Chapter 10. Quantitative Toxicology

1. Classification of Toxic Responses (p. 487)

a) important factors influencing toxicity
- dose; "*the dose makes the poison*"
- exposure period; acute (1 day), subchronic (2 weeks - 7 years)
  chronic (> 7 years)
- exposure route; oral, dermal, inhalation

b) toxic endpoint
- irreversible vs. reversible
- cancer vs. noncancerous effects (i.e., developmental, teratogenic,...)

c) dosage vs. dose
- dosage; the total mass of chemical to which an organism is exposed
- dose; the chemical dosage normalized for body weight (e.g., mg/kg)

2. Acute toxicity: The LD_{50} (p. 489)

a) acute toxicity data normally show Gaussian distribution (Fig. 10.1)
<- due to inherent diversity of biological populations

b) dose-response relationship (Fig. 10.2)
- cumulative response vs. Log (dose)
- sigmoidal shape curve
- when 'death' is used as a response; LD_{50} (leathal dose 50, the dose that results in death to 50% of the population; Table 10.2)
- when other responses are used; ED_{50} (effective dosse 50)
- LC_{50}; to quantify the lethality of chemicals in the air and water to which organisms are exposed (e.g., mg/m^3, mg/L)

c) limitations in using data from surrogates (i.e, animals) to humans
- extrapolation from animal dose-response relationships to humans
- small sample sizes of test animals
- uncertainty in biological responses between animals and humans
- extrapolation from higher dose animal data to human usually exposed to low dose in the environment

d) human epidemiological data are the best, BUT due to so many "uncontrollable factors" less evidence of cause-effect relationships are provided
-> well-controlled animal data would be more reliable

3. Quantitative Evaluation of Acute Toxicity (p. 494)

a) establishing dose-response relationship
- normal distribution curve (Fig. 10.1)
- cumulative rsponse vs. Log (dose) (Fig. 10.2)
  . never reach to zero

. almost linear dose-response relationship in the middle region

b) Probit analysis (Fig. 10.3)
- transform raw dose data to probits (Table 10.4)
- a complete linear relationship
- Example 10.3

c) slope of dose-response curve
- indicates a margin of safety
  . the higher the slpoe, the greater the change in toxicity with dose
    -> less safety margin
- Therapeutic Index (TI)
  . developed for drug responses as a margin of safety
  . $TI_{50} = ED_{50}/LD_{50}$

d) potency
- relative toxicity among dose-response curves of chemcials
- different relative toxicities depending on doses (Fig. 10.5)

4. Chronic Industrial Exposure: The Threshold Limit Value (p. 501)

a) a typical dose-response curve for chronic toxicity (Fig. 10.6)

b) Threshold Limit Value (TLV)
- the point where detoxification mechanisms are overwhelmed and thus toxic response(s) is expressed
- TLV 0 -> no threshold (i.e., carcinogens)

5. Maximum Contaminant Levels (p. 505)

a) MCLs developed for drinking water safety (Safety Drinking water Act)

b) Table 10.6 (note the very low concentrations, ppb)

c) applied as "Applicable or Relevant and Appropriate Requirements (ARARs)"
- generally used as cleanup criteria for contaminated goundwater

6. Quantifying the Chronic Toxicity of Noncarcinogens (p. 508)

a) noncarcinogens; threshold levels exist (TLV values)

b) toxicity measure parameters
- No Observed (Adverse) Effect Level (NO(A)EL)
- Low Observed (Adverse) Effect Level (LO(A)EL)

c) Acceptable Daily Intake (ADI)
- a level of daily ingestion or inhalation of a toxic compound that dose not produce an adverse health effect
- ADI = $\frac{NO(A)EL}{safety\ factors}$
  ; variations in the population

d) Reference Dose (RfD)

- similar to ADI, mostly used for contaminants whereas ADI for foods
- RfD = $\frac{NO(A)EL}{safety\ factors}$

  ; 10 for variation among individuals
  10 for extrapolation from animals to humans
  1-10 for professional judgement ("modifying factor")
- Table 10.7

7. Dose-Response Relationships for Carcinogens (p. 510)

a) extraplation problems (Fig. 10.7)

b) prediction the probability of cancer

- tolerance models (e.g., dose-response relationship)
- mechanistic models (e.g., one-hit, gamma, multihit,...)
  . usually accepted by US EPA
  . "one molecule can initiate cancer"
  . no tresholds for carcinogens

c) Cancer Potency Factor (CPF)

- the slope of dose-response curve at low exposures (doses)
- commonly acceptable risk; 1×10^{-6}
- Slope Factor (SF); $[mg/(kg\text{-}day)]^{-1}$
- Table 10.7

8. Sources of Toxicity Information (p. 512)

Chapter 11. Hazardous Waste Risk Assessment

- the goal of risk assessment
  . to provide a quantitative bases for making decisions involving hazardous waste treatment, remediation, and disposal options, waste minimization, and siting new facilities,...
- potential risk (Fig. 11.1)

1. Principles, Definitions, and Perspectives of Hazardous Waste Risk Assessments (p. 521)

a) hazard
   - the intrinsic capability of a chemical to cause harm

b) risk
   - the chance of encountering the potential adverse effects of receptors to environmental hazards
   - the probability of harm
   - risk = hazard + exposure (probability)

c) general procedure
   - hazard identification
     . the chemicals present at the site and their characterisitcs
     . source analysis
   - exposure assessment
     . potential transport of the chemcials to receptors and levels of intake
     . pathway analysis
   - toxicity assessment (Dose-Response assessment)
     . determination of numerical indices of toxicity
     . receptor analysis
   - risk characterization
     . determination of a number of that expresses calculated risk at the site
     . determine the risk is acceptable or not

d) limitations
   - many assumptions involved -> inherent uncertainties

2. The Risk Assessment Process (p. 522)

1) Hazardous identification

a) a detailed evaluation of the source
   - identity, nomenclature, concentration, properties of contaminants

b) concentration-toxicity screeing
   - select surrogate chemical(s) among many chemicals present at a site
   - Chemical Score (R); Table 11.1 & Example 11.1

2) Exposure assessment

a) contact of receptors with contaminant(s)

b) estimation of the magnitude, frequency, duration, and route of exposure

c) assessment includes

- identifying potentially exposed concentrations
- identifying potential exposure pathways
- estimating exposure concetrations
- estimating chemical intakes
- further land use is also important

d) sampling (monitoring) data are usually used, BUT in some cases, calculated values using mathematical models are required

e) mean exposure concentration

- in case of water ingestion

$$I = \frac{CW \times IR \times EF \times ED}{BW \times AT}$$

I; intake of a chemical by ingestion (mg/kg-day)
CW; chemical conc. in water (mg/L)
IR; ingestion rate (L/day)
EF; exposure frequency (days/year)
ED; exposure duration (years)
BW; body weight (kg)
AT; averaging time

input values

CW; determined or calculated (site-specific)
IR; 2L/day (adult, 90th percentile)
EF; dependent on the activity of receptors (pathway-specific)
ED; 70 years (lifetime)
30(9) years (90(50)th percentile at one residence, USA)
BW; 70 kg (adult, average)
AT; ED x 365 days/year for noncarcinogens
70 years x 365 days/year for carcinogens

- in case of inhalation

$$I = \frac{CA \times IR \times ET \times EF \times ED}{BW \times AT}$$

I; intake by inhalation (mg/kg-day)
CA; contaminant conc. in air (mg/m^3)
IR; inhalation rate (m^3/hour)
ET; exposure time (hours/day)

input values

CA; determined or calculated (site-specific)
IR; 20 - 30 m^3/day (adult)

3) Toxicity assessment and risk characterization

a) toxicity assessment

- obtaining RfD, SF data for contaminants

b) risk charactrization

- calculate riks for all of the exposure routes
- for noncarcinogens, use Hazard Index (HI)

$$HI = \frac{I}{RfD}$$

. calculate for all exposure routes ("additive value")

. if cumulative HI is less than 1.0 -> no harmful effect expected

- for carcinogens,

Risk = I x SF

. carcinogenic risk of 1×10^{-6} is a commonly acceptable goal

3. Ecological Risk Assessments (p. 531)

- receptor is the environment, not humans
- the similar concept and procedures as the human risk assessment

4. Sources of Uncertainties in Risk Assessment (p. 534)

- risk calculations; inherent uncertainties

a) source characterization

- inaccurate source samplings and analyses
- unknown toxicity of metabolites and undetectable chemicals

b) lack of available data

- information on a contaminated siite
- toxicological data (e.g., IRIS, HEAST,...)

c) exposure assessment models and methods

- many models are available, BUT....

5. Risk Management and Risk Communication (p. 536)

- risk management

. tool (not science)

. decision-making process

. professional judgements related to economic. political, social, and technical factors are included in additon to risk assessment data

- risk communication