Hazard Characterization

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Schedule

3-4pm: lecture on hazard characterization

4-5pm: exercise on species sensitivity distribution

Dose-response assessment

Description of hazards

"Ice cream consumption, exposure, intervention, experiment"

With or without a description of dose pertaining to the hazard:

- Consuming *water* can cause death
- Consuming *1000 liters water* can cause death
- Consuming *1000 liters water in 1 hour* can cause death

A complete description of hazard must include dose

With enough dose, everything could be lethal

"*dosis sola facit venenum*" - Paracelsus, 1538

"Only the dose makes the poison"

Hazard characterization, aka dose-response assessment:

After the **identification** of hazard, how the adverse outcome changes quantitatively in response to the changes in hazard?

Why move away from NOAEL/LOAEL for dose-response assessment?

Example 1

tolerated probability of type I error: 0.01

Dose	Response	p value
0	10.0	-
5	10.5	0.34
25	11.3	0.002
50	18.3	< 0.001

1. Can you find a NOAEL?
2. Can you find a LOAEL?

Example 2

Dose	Response	p value
0	10.0	-
10	10.5	0.005
25	11.3	< 0.001
50	18.3	< 0.001

1. Can you find a NOAEL?
2. Can you find a LOAEL?
3. What's the difference between example 1 and 2? How the differences affect NOAEL/LOAEL?

Problems of NOAEL/LOAEL approach

- Limited by dosage setup in study design
- Limited use of data
- NOAEL not always available
- No expression of uncertainty

Benchmark dose modeling

What is BMD?

1. fit a statistical model to all dose-response data
2. Determine a BMR: a level of response of practical interest, e.g., not considerably adverse in the population
3. **Estimate the dose that causes the BMR using the fitted model**

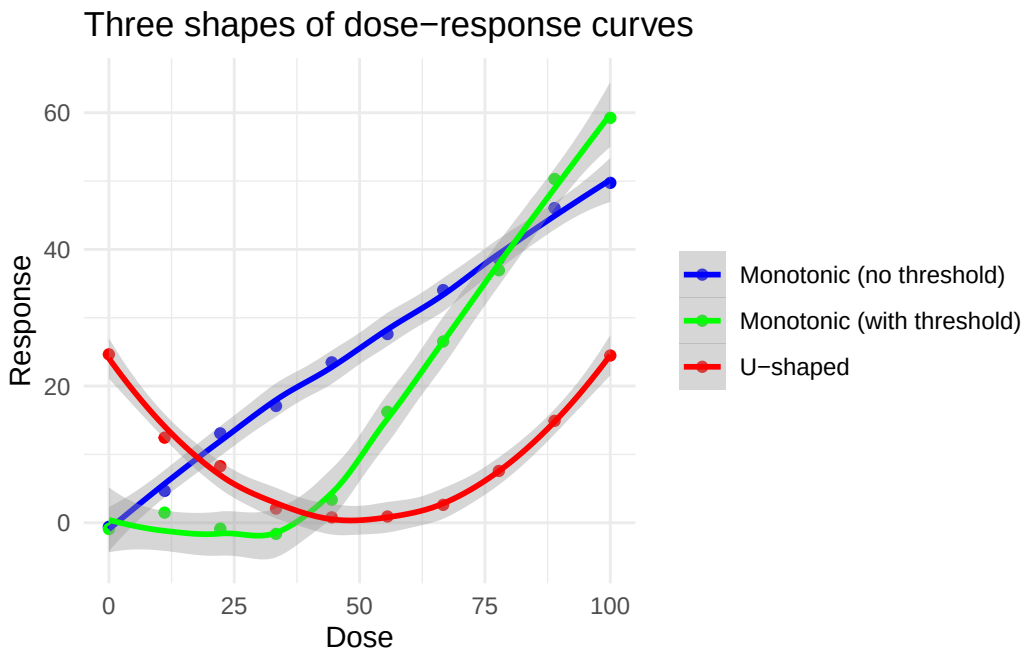
Strength

1. Proper use of all dose-response data
2. Much less limited by dosage setup in study design
3. Not requiring the data to show a NOAEL
4. Allow the expression of uncertainty as distributions

Challenges

1. Require more and complicated statistical analysis
2. Sensitive to selection of BMR
3. Sensitive to choices in statistical modeling

Example benchmark dose models



1. Monotonic, threshold

Threshold: a level of **dose** beyond which the level of **responses** changes significantly

- Most ideal shape for decision making
- Require more data for modeling
- Majority of chemicals: non-mutagenic, safe below threshold
- BMD around the threshold

2. Monotonic, no threshold

- Easy to model
- Mutagenic chemicals: one molecular can cause cancer, no safe level
- BMD around the dose that causes considerable risk, e.g., >= 1 cancer in 100,000 population

3. Non-monotonic

- Hormesis
- Essential chemicals

BMD tools

We will exercise with:

EFSA PROAST web (by RIVM): https://proastweb.rivm.nl/

BMDS online (by US EPA): https://www.epa.gov/bmds/bmds-online

Other options, not in our exercise:

PROAST full (R package): https://www.rivm.nl/en/proast

EFSA Bayesian BMD (by Hasselt University, Belgium): https://r4eu.efsa.europa.eu/app/bmdbayesian