SPINOFFS

Spinoffs are relatively short learning modules inspired by the LTAs. They can be easily implemented to support student learning in courses ranging from prealgebra through calculus. The Spinoffs typically give students an opportunity to use mathematics in a real world context.

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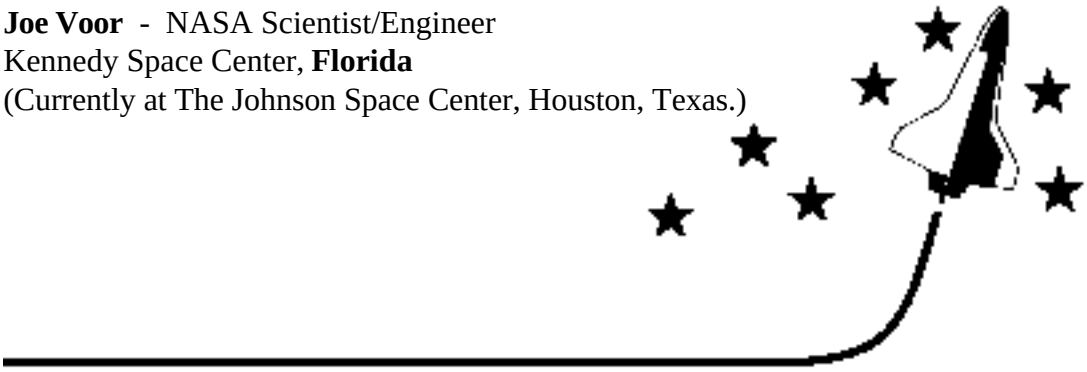

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SPINOFF 5C

Calculating the Reference Dose

How does the Environmental Protection Agency determine if a chemical is toxic? If the chemical is toxic, then how much exposure to the chemical (if any) can we have and still be "safe"? The answers to these questions can greatly affect risk calculations done by a risk assessor. If the answers are incorrect, they can force an unnecessary clean up of a polluted site or they can leave a site dangerously polluted. This Spinoff will help you see how some of these questions are answered.

You may recall from LTA 5 that risk assessors can calculate a value called the Hazard Quotient for each potentially toxic chemical. The Hazard Quotient is calculated in the following manner:

$$\text{Hazard Quotient} = \frac{(\text{Chemical Concentration}) \times (\text{Non - carcinogenic Intake Factor})}{(\text{Reference Dose})}$$

Recall that the Hazard Quotient is used to analyze the toxic effects of non-carcinogenic chemicals on humans. Although non-carinogenic chemicals have not been shown to cause cancer, they can still affect your health. The Environmental Protection Agency makes the assumption that humans can withstand a certain amount of daily exposure to a non-carcinogenic chemical. The amount of exposure that humans can withstand each day throughout their lifetime is called the Reference Dose. For example, the Reference Dose used for beryllium is $2.16\text{E-}01 \frac{\left(\frac{\text{mg}}{\text{kg}}\right)}{\text{day}}$. This number means that you can ingest 0.216 mg of beryllium for every kilogram of your weight each day of your life and be relatively confident you will not get sick due to exposure to beryllium. For example, if you weigh 70 kg then you can ingest 15.12 mg per day and be relatively safe. (Can you check this calculation?) Instead of writing the units for the Reference Dose as $\frac{\left(\frac{\text{mg}}{\text{kg}}\right)}{\text{day}}$, we shall use the more convenient notation $\frac{\text{mg}}{\text{kg - day}}$.

How is a Reference Dose calculated? To calculate a Reference Dose, the EPA follows this procedure:

1) A group of scientists working with the EPA researches scientific literature for studies that have been done to determine how toxic the chemical is to humans. If the scientists are fortunate, they will find a study of humans, but more often than not they will have to rely on animal studies.

2) Of all the studies in the scientific literature, the scientists choose one study to be the "critical study". This is the study the scientists feel gives the best evidence that the chemical in question could be toxic.

3) The critical study will identify either a NOAEL or a LOAEL or both. NOAEL is shorthand for "no-observed-adverse-effect-level". The NOAEL is the highest dose of chemical found in the study that **did not** produce a statistically significant adverse effect (such as increased body weight or tissue damage). LOAEL is shorthand for "lowest-observed-adverse-effect-level". The LOAEL is the lowest dose observed in the study that **did** produce a statistically significant adverse effect.

4) The EPA then calculates the Reference Dose as follows:

$$\text{Reference Dose} = \frac{\text{NOAEL}}{\text{UF}} \text{ or Reference Dose} = \frac{\text{LOAEL}}{\text{UF}}$$

UF is called the uncertainty factor. Uncertainty factors are products of 10 that are used to lower the NOAEL or LOAEL due to the uncertainty in the critical study. The following criteria are used to calculate uncertainty factors:

- Use one factor of ten called "10H"to account for the variation in sensitivity to the chemical among members of the human population. This factor of ten is used nearly every time.
- Use one factor of ten called "10A" to account for the uncertainty of extrapolating data from animal studies to humans.
- Use one factor of ten called "10S" to account for use of data from a subchronic study. A subchronic study is one that exposes an animal to the chemical for a short amount of its lifetime, usually less than 3 months. In contrast, a chronic study is one that exposes the animal to the chemical over extended periods of its lifetime. There is no "10" associated with a chronic study.
- Use one factor of ten called "10L" when the LOAEL is used instead of the NOAEL

Here is an example of a Reference Dose calculation

The EPA has found a 90-day study of the effect of a toxic chemical on rats that it believes is an excellent scientific study. The toxic chemical was fed to the rats over the 90-day period at the levels shown in the following table:

Group	**Dose (in mg/kg-day) Over the 90 day period**	**Results**
Control group	0	No adverse effects observed
1	1	No statistically significant differences between group 1 and the control group
2	5	No statistically significant differences between group 2 and the control group
3	25	Statistically significant adverse effects observed with respect to the control group

From the table, we see that the NOAEL for this study is 5 mg/kg-day (Group 2). This is the highest dose observed where no statistically significant effects were shown. The LOAEL for this study is 25 mg/kg-day (Group 3). This is the lowest dose observed where a statistically significant effect was shown. If present in the critical study, the NOAEL is used to determine the Reference Dose. If the critical study does not have a NOAEL, then the LOAEL is used to calculate the Reference Dose.

To calculate the Reference Dose using the NOAEL, we use the following UF

$$UF = 10H \times 10A \times 10S = 1000$$

The study was an animal study (so 10A is used) and was subchronic (only for 90 days, so 10S is used).

Hence, the Reference Dose is

$$\text{Reference Dose} = \frac{\text{NOAEL}}{\text{UF}} = \frac{5}{1000} = 0.005 \ \frac{\text{mg}}{\text{kg - day}}$$

If no NOAEL was available, we would have to use the LOAEL, and the UF would be

$$UF = 10H \times 10A \times 10S \times 10L = 10000$$

The Reference Dose is:

$$\text{Reference Dose} = \frac{\text{LOAEL}}{\text{UF}} = \frac{25}{10000} = 0.0025 \ \frac{\text{mg}}{\text{kg - day}}$$

Questions

1) Consider the following Reference Doses for toxic chemicals. Calculate the mg of each chemical a person weighing 70 kg could ingest each day for his/her lifetime. Then calculate the amount a person weighing 180 lbs could ingest each day. Then calculate the amount **YOU** (using your weight) could ingest each day. Recall 2.2 lbs = 1 kg.

Chemical Name	**Reference Dose** (mg/kg-day)
Acetone	1E-01
Benzoic Acid	4.0E+00
Calcium Cyanide	4.0E-02
Isobutyl Alcohol	3.5E-01
Cadmium	5.0E-04

2) Use the descriptions of the studies below to calculate a Reference Dose for each potentially toxic chemical. For each study identify the NOAEL and LOAEL (if available), and do the calculation using both measures if possible. Write a paragraph that explains the process you used to calculate the Reference Dose in each case.

a) Three groups of rats were exposed to differing concentrations of beryllium over their entire lifetime. The results from the study are as follows:

Group	**Dose given** (mg/kg-day)	**Results**
Control	0	No adverse effects noted
1	5.65	No statistically significant results noted
2	10.876	Statistically significant adverse effects noted

b) Four groups of rats were given acetone as part of their diet in a 90 day study. The results from the study are as follows:

Group	**Dose Given** (mg/kg-day)	**Results**
Control	0	No adverse effects noted
1	50	No statistically significant results noted
2	100	No statistically significant results noted
3	500	Statistically significant adverse effects notes

c) A study was done of individuals in China who were exposed to selenium over a period of 20 years. The results of this study are as follows:

Group	**Dose of Exposure** (mg/kg-day)	**Results**
Control	0	No adverse effects
1	0.023	Statistically significant adverse effects noted

d) Three groups of rats were exposed to toluene in a 13 week study. Assume this is considered a chronic study. The results of the study are as follows:

Group	**Dose of Exposure** (mg/kg-day)	**Results**
Control	0	No adverse effects noted
1	100	No adverse effects noted
2	233	No statistically significant adverse effects noted
3	625	Statistically significant adverse effects noted

Group Discussion Questions

What is your confidence in the Reference Dose as a measure of the amount of exposure that a human can have to a chemical in a lifetime? Do you think the Reference Dose calculation method is too cautious or perhaps not cautious enough? Discuss these questions in your groups, and write a paragraph explaining your opinions and reasoning.