Lecture 5

CHEMICAL RISK

Course: Water Reuse

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Chemical risk assessment

- The toxicology of chemical substances found in drinking water can be divided into three broad classes:
  - (1) acute or chronic toxicity
  - (2) carcinogenicity
  - (3) reproductive, developmental, and neurotoxicity
- The same substance may be capable of causing any and all of the effects depending upon the dose and individual's characteristics

Incremental lifetime risk

Incremental lifetime risk = CDI × PF

The chronic daily intake (CDI) is computed as follows:

$$\text{CDI} = \frac{\text{average daily dose, mg/d}}{\text{body weight, kg}}$$

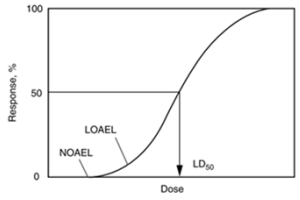
where CDI = chronic daily intake over a 70 yr lifetime, mg/kg•d
PF = potency factor, $(\text{mg/kg}\cdot\text{d})^{-1}$

$$\text{Total dose, mg/kg}\cdot\text{d} = \begin{pmatrix}\text{constituent}\\ \text{concentration}\end{pmatrix}\begin{pmatrix}\text{intake}\\ \text{rate}\end{pmatrix}\begin{pmatrix}\text{exposure}\\ \text{duration}\end{pmatrix}\begin{pmatrix}\text{absorption}\\ \text{factor}\end{pmatrix}$$

Recommended standard values of weight and water ingestion for daily intake calculations have also been developed by the U.S. EPA. The average body weights used for an adult and child are 70 and 10 kg, respectively, and the corresponding rates of water ingestion are 2 and 1 L/d

Potency factor (PF) = slope factor

- Is the slope of the dose-response curve at very low doses. The PF corresponds to the incremental risk above background resulting from a lifetime average dose of a toxicant.
- The relative potency of the chemical constituents can be assessed by comparing the magnitude of the PF



Integrated Risk Information System

Chemical constituent	CASRN[c]	Potency factor, PF: Oral route, $(mg/kg \cdot d)^{-1}$	Potency factor, PF: Inhalation route, $(\mu g/kg \cdot d)^{-1}$
Arsenic, inorganic	7440-38-2	1.5 E+0	3.0 E-2
Benzene	71-43-2	1.5 to 5.5 E-2	1.54 to 5.45 E-5
Bromate	15541-45-4	7 E-1	na
Chloroform	67-66-3	6.1 E-3	1.6 E-4
Dieldrin	60-57-1	1.6 E+1	3.2 E-2
Heptachlor	76-44-8	4.5 E+0	9.1 E-3
N-Nitrosodiethylamine	55-18-5	1.2 E+2	3.0 E-1
N-Nitrosodimethylamine	62-75-9	5.1 E+1	9.8 E-2
Vinyl chloride[d]	75-01-4	7.2 E-1	3.1 to 6.2 E-5

[a]Adapted from U.S. EPA IRIS database (1996) (http://www.epa.gov/iris).

[b]Because the data in the IRIS data base is being revised continuously, it is important to check the data base for the most current values.

[c]Chemical Abstracts Service Registry Number.

[d]Continuous lifetime exposure during adulthood.

Example

EXAMPLE 5-2. Risk Assessment for Lifetime Consumption of Drinking Water Containing *N*-Nitrosodimethylamine.

Estimate the incremental lifetime risk for an adult associated with drinking groundwater containing 2.0 μg/L of *N*-Nitrosodimethylamine (NDMA). Determine the concentration that would be needed to limit the risk to 1 in 100,000.

Solution

Compute the CDI in mg/kg·d using Eq. (5-11).

$$\text{CDI} = \frac{\text{(average daily dose, mg/d)}}{\text{body weight, kg}}$$

$$\text{CDI} = \frac{(2.0\ \mu g/L)\,(2\ L/d)\,(1\ mg/10^{-3}\ \mu g)}{70\ kg} = 0.57 \times 10^{-4}\ mg/kg \cdot d$$

Incremental lifetime risk = CDI × PF

The PF of NDMA from Table 5-8 for the oral route is $5.1 \times 10\ (mg/kg \cdot d)^{-1}$

Incremental lifetime risk = $(0.57 \times 10^{-4}\ mg/kg \cdot d)\ [5.1 \times 10\ (mg/kg \cdot d)^{-1}]$
$= 0.29 \times 10^{-2}$

Thus, the calculated estimated probability of developing cancer as a result of lifetime consumption of water containing 2.0 mg/L of NDMA would be 2.9 per 1000 persons.

Solution

Determine the concentration of NDMA to limit the risk to 1 in 100,000.

a. Estimate the CDI based on the determined risk and PF listed in Table 5-8.

$$10^{-5} = (\text{CDI})\ [5.1 \times 10\ (mg/kg \cdot d)^{-1}]$$

$$\text{CDI} = 1.96 \times 10^{-7}\ mg/kg \cdot d$$

b. Estimate the concentration of NDMA by rearranging Eq. (5-12).

$$\frac{(C,\ \mu g/L)\,(2\ L/d)\,(1\ mg/10^{-3}\ \mu g)}{70\ kg} = 1.96 \times 10^{-7}\ mg/kg \cdot d$$

$$C = 0.0069\ \mu g/L$$

Comment

NDMA is a member of a family of extremely potent carcinogens, the *N*-nitrosamines. Until recently, concerns about NDMA focused mainly on the presence of NDMA in food, consumer products, and polluted air. However, current concern focuses on NDMA as a drinking water contaminant resulting from reactions occurring during chlorination or via direct industrial contamination. Because of the relatively high concentrations of NDMA formed during wastewater chlorination, the fate of NDMA in planned or unplanned indirect potable reuse is a particularly important area of concern.

Reference dose

- The RfD values represent an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive sub groups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.
- Values for RfDs are available in the IRIS database.

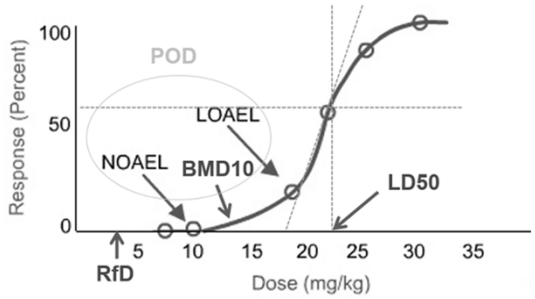
$$\text{RfD} = \frac{\text{NOAEL or LOAEL}}{(\text{UF}_1 \times \text{UF}_2 \ldots) \times \text{MF}}$$

The numerator is called the "Point of Departure"

where NOAEL = no observable adverse effect level
LOAEL = lowest observable adverse effect level
UF_1, UF_2 = uncertainty factors
MF = modifying factor

Point of departure (PoD)

- The most common PoD used to derive RfD is NOAEL, the next priority is LOAEL, and more recently, the statistical benchmark dose (BMD) is becoming popular.



Reference dose

- The modified RfD for long-term or lifetime exposure for an adult can be computed by multiplying the NOAEL (in mg/kg/day) by the reference weight of a typical adult (70 kg) and dividing by the safety (uncertainty) factor.

$$\text{RfD, mg/person} \cdot \text{d} = \frac{(\text{NOAEL, mg/kg} \cdot \text{d})(70 \text{ kg/person})}{\text{safety (uncertainty) factor}}$$

- Because the RfD is intended to account for total daily intake of the toxicant, inhalation and food intake, as well as water, should be accounted for

$$\text{Drinking water target, mg/L} = \frac{[(\text{RfD, mg/person} \cdot \text{d}) - (\text{inhalation, mg/person} \cdot \text{d}) - (\text{food, mg/person} \cdot \text{d})]}{2 \text{ (L/person} \cdot \text{d)}}$$

Relative source contribution

- The relative source contribution (RSC), the contribution from each route of exposure, should be factored into the ultimate maximum concentration level (MCL)
- Typically, the U.S. EPA will assume an RSC of 20% from drinking water for inorganic chemicals with higher values for volatile organic chemicals (VOCs).
- Note that as the RSC value decreases, the drinking water standard will become more stringent, which is somewhat counter-intuitive because the burden on the drinking water supplier increases as the significance of the drinking water contribution to health risk decreases.

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Example

- For a NOAEL value of 20 mg/kg·d, a 70-kg person, and an uncertainty factor of 1000, what is the RfD value?
- What is the drinking water equivalent level (DWEL) calculated by using the default assumption of 20 percent of the daily dose allocated to drinking water?

Solution

$$\text{RfD, mg/person} \cdot \text{d} = \frac{(20\ \text{mg/kg} \cdot \text{d})\ (70\ \text{kg/person})}{1000} = 1.4\ \text{mg/person} \cdot \text{d}$$

$$\text{DWEL} = \frac{(1.4\ \text{mg/person} \cdot \text{L})}{(2\ \text{L/person} \cdot \text{d})} \times 0.20 = 0.14\ \text{mg/L}$$

- **Note:** The validity of a RfD is dependent entirely on the selection of the safety (uncertainty) factor, which is judgmental. The quality of the experimental evidence determines the magnitude of the safety (uncertainty) factor to be applied. The lesser the understanding of the toxicology, the greater the uncertainty factor and the lower the RfD or MCL.

Safety factor guidelines

- **10 Factor:** Valid experimental results from studies on prolonged human ingestion.
- **100 Factor:** Experimental results of studies of human ingestion not available. Valid results from long-term feeding studies on animals.
- **1000 Factor:** No long-term or acute human data. Scant results on experimental animals.
- Additional modifying factors ranging from 1 to 10 can be used for poor data, significant effects, or other concerns, particularly for high-risk populations such as children.

Safety factor guidelines

$$RfD\ or\ RfC = \frac{Point\ of\ Departure\ (POD)[Modification\ if\ necessary]}{UF1 * UF2 * UF3 * UF4 * Modifying\ Factor\ (MF)}$$

US EPA Uncertainty Factor (UF) for Risk Assessment		Value
UF1	Account for the variation in sensitivity among the members of the human population	10
UF2	Account for the uncertainty when extrapolating from animal data to humans	10
UF3	Account for the uncertainty when extrapolating from sub-chronic NOAELs to chronic NOAELs	10 (default is 1)
UF4	Account for the uncertainty when using LOAEL instead of NOAEL/BMD as POD	10 (default is 1)
MF	Account for additional uncertainty factors such as data quality, confidence in data set.	0<MF<=10 (default is 1)

How to use safety factors?

Example:

If **2** NOAEL values have been identified from long-term rat studies (**10mg/kg bw/day** for reproductive toxicity, **50mg/kg bw/day** for dietary chronic toxicity), the point of departure (POD) will be **10mg/kg bw/day** (the lowest NOAEL). The derived **RfD** for human health effects will be **0.1mg/kg bw/day** (10mg/kg bw/day divided by 100). If human exposure level to a chemical substance by oral route is less than RfD 0.1mg/kg bw/day, the risk of the substance is acceptable.

WHO guidelines for drinking-water quality (4th edition, 2017)

- Tolerable burden of disease: a 10^{-5} excess lifetime risk of cancer (i.e. 1 excess case of cancer per 100 000 people ingesting drinking-water at the water quality target daily over a 70-year period). In some cases this may not be practical, so even a 10^{-4} lifetime risk could be acceptable
- The various hazards from water can have very diverse health outcomes with different impacts ranging from mild diarrhea to severe cancer. A common metric (DALY) is used to quantify and compare the burden of disease associated with different water-related hazards, taking into account varying probabilities, severities and duration of effects.

Disability-adjusted life year (DALY)

- A key advantage of using the DALY is its aggregation of different impacts on the quality and quantity of life and its focus on actual outcomes rather than potential risks; hence, it supports rational public health priority setting.

Disability-adjusted life year (DALY)

- The basic principle of the DALY is to weight each health impact in terms of severity within the range of 0 for good health to 1 for death.
- The weighting is then multiplied by duration of the effect and the number of people affected. In the case of death, duration is regarded as the years lost in relation to normal life expectancy.
- Using this approach, a mild diarrhea with a severity weighting of 0.1 and lasting for 7 days results in a DALY of 0.002, whereas death resulting in a loss of 30 years of life equates to a DALY of 30.

Example

- Assuming that the following is true in developed countries, what is the DALY of the rotavirus in these countries?

- mild diarrhoea (severity rating of 0.1) lasting 7 days in 97.5% of cases;
- severe diarrhoea (severity rating of 0.23) lasting 7 days in 2.5% of cases;
- rare deaths of very young children in 0.015% of cases.

Solution

- We know that:

DALY = YLL (years of life lost) + YLD (years lived with a disability or illness).

- So:

$$\begin{aligned} DALY &= (0.1 \times 7/365 \times 0.975) + (0.23 \times 7/365 \times 0.025) + (1 \times 70 \times 0.00015) \\ &= 0.0019 + 0.0001 + 0.0105 \\ &= 0.0125 \end{aligned}$$

Qualitative assessment of carcinogens

Group A—Human carcinogen: sufficient evidence in humans.

Group B—Probable human carcinogen: limited evidence in humans or no evidence in humans but sufficient evidence in animals.

Group C—Possible human carcinogen: limited or equivocal evidence in animals in the absence of human data.

Group D—Not classifiable as to human carcinogenicity: inadequate or no data available.

Group E—No evidence of carcinogenicity for humans: negative evidence in at least two species.

Category I: Group A and B substances: Goal equals zero (aspirational goal).

Category II: Group C substances: The goal equals 10^{-5} to 10^{-6} (1 per 100,000 to 1 per 1,000,000) hypothetical excess cancer risk per 70 yr lifetime, or the goal equals the RfD value converted to DWEL with an additional safety factor applied to allow for an adequate margin of safety due to uncertainties in the substances carcinogenic potential to humans.

Category III: Group D and E substances: Goal is calculated using the RfD approach with a portion allocated to drinking water.