Introduction to Risk Assessment

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Course Description

The course will consider how evidence from epidemiology and toxicology is used to estimate the human health risks posed by exposure to environmental contaminants and will examine how these estimates of risk may be used to inform decisions. The four elements of risk assessment -- hazard identification, exposure assessment, dose-response analysis, and risk characterization will be discussed. Statistical concepts important for exposure assessment, dose-response analysis and uncertainty analysis will be covered. Standard regulatory approaches for estimating cancer potency factors and reference doses from animal studies will be introduced. Dose response models such as the one hit, the multistage, the probit and the Weibull will be discussed. A variety of methods for interspecies scaling will be considered -- including body weight scaling, surface area scaling and pharmacokinetic modeling. Basic elements of decision analysis will be reviewed. Sources of uncertainty in environmental health risk assessments will be discussed and various methods for characterization of uncertainty in final estimates of risk will be considered. The implications for decision making of uncertainty in estimates of risk will be evaluated.

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Abbreviated Syllabus

Day 1 – June 4, 2012

	9:15 to 9:30 AM	Registration & Introduction
S1	9:30 to 11 AM	Introduction & Overview
	11 to 11:30 AM	Coffee Break
S2	11:30 AM to 1:00 PM	"Non-Cancer" Risk Assessment
	1:00 to 2:00 PM	Luncheon
W1	2:00 to 3:30 PM	Workshop 1: Dose-Response – NOAEL & BMD
S3	3:30 to 4:30 PM	Exposure Assessment / Environmental Statistics

Day 2 – June 5, 2012

	9:15 to 9:30 AM	Introduction
S4	9:30 to 11:00 AM	Cancer Risk Assessment
	11 to 11:30 AM	Coffee Break
S5	11:30 AM to 12:30 PM	Expert Judgment (+Calibration Exercise)
	12:30 to 1:30 PM	Luncheon
W2	1:30 to 3:00 PM	Workshop 2: Dose-Response – Cancer Potency
S6	3:00 to 4:30 PM	Value of Information

Optional Material

S7	*Not Scheduled*	*Parameter Uncertainty*
S8	*Not Scheduled*	*Model Uncertainty*

Overview of Risk Assessment

[Refer to handouts for Lecture L1 – Overview of Risk Assessment.]

What is a risk assessment? The elements of risk assessment – hazard identification, exposure assessment, dose-response analysis, risk characterization. The distinction between risk assessment and risk management. Basic framework for cancer risk assessment. Basic framework for non-cancer risk assessment.

Assignment:

Read the chapter from Gilbert Masters and come prepared to discuss the reading. Use the handout "Some Questions about Risk Assessment," as a guide in preparing for class.

Masters, G.M. "Risk Assessment," Chapter 4, and the section on ***units*** from "Mass and Energy Transfer," Chapter 1 in *Introduction to Environmental Engineering and Science*, 2nd Ed., Prentice Hall, Englewood Cliffs, NJ, 1998.

"Non-Cancer" Risk Assessment

[Refer to handouts for Lecture L2 – Non-Cancer Risk Assessment]

How are "safe" levels of exposure for compounds that cause health effects other than cancer established? The nature of the individual threshold. Heterogeneity in sensitivity and its relationship to the tolerance distribution. Definition of the reference dose, RfD, and the reference concentration, RfC. Defining adversity. Quantal and continuous data sets. Use of the no adverse effects level and no observed adverse effects level as proxies for animal thresholds. Limitations of the NOAEL. Definition of benchmark dose. Extrapolation from animals to humans. Adjusting for heterogeneity in human sensitivity. Compensating for limitations of animal data – acute or sub-chronic studies; studies which failed to yield NOAELs; incomplete sets of studies. Historical basis for the 10 fold "safety" or "uncertainty" factors.

Assignment:

Read the selections from Rodricks' book *Calculated Risks*. Refer to the handout "Questions About Non-Cancer Risk Assessment," to guide your reading. Also read the brief section on the reference concentration (RfC) from the Rees and Hattis chapter of the Wallace Haye's Principles and Methods of Toxicology

Rodricks, JV "From Dose to Toxic Response," Chapter 3, pp. 64-75 and "Risk Assessment II; Applications," Chapter 8, pp. 230-239, in *Calculated Risks*, 2nd Edition, Cambridge University Press, Cambridge, England, 2007.

Rees, C. and D.W. Hattis, Section on Inhalation Reference Concentration in "Developing Quantitative Strategies for Animal to Human Extrapolation," Chapter 8 in Hayes, W.A., ***Principles and Methods of Toxicology***, 3rd Edition, Raven Press, New York, 1994. (pp. 279-281).

If you are unfamiliar with the binomial distribution, consult Chapter 3, "Review of Statistics for Risk Assessment," in Kammen, DM and DM Hassenzahl, ***Should We Risk It?: Exploring Environmental, Health and Technological Problem Solving***, Princeton University Press, Princeton, NJ, 1999.

Computer Workshop #1 – NOAEL, BMD and RfD

[Refer to handouts for Computer Workshop #1]

Use EXCEL to plot the data, estimate the 95% confidence intervals for each point. Then visually fit the Weibull model R = 1 – exp (-ln2 x ((d-T)/d50) ^ v) and the logistic model R(d) = 1 / (1 + exp (- a – b x d)) to the data. Finally, download the US EPA's Benchmark Dose software from the website www.epa.gov and use it to formally estimate the ED10 and the LED10 (i.e., the BMD).

Assessing Human Exposure to Environmental Contaminants

[Refer to handouts for Lectures L3a – Exposure Assessment.]

What is exposure and how is it measured or estimated? The distinctions between concentration, exposure and dose. Definition and choice of averaging time. The population distribution of exposure. The distinction between uncertainty and variability. Two basic approaches for exposure assessment – direct and indirect. Nature, strengths and weaknesses of each approach.

Statistics for Exposure & Risk Assessment

[Refer to handouts for Lecture L3b – Probability Distributions.]

How are inferences about the mean exposure of the population made from data collected from a sample? The importance of random sampling. Estimating the uncertainty in an estimate of the mean. Central limit theorem. Distinction between standard deviation and standard error of the mean. The normal, lognormal and binomial distributions.

Assignment:

Read the paper by Wayne Ott and come prepared to discuss the reading. Use the handout "Some Questions about Exposure Assessment," as a guide in preparing for class. Consult the selections from Lyman Ott for background information on statistics.

Ott, W.R. "Total Human Exposure," *Environmental Science and Technology*, 19:880-886, 1985.

Ott, L., "The Normal Probability Distribution," Chapter 3 and "Count Data," Chapter 10 (pp. 265, 275-277) in A*n Introduction to Statistical Methods and Data Analysis?* Duxbury Press, Belmont, CA. 1977.

Cancer Risk Assessment

[Refer to handouts for Lectures L4a/L4b – Cancer/Interspecies Scaling]

How are individual and population cancer risks from exposure to pollutants in the environment, food or the workplace estimated? What sources of evidence are considered? The nature, role, strengths, and weaknesses of epidemiology, animal toxicology, mutagenicity tests and structure-activity analysis are considered.

How is the standard rodent bioassay conducted? Why are rodents used? What information comes from the bioassay? What level of risks can the bioassay detect? What levels of risk are of interest for regulation? How do the needs to extrapolate from high to low dose and from animals to humans complicate the interpretation of results from animal studies?

What is the goal of scaling? Approaches for scaling from animals to humans. The allometric method. Rationale and empiricism underlying body weight and surface area scaling. What is the "best" approach? How much uncertainty is there in estimates produced using the "best" approach? Evidence from NOAELs, LD50s and TD50s. Pharmacokinetic models – both empirical and physiologically-based.

Assignment:

Read the selections from Rodricks' book *Calculated Risks*. Refer to the handout "Questions About Cancer Risk Assessment," to guide your reading. Consult the chapter from Kammen and Hassenzahl to learn the mathematics underlying estimates of potency.

Rodricks, J.V., "Risk Assessment II: Applications," pp. 239-247 from Chapter 8 in *Calculated Risks*, 2nd Edition, Cambridge University Press, Cambridge, England, 2007.

Computer Workshop #2 – Estimating Cancer Potency / BMDs – Maximum Likelihood

[Refer to handouts for W#2 – Estimating Cancer Potency – for problem statements.]

Part A -- Use either Excel or Analytica to estimate find the maximum likelihood estimates of cancer potency and BMDs from data sets to be provided.

Decision Analysis – Probabilities, Consequences & Utilities

[Refer to handouts for L5 – Decision Analysis; and Study Questions – Decision Analysis.]

What is decision analysis? The elements of decision analysis – decision, chance, consequence. The use of decision trees to organize and analyze the interplay of these elements. Probability – objective and subjective. Criteria for decision making under uncertainty – expected monetary value and expected utility.

Assignment:

Read the chapter from Lindley and come prepared to discuss the reading.

Lindley, D.V., "Decisions and Uncertain Events," Chapter 1 in Making Decisions, 2nd Edition, John Wiley & Sons, New York, 1985.

Risk Characterization -- Assessing & Propagating Uncertainty

[Refer to handouts for Lectures L6/L7 – Propagation of Uncertainty/Expert Judgment]

What are the basic approaches for analyzing the propagation of uncertainty in exposure and risk models? Gauss' Law (delta method, quadrature); lognormal approach for multiplicative models; Monte Carlo analysis. Nature, strengths and weaknesses of each approach.

What approaches can be used to characterize the current state of knowledge? Subjective probability. Expert judgment. Heuristics and biases. Informativeness and Accuracy. Calibration. Combination of Judgment.

EXAMPLEs and ILLUSTRATIONs – Propagation of uncertainty in measurement of airborne particulate matter. Carcinogenic Potency of Chloroform; Mortality from Fine Particles; Calibration Exercise from Wright. *Behavioral Decision Theory: An Introduction*, Sage Publications, Berkeley, CA, 1984.

Assignment:

For our first class, read the selections from Chapter 8 in Morgan and Henrion's book *Uncertainty*. Refer to the handout "Guidelines for Reading – Propagation of Uncertainty," to guide your reading.

For our second class, read the selections from Chapters 4 and 6 of Morgan and Henrion's book Uncertainty. Refer to the handout "Guidelines for Reading – Expert Judgment," to guide your reading.

> Morgan, M.G. and M. Henrion, "The Propagation and Analysis of Uncertainty," Chapter 8, and "The Nature and Sources of Uncertainty," Chapter 4, and "Human Judgment about and with Uncertainty," Chapter 6 in *Uncertainty: A Guide to Dealing with Uncertainty in Quantitative Risk and Policy Analysis,* Cambridge University Press, Cambridge, UK, 1990.

Computer Workshop #3– Propagation of Uncertainty/Value of Information

Use Analytica to analyze the propagation of uncertainty in the assigned risk assessment problem.

Value of Information

[Refer to handouts for Lecture L8 – Value of Information (CHEF).]

How can information about uncertainty in current estimates of risk be used to prioritize research? Decision analysis as a framework for decision making under uncertainty. Value of information analysis. Bayes' Theorem.

Assignment:

Read the chapter from Lindley in preparation for class.

Lindley, D.V. "Value of Information" Chapter 7 in *Making Decisions*, 2nd Ed., Wiley, London, 1985.

Supplementary Reading

Non-Cancer Risk Assessment:

Dourson, M.L. and J.F. Stara, "Regulatory History and Experimental Support for Uncertainty (Safety) Factors," *Regulatory Toxicology and Pharmacology*, 1983.

Crump, K.S., "A New Method for Determining Allowable Daily Intakes," *Fundamental and Applied Toxicology*, 4, 854-871, 1984.

Bokkers, B.G.H. and W. Slob, "Deriving a Data-Based Interspecies Assessment Factor Using the LOAEL and BMD Approaches," *Critical Reviews in Toxicology,* 2007.

Hattis, D., Banati, P., Goble, R. and D.E Burmaster, "Human Interindividual Variability in Parameters Related to Health Risks," Risk Analysis, 19(4): 711-726, 1999.

US Environmental Protection Agency, Integrated Risk Information System (IRIS), "Reference Dose (RfD): Description and Us in Health Risk Assessments, March 15, 1993 (www.epa.gov/iris/rfd.htm).

Cancer Risk Assessment:

Kammen, D.M and D.M. Hassenzahl, "Toxicology," Chapter 5 in *Should We Risk It?* Princeton University Press, Princeton, NJ. 1999.

Rodricks, J.V., "Carcinogens," pp. 136-161 Chapter 5 in *Calculated Risks*, 2nd Edition, Cambridge University Press, Cambridge, England, 2007.

US EPA Risk Assessment Forum, Introduction (pp. 1-22) from "Guidelines for Carcinogen Risk Assessment," EPA/630/P-03/001F, US EPA, Washington, DC, March 2005.

Risk Characterization:

Roman, H. A., Walker, K.D., Walsh, T.L, Conner, L., Richmond, H.M., Hubbell, B.J. and P.L. Kinney, "Expert Judgment Assessment of the Mortality Impact of Changes in Ambient Fine Particulate Metter in the U.S.," *Environmental Science and Technology,* 42(7):2268-2274, 2008.

Fraas, A.G., *The Treatment of Uncertainty in EPA's Analysis of Air Pollution Rules: A Status Report,* Discussion Paper RFF DP 10-04, Resources for the Future, Washington, DC, February 2010.

Evans, J.S., Rhomberg, L.R., Williams, P.L., Wilson, A.M. and S.J.S. Baird, "Reproductive and Developmental Risks from Ethylene Oxide: A Probabilistic Characterization of Possible Regulatory Thresholds, Risk Analysis, 21 (4): 697-717, 2001.

Value of Information:

Lave, L.B., Ennever, F.K., Rosenkranz, H.S. and G.S. Omenn, "The Information Value of the Rodent Bioassay," *Nature*, 336, 631-633, 1988.