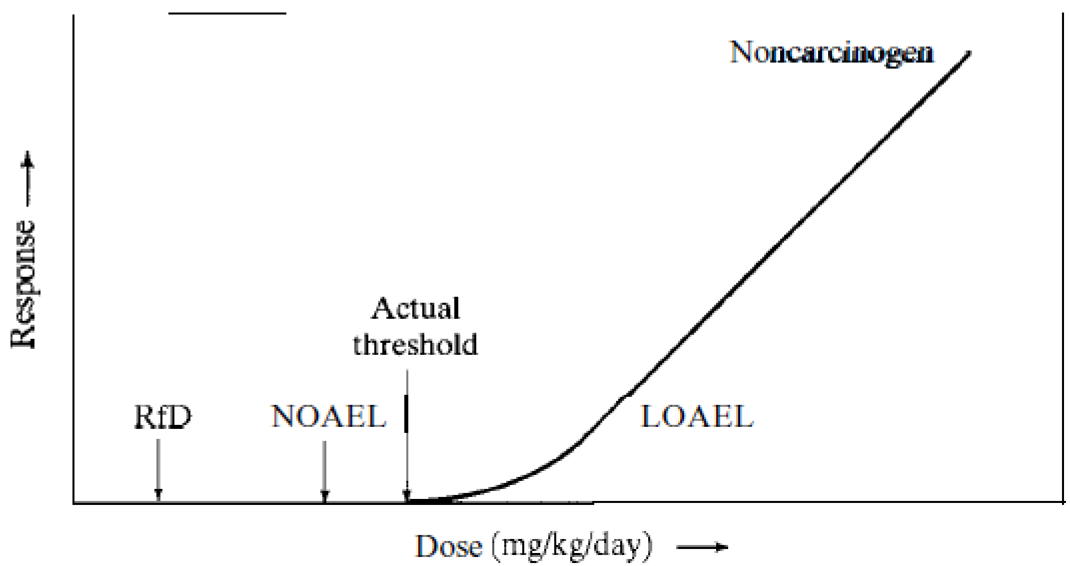
Step 2 - Dose-Response Assessment:

The Reference Dose for Noncarcinogenic Effects

- *Reference dose (RfD), or acceptable daily intake (ADI),* and is intended to give an indication of a level of human exposure that is likely to be without appreciable risk

- RfD = NOAEL / *uncertainty factor (or* safety factor)

- A 10-fold uncertainty factor is used to account for differences in sensitivity between the most sensitive individuals in an exposed human population, such as pregnant women, babies, and the elderly, and "normal, healthy" people.
- Another factor of 10 is introduced when the NOAEL is based on animal data that is to be extrapolated to human
- Another factor of 10 is sometimes applied when there are no good human data and the animal data available are limited
- Human levels are established at doses that are anywhere from one-tenth to one-thousandth of the NOAEL, which is itself somewhat below the actual threshold.


Noncarcinogen
Response
Actual
threshold
RfD
NOAEL
LOAEL
Dose (mg/kg/day)

Step 2 - Dose-Response Assessment:

Hazard Index for Noncarcinogenic Effects

- Hazard Quotient = Average daily dose during exposure period/ RfD
- **The daily dose is averaged only over the period of exposure, which is different from the average daily dose used in risk calculations for carcinogens**
- For non-carcinogens, the toxicity is important only during the time of exposure.
- The hazard quotient has been defined so that if it is less than 1.0,there should be no significant risk of systemic toxicity. Ratios above 1.0 could represent a potential risk, but there is no way to establish that risk with any certainty
- When exposure involves more than one chemical, the sum **of the individual hazard** quotients for each chemical is used as a measure of the potential for harm. This sum is called the ***hazard index:***
- Hazard index = Sum **of the hazard quotients**

TABLE 4.11 Oral RfDs for chronic noncarcinogenic effects of selected chemicals.

Chemical	RfD (mg/kg-day)
Acetone	0.100
Arsenic	0.0003
Cadmium	0.0005
Chloroform	0.010
1,1-dichloroethylene	0.009
cis-1,2-Dichloroethylene	0.010
Fluoride	0.120
Mercury (inorganic)	0.0003
Methylene chloride	0.060
Phenol	0.600
Tetrachloroethylene	0.010
Toluene	0.200
1,1,1-Trichloroethane	0.035
Xylene	2.000

Source: U.S. EPA. http://www.epa.gov/iris

- Due to contamination from hazardous waste originating from a hazardous waste industry, drinking water contains 1.0 mg/L of toluene and 0.01 mg/L of tetrachloroethylene. A 70-kg adult drinks 2 L per day of this water for 10 years.
- **Would the hazard index suggest that this was a safe level of exposure?**

Solution

- First we need to find the average daily doses (ADD) for each of the chemicals and then their individual hazard quotients.
- For toluene, the RfD = 0.200 mg/kg-day
- **ADD (toluene) = 1.0 mg/L * 2 L/day / 70 kg = 0.029** mg/kg-day
- **Hazard quotient (toluene)** = **ADD/RfD= 0.029/0.200** = 0.14
- The RfD for tetrachloroethylene = 0.01 mg/kg-day
- **Hazard quotient (tetrachloroethylene)** = **0.00029/0.01**= 0.029
- **Hazard index** = 0.14 + 0.029 = 0.17 <1.0

The hazard index suggests that this water is safe