SYMPOSIUM ON BIOSTATISTICAL AND BIOMATHEMATICAL PROBLEMS IN ENVIRONMENTAL HEALTH

Friday, June 7, 2002

National Institute of Environmental Health Sciences (NIEHS)
Rodbell Conference Center
Rall Building, South Campus
111 T.W. Alexander Drive
Research Triangle Park, NC 27709

Sponsored by:
National Institute of Environmental Health Sciences
University of North Carolina, Department of Biostatistics
University of North Carolina, Center for Environmental Health and Susceptibility

8:30 – 8:50 a.m.	Registration	NIEHS Lobby
8:50 – 9:00 a.m.	Opening Remarks • Dr. Lutz Birnbaumer, NIEHS • Dr. Lawrence Reiter, U.S. Environmental Protection Agency (EPA) • Dr. Lawrence Kupper, University of North Carolina	
9:00 – 9:30 a.m.	Predictive Simulation Modeling for Antiandrogen Impacts on Rodent Prostate Dr. Hugh Barton, U.S. EPA	
9:30 – 10:00 a.m.	Discussion	
10:00 – 10:30 a.m.	Advantages of Bayesian Applications in Regulatory Risk Assessment Dr. Annie Jarabek, U.S. EPA	
10:30 – 11:00 a.m.	Discussion	
11:00 – 11:30 a.m.	Pooling Specimens Can Improve Efficiency of Case-Control Studies Dr. Clarice Weinberg, NIEHS	
11:30 – 12:00 p.m.	Discussion	
12:00 – 1:00 p.m.	Lunch	
1:00 – 1:30 p.m.	Statistical Issues Associated with Ecotoxicology Endpoints Dr. John Bailer, Miami University/NIEHS	
1:30 – 2:00 p.m.	Discussion	
2:00 – 2:30 p.m.	Statistical Methods for Evaluating Exposure-Biomarker Relationships Dr. Douglas Taylor, University of North Carolina	
2:30 – 3:00 p.m.	Discussion	
3:00 – 3:30 p.m.	Analyzing Biological Data in the 21st Century – Going Beyond Statistics, Biomathematics and Computer Science Dr. Christopher Portier, NIEHS	
3:30 – 4:00 p.m.	Discussion	
4:00 – 4:30 p.m.	Public Debate	

How to Access the NIEHS Campus:

The NIEHS has moved to a higher level of security awareness. More stringent requirements for access to NIEHS' campus have been implemented. Any individual seeking access to the NIEHS campus to attend a conference/seminar will need to be prepared to show 2 forms of identification, i.e., driver's license plus one of the following: company ID, government ID or university ID and to provide pertinent information about the conference/seminar, i.e., name of the speaker, host of the conference/workshop or title of the conference/workshop. These are difficult times and the NIEHS is attempting to make everyone's visit to our campus a safe one. Thank you for your cooperation.

A B S T R A C T S

Talk 1: Predictive simulation modeling for antiandrogen impacts on rodent prostate

HA Barton[1], RW Setzer[1], LK Potter[1,2]
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[2]Curriculum in Toxicology, UNC, Chapel Hill, NC

Changes in rodent prostate weight and function are very sensitive endpoints associated with adult and pubertal exposures to several classes of antiandrogens. We are extending a published model for the adult rat central axis (testosterone and luteinizing hormone pharmacokinetics and feedback regulation) to include the prostate and 5alpha-reductase conversion of testosterone to dihydrotestosterone. The goal is to predict how perturbations of the biological system create dose-response behaviors and evaluate assumptions of thresholds for the antiandrogenic impacts on prostate. The targets of antiandrogens include androgen receptor binding (e.g. vinclozolin or flutamide), testosterone synthesis (e.g. phthalates), and dihydrotestosterone synthesis (e.g. finasteride). Impacts on prostate being modeled include alterations in the expression of androgen receptor, 5alpha-reductase, and other genes that result in decreased fluid production, decreased cell proliferation, and increased apoptosis. The model will be a system of delayed differential algebraic equations and may be extended to describe pubertal animals. (This abstract does not represent EPA policy.)

Talk 2: Advantages of Bayesian applications in regulatory risk assessment

Annie M. Jarabek
National Center for Environmental Assessment, US EPA.

New testing strategies and an emphasis on the use of mechanistic information in environmental risk assessment has stimulated interest in developing quantitative approaches to dose-response analysis for new endpoints. Bayesian approaches, well established in clinical trials and epidemiological studies, have begun to be employed to address specific challenges posed by these new data. Particularly useful attributes of Bayesian approaches include formal data combination that results in tighter credible interval bounds when more data are utilized, the ability to combine data for various types of outcome measures (dichotomous or continuous), and expression of the resultant risk estimate as a probability density function. Other Bayesian approaches provide for weighting of variables or the tracking of latent variables across time. The purpose of this presentation is to provide a conceptual overview of some recent Bayesian applications to address the problems posed by evolving issues in regulatory risk assessment including: data combination, risk above reference levels, the use of mode of action data, and analysis of endpoints from multigeneration studies.

Talk 3: Pooling specimens can improve efficiency of case-control studies

Clarice R. Weinberg and David M. Umbach
Biostatistics Branch, NIEHS

Assays (e.g. for dioxin) can be so expensive that interesting hypotheses become impractical to study epidemiologically. One need not, however, perform an assay for everyone providing a biologic specimen. We propose pooling equal-volume aliquots from randomly grouped sets of cases and randomly grouped sets of controls, and then assaying the smaller number of pooled samples. If an effect modifier is of concern, the pooling can be done within strata defined by that variable. For covariates assessed on individuals (e.g. questionnaire data), set-based counterparts are calculated by adding the values for the individuals in each set. The pooling set then becomes the unit of statistical analysis. We show that, with appropriate specification of a

set-based logistic model, standard software yields a valid estimated exposure odds ratio, provided the multiplicative formulation is correct. Pooling minimizes depletion of irreplaceable biologic specimens and can enable additional exposures to be studied economically. Statistical power suffers very little compared to the usual, individual-based analysis. In settings where high assay costs constrain the number of people an investigator can afford to study, specimen pooling can make it possible to study more people and hence improve the study's power, with no increase in cost.

Talk 4: Statistical issues associated with ecotoxicology endpoints

A John Bailer
Miami University and NIEHS

Legal mandates exist for the protection of aquatic life and human health from the impacts of toxins released into receiving waters. To accomplish this objective, numeric environmental quality criteria are set. Bioassay data are analyzed in the development of such criteria. The statistical endpoints employed as water quality criteria include no-observed-effect concentrations (NOECs), lowest-observed-effect concentrations (LOECs) and effective concentrations (ECs). The NOEC and LOEC are design-sensitive indices, and are open to strong criticism. The EC indices are often estimated through the inversion of a parametric regression model fit. One criticism leveled against the EC estimation routines has been that one model cannot be appropriate for the variety of different biological endpoints that are studied in aquatic toxicology. Recent regression-based potency methods have addressed this concern in the context of generalized linear models. Non-monotonic concentration response patterns, sometimes characterized as “hormesis”, may lead to alternative definitions of baseline responses for inhibition concentration calculations. Other indices are currently being considered for describing how a toxicant accumulates within an organism relative to environmental levels, so-called bio-accumulation factors (BAF). Statistical questions related to potency estimation, baseline definitions and BAFs are considered. Finally, the pooling of evidence across multiple response categories to yield a weight of evidence assessment of contaminated sites will be discussed.

Talk 5: Statistical Methods for Evaluating Exposure-Biomarker Relationships

Douglas J. Taylor[1], Lawrence L. Kupper[1], Stephen M. Rappaport[2].
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In conjunction with measurements of external exposure, biomarker measurements have been used in an attempt to provide information about the uptake, bioactivation, and detoxification of toxic chemicals in humans. Such information would be quite valuable since it would reduce reliance solely on animal models for making extrapolations about disease risks in humans. However, valid and precise quantification of exposure-biomarker relationships has been hampered by at least three problems: i) large variability in observed exposure and biomarker levels both within and between subjects; ii) errors in the measurement of both exposure and biomarker levels; iii) exposure and biomarker levels that fall below known detection limits. In this paper, we describe maximum likelihood methods that appropriately adjust for these problems and that are applicable for biomarkers that are either short-term or long-term in nature. These methods allow valid and precise statistical inferences to be made about important regression parameters and variance components in latent variable models. Functions of these parameters can be used to characterize the relationships between true (but unobservable) exposure and biomarker mean levels. To illustrate their utility, these maximum likelihood methods are used to analyze and interpret some exposure-biomarker data.

Talk 6: Analyzing Biological Data in the 21'st Century - Going Beyond Statistics, Biomathematics and Computer Science

Christopher J. Portier
Environmental Toxicology Program, NIEHS

This talk will summarize the combined roles of mathematics, statistics and computer science in the analysis of complex biological systems. Highlights of recent activities in this area will be presented and an audience discussion will follow focusing on the future directions of research in systems biology.