Lecture 4

RISK ASSESSMENT

Course: Water Reuse

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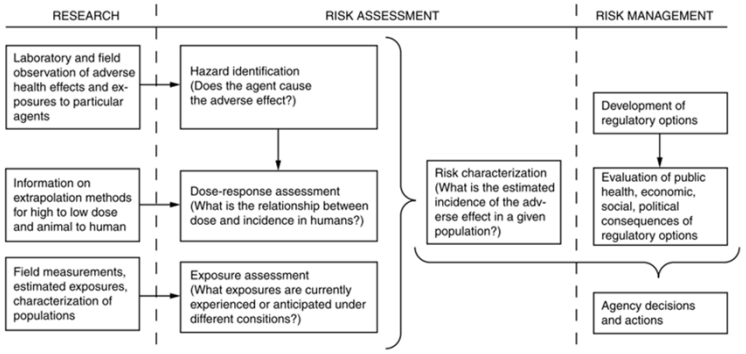
Elements of risk analysis

- 1. Risk assessment
  - Qualitative or quantitative characterization and estimation of potential adverse health effects
- 2. Risk management
  - Policy alternatives are examined and appropriate control options are selected and implemented (including regulatory measures)
- 3. Risk communication
  - interactive exchange of information and opinions among stakeholders

- Risk assessment can be defined broadly as the process of estimating the probability of occurrence of an event and the probable magnitude of adverse effects on safety, health, ecology, or finances over a specified time period.



Chemical hazard identification

- Although the question of whether a chemical can cause adverse health effects is theoretically a yes-no question, there are few chemicals on which human data are definitive. Therefore, the question is often restated in terms of effects in laboratory animals or other test systems, for example, "Does the agent induce cancer in test animals?"
- Positive answers to such questions are taken typically as evidence that an agent may pose a cancer risk for any exposed humans.

Dose response assessment

- Is the process of characterizing the relationship between the dose of an agent and the incidence of an adverse health effect in exposed populations; and then estimating the incidence of the effect as a function of human exposure to the agent
- A dose-response assessment usually requires extrapolation from high dose to low dose and extrapolation from animal test results to estimate human effects.
- The extrapolations must be justified carefully

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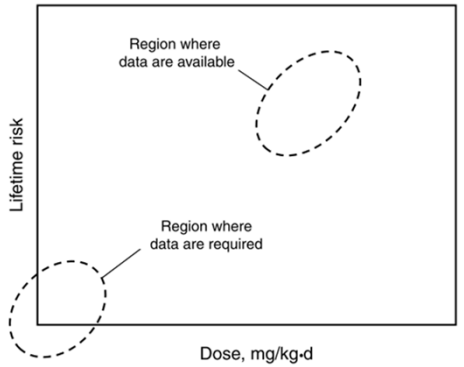
Why extrapolations are required



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Dose response models

- Relate the probability of adverse effects to the mean dose of exposure (i.e. infection vs. ingestion)
- Single-Hit Model

The simplest form of the single-hit model is:

$$P_{inf}(n_p, r) = 1 - (1 - r)^{n_p} \quad (5\text{-}1)$$

where P_{inf} = the probability of infection which is a function of n and r
n_p = number of pathogens ingested
r = the nonzero probability that an ingested pathogen will survive all barriers and colonize the host

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Exponential single hit model

- Variation of the single-hit model assuming agents are distributed in water randomly, for adverse effects to occur at least one agent must survive within the host, and the probability of adverse effect per ingested or inhaled agent is constant
(implication = members of the challenged population are equally likely to become infected)

$$P_{inf}(r, d) = 1 - \exp(-rd) \quad (5\text{-}2)$$

where P_{inf} = the probability of infection which is a function of r and d
r = empirical parameter assumed to be constant for any given host and given pathogen picked to fit the data
d = mean ingested dose

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Beta-Poisson Model

- Based on similar assumptions to the exponential model except that the third assumption (that the probability of infection per ingested organism is constant) is relaxed.
- This model allows the probability of infection per ingested or inhaled organism to vary with the population.

The median dose is given by the following expression:

$$N_{50} = \frac{\beta}{2^{1/\alpha} - 1}$$

Two popular Beta-Poisson estimations

$$P_{inf}(d, \alpha, \beta) \simeq 1 - \left(1 + \frac{d}{\beta}\right)^{-\alpha}$$

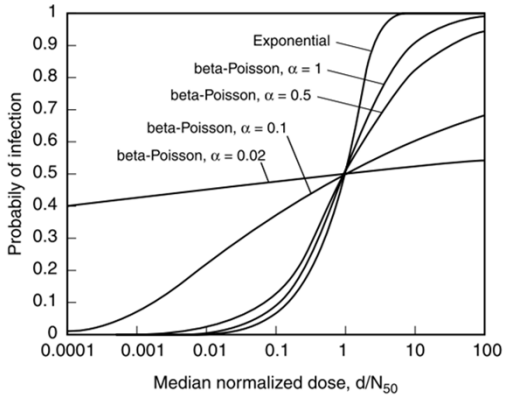
where P_{inf} = the probability of infection which is a function of d, α, and β
d = mean ingested dose
β = a slope parameter, which holds when $\beta \geq 1$ and $\alpha \leq \beta$
α = a slope parameter

and

$$P_{inf}(d, \alpha, N_{50}) \simeq 1 - \left[1 + \frac{d}{N_{50}}(2^{1/\alpha} - 1)\right]^{-\alpha}$$

where N_{50} = the median dose
other terms are defined as above.

Visualization



Annual and daily probabilities

- Often it is necessary to convert interchangeably between annual and daily probability of infection, as shown in the following expression:

$$P_{yr} = 1 - (1 - P_d)^n$$

where P_{yr} = acceptable annual risk of infection caused by a pathogenic organism
P_d = acceptable daily (single) exposure risk caused
n = number of exposure events per year (events/yr)

Exp. and Beta-Poisson parameters

Constituent	Model: Exponential r	Model: beta-Poisson α	Model: beta-Poisson β	Reference
Virus				
Echovirus 12		0.374	186.69	Regli et al. (1991)
Rotavirus		0.253	0.422	Ward et al. (1986)
Poliovirus 1	0.009102	0.1097	1524	Regli et al. (1991)
Poliovirus 3		0.409	0.788	Regli et al. (1991)
Bacteria				
Salmonella	0.00752			Regli et al. (1991)
		0.33	139.9	
Shigella flexneri		0.2	2000	
Escherichia coli		0.1705	1.61×10^6	Regli et al. (1991)
Campylobacter jejuni		0.145	7.589	Black et al. (1988)
		0.039	55	
Vibrio cholerae		0.097	13,020	
Protozoa				
Cryptosporidium	0.004191			Regli et al. (1991)
Giardia lamblia	0.02			Regli et al. (1991)

Example

A drinking water source contaminated with *Campylobacter jejuni* contains 1200 organisms/100 mL. Using the beta-Poisson model, estimate the probability of infection for an individual who ingests 250 mL of the drinking water. The coefficients for the beta-Poisson model for *C. jejuni* have been determined to be $\alpha = 0.145$ and $\beta = 7.589$ (see Table 5-4).

Solution

1. Calculate the dose obtained from ingestion of the drinking water.

   Dose = (1200 org/100 mL)(250 mL) = 3000 organisms

2. Estimate the probability of infection using Eq. (5-4).

$$P_{inf} \simeq 1 - \left(1 + \frac{d}{\beta}\right)^{-\alpha} \simeq 1 - \left(1 + \frac{3000\ \text{org}}{7.589}\right)^{-0.145} = 0.58$$

Comment

As shown in the above computation, ingestion of 3000 *C. jejuni* cells is expected to result in infection in 58 percent of individuals. A portion of the infected individuals may further develop a clinical illness (a disease with clinical signs and symptoms that are recognizable).

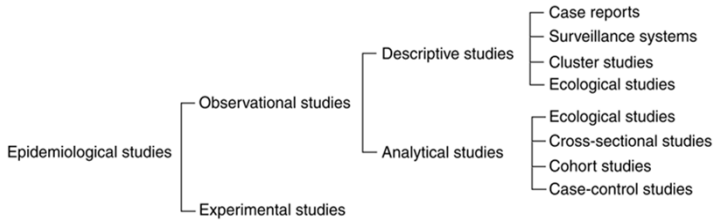
Exposure

- Exposure assessment is the process of measuring or estimating the intensity, frequency, and duration of exposures (human or non-human) to an agent
- Risk characterization integrates hazard identification, dose response assessment, and exposure assessment to obtain a risk estimate.
- Risk characterization results in a qualitative or quantitative estimate of the likelihood and severity of the possible adverse effects, including uncertainties (may require simulations).

Epidemiology

- **Epidemiology:** In its broadest sense is the study of disease patterns in human populations.
- **Incidence (morbidity)**: the number of people who contract a disease during a specific period of time
- **Prevalence:** incidence plus the number of people who already had and still have the disease
- **Mortality:** the number of people who died during the specific period of time
- **Toxicology:** the study of the adverse effects of chemicals on living organisms

Epidemiological studies



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Epidemiological studies

Experimental	In experimental studies, baseline conditions are recorded first, and then exposed and nonexposed status is randomly assigned. Both groups are followed prospectively over time for the occurrence of disease or other outcome of interest. A major advantage in experimental studies is that unknown statistical confounders can be controlled by randomization. For ethical and other reasons, however, subjects cannot be assigned deliberately to receive a known risk. Therefore, experimental studies are used mostly in clinical trials in a treatment or preventive measure, but cannot be used in the study of health effects of toxic substances.
Observational	As a follow-up to anecdotal evidence and case histories, epidemiologists conduct two major types of observational studies to assess the relationship or association between suspected risk factors and disease: (1) descriptive and (2) analytical. These studies are used most commonly to monitor: (1) disease, study risk and other risks apart from the exposure of interest, (2) person and host characteristics, and (3) environmental conditions, without altering the conditions of the sample.
Descriptive (observational)	Descriptive studies are implemented when little information is available about a disease, exposure, or trait. In descriptive studies, current conditions are reported but no attempt is made to link any of the variables. Rather, descriptive studies generate hypotheses to be tested. Descriptive studies include case reports, cluster studies, ecologic studies, and surveillance systems.
Analytic (observational)	Analytic studies are conducted when sufficient information is available to form an *a priori* hypothesis. Analytic studies include case-control studies, cohort studies, and cross-sectional studies.

Descriptive epidemiological studies

Case report	A case report is a descriptive study of a single individual or small group of individuals. An association between an observed effect and a specific environmental exposure is studied based on detailed clinical evaluations and histories of the individual(s).
Cluster	A cluster study is a descriptive study of the population in a geographic area, occupational setting, or other small group in which the rate of a specific adverse effect is much higher than expected.
Ecological	In ecological studies, the relationship between two or more variables is examined at the population level. Ecological studies are most useful when large sets of data are available. Statistical confounders are not important in ecological studies due to a broad scale analysis. Ecological studies are generally categorized as descriptive, but the study could be analytic depending on the type of analysis used. Ecological studies are often used in attempt to assess the health effects of environmental pollutants.
Surveillance systems	Surveillance systems provide broad-scale information on specific populations for which epidemiologic analyses can be conducted.

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Analytical epidemiological studies

Case-control	Case-control studies are used to investigate the relationships between potential risk factor and disease by observing two groups of subjects: one with disease, trait, or condition of interest (case); the other without these conditions (control). Case-control studies usually depend on retrospective data. In a case-control study, selection of cases and controls is a crucial part of the study design. Cases must be selected so that the data can be generalized to all patients with the disease. Controls can be individuals without disease selected from the same group of people.
Cohort	In a cohort study, a group of exposed individuals and a group of nonexposed individuals are observed and followed through time to evaluate changes in the incidence of disease. There are two particular types in cohort studies: prospective (historical) study and retrospective (concurrent) study. In the prospective cohort study, the exposure status at present time is identified and the samples are followed up to determine any future disease onset. In the retrospective approach, exposure status of cohort(s) in the past is identified and they are followed up until the present time. Questionnaires or laboratory tests are generally used in cohort studies to measure both exposure and outcome.
Cross-sectional	In cross-sectional studies, the status of exposure and the state and/or occurrence of disease are measured at a single point in time. A population is first defined, and presence or absence of exposure and presence or absence of disease for individuals is determined. Advantages in cross-sectional studies include (1) one-stop, one-time collection of data, (2) less expensive and more expedient to conduct, and (3) associations and correlation between variables can be easily evaluated. A case-control study is desirable when the disease occurrence is rare, because investigation of rare disease with a cohort study will require a tremendous number of people to be followed to generate enough cases for the study, and may not be practical.

In vitro testing

- Are biological studies which take place in isolation from a living organism such as in a test tube or Petri dish
- A classic example of an in vitro test is the Ames mutagenicity test which examines the agent's capability to cause mutations in *Salmonella typhimurium*
- In vitro assays are used increasingly because they are less costly and quicker than other types of tests
- However, it is difficult to establish a correlation between the observed effects and actual toxicity or carcinogenicity

In vivo testing

- Studies which take place within a living organism
- The chemical compound of interest is administered to the experimental animals to examine short-term acute toxicity or long-term chronic toxicity
- Human toxicity is estimated using the results of in vivo tests with various assumptions.
- **Advantage:** the similar exposure pathways for human toxicity can be examined with mammalian animals.
- **Disadvantages:** a large number of animals is required, they are expensive to conduct, and are time consuming.

Definitions

- **LD_{50}:** Median lethal dose, is the dose of agent at which 50% of the population under the defined conditions dies.
- **LC_{50}:** Medican lethal concentration, is the concentration of a toxicant in the defined environment at which 50 percent of the population will be killed.
- **NOAEL and LOAEL:** The toxicity of a chemical from subchronic exposure (usually exposed for 30-90 days) is examined to establish a "no observed adverse effect level" and the "lowest observed adverse effect level"
- **NOAEL** important for regulations: with a safety factor, a reference dose (RfD) is established which is "acceptable"

Visualization