Division of Biometry and Risk Assessment

Research in the Division of Biometry and Risk Assessment

Linking exposure to hazard through dose-response analysis to characterize the likelihood of harm to humans

Hazard Identification

Does a substance pose a health hazard and, if so, how is it characterized?

Dose-Response Assessment

What is the relationship between the exposure (dose) and the adverse health effect?

Exposure Assessment

Who are the exposed populations, and what are the magnitudes and durations of exposure?

Risk Characterization

What is the estimated incidence of the adverse health effect in a target population, and which individuals are at most risk?

Areas of Expertise

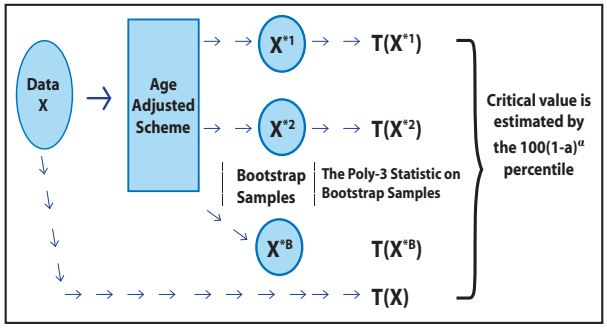
- Acrylamide
- Adjusted p-values
- Benchmark dose estimation
- Chemical mixtures
- Classification algorithms
- Computational toxicology
- Decision theory
- Dose-response modeling
- Gene ontology testing
- Generalized linear models
- Genistein
- Genomic profiles
- Infection models
- Managing uncertainty
- Methyl mercury
- Microarray data analysis
- Model averaging
- Multiple endpoints
- Personalized medicine
- Peto and Poly-k tests
- Pharmacodynamic models
- Pharmacokinetic models
- Photocarcinogenicity
- Physiological models
- Pre & Postnatal growth
- Probabilistic hierarchies
- Retinoic acid
- Sensitive subpopulations
- Windows® PBPK software

Hazard Identification:

Statistical Tests for Dose-Related Trend

Animal bioassays are routinely used to evaluate the lifetime carcinogenic potential of chemical substances to which humans are exposed. The primary goal is to assess a dose-related trend for the lifetime risk of tumors. Because most tumors in these bioassays occur in internal organs and cannot be observed in live animals, determining the numbers of animals at risk of tumors during the course of an experiment is challenging. For valid statistical tests, adjustments need to be made for animals that die prematurely from causes unrelated to the tumor of interest. NCTR mathematical statisticians develop novel statistical tests that properly account for inter-current mortality to ensure correct Type I error rates while not sacrificing power to detect differences.

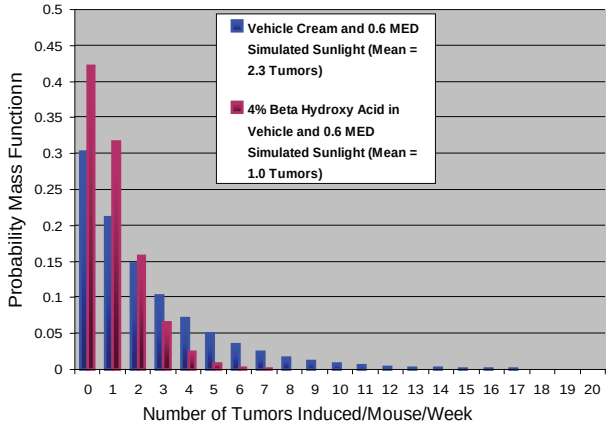
An Age-Adjusted Bootstrap-Based Poly-k Test for Dose-Related Trend



Statistical Methods to Identify Photocarcinogenesis Risks

For chemical agents that affect the skin, tumors can be observed in live animals, so that adjustments for inter-current mortality are not needed. The defining characteristic of photocarcinogenesis experiments is that multiple skin tumors occur in most animals. In collaboration with scientists in NCTR's Center for Phototoxicology, Division mathematical statisticians have developed new statistical tests that use the tumor multiplicity data to separate effects on tumor frequency from effects on tumor latency. These tests can be applied to photocarcinogenesis data on transgenic animals to assess and to characterize hazards from cosmetics and other skin products.

Frequency Distributions: Protective Treatment Effect



Dose-Response Assessment:

Mathematical Models for Estimating Safe Exposure Levels

Mathematical models are essential tools that risk assessors use to predict levels of exposure (doses) of toxic substances associated with specific levels of adverse effects. Such doses are often termed benchmark doses. Division mathematical statisticians develop dose-response models based on postulated biological mechanisms and fit these models to observed data to estimate benchmark doses. The structure of these models can vary substantially for various types of adverse effects, and specialized software is required. Because, even for a given toxic response, there are many choices among mathematical models, Division statisticians have developed and applied model-averaging techniques to account for model uncertainty.

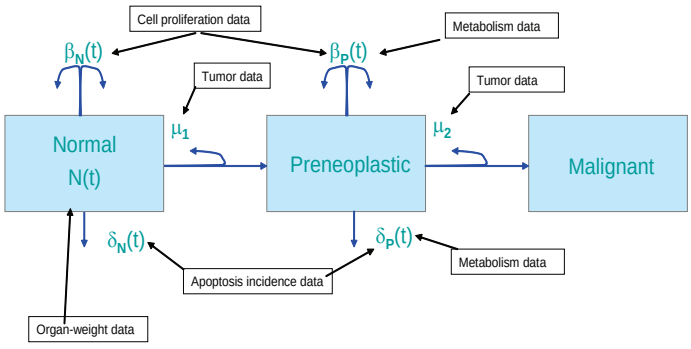
Dose-Response Models

- **Microbial illness:**
  - Beta-Poisson Model
    $P(d;\alpha,\beta)=1-(1+d/\beta)^{-\alpha}$ $\quad \alpha > 0, \beta > 0$
  - Log-Logistic Model
    $P(d;\alpha,\beta)=1/\{1+\exp[-(1n d-\alpha)/\beta]\}$ $\quad -\infty<\alpha<\infty,\ \beta>0$
- **Cancer:**
  - Multistage Model
    $P(d;\beta_0,\beta_1,\ldots,\beta_k)=1-\exp[-(\beta_0+\beta_1 d+\beta_k d^k)] \quad \beta_0\geq 0,\ \beta_1\geq 0,\ldots,\beta_k\geq 0$
  - Two-Stage, Clonal-Expansion Model
    $P(d;\beta_N(t),\beta_P(t),\delta_N(t),\delta_P(t),\mu_1,\mu_2,N(t))=1-z'_N(t)^{N(0)}$
    $where\ z'_N(t)=-\beta_N(t)z_N(t)^2+[\beta_N(t)+\delta_N(t)+\mu_1]z_N(t)-\mu_1 z_N(t)z_P(t)-\delta_N(t)$
    $z'_N(t)=-\beta_P(t)z_P(t)^2+[\beta_P(t)+\delta_P(t)+\mu_1]z_P(t)-\delta_P(t)$
    $z_N(0)=z_P(t)=1$
- **Developmental Toxicity:**
  - Litter-Effect Model
    $P(d,s,s_j;\alpha,\beta,\theta_1,\theta_2,w,d_0)=1-\exp\{-[\alpha+\theta_1(s_j-s)+(\beta+\theta_2(s_j-s)(d-d_0)^w]\}$
    $\alpha\geq 0,\ \beta\geq 0, d_0\geq 0, w\geq 1, \alpha+\theta_1(s_j-s)\geq 0\ \forall s_j, \beta+\theta_2(s_j-s)\geq 0\ \forall s_j$

Mechanistic Models

In the somewhat rare situation when data on hypothesized mechanisms of action are available for cancer risk assessment, sophisticated mathematical models can be used to incorporate such data to enhance risk predictions. In collaboration with other NCTR scientists, Division mathematical statisticians and research biologists have formulated specific parameterizations of such models, based on working hypotheses of mechanisms of action and have used mechanistic data to develop each component of the models. A model is validated by comparing its predictions to observed tumor rates, with success being measured by the model's ability to generalize across sexes and/or species.

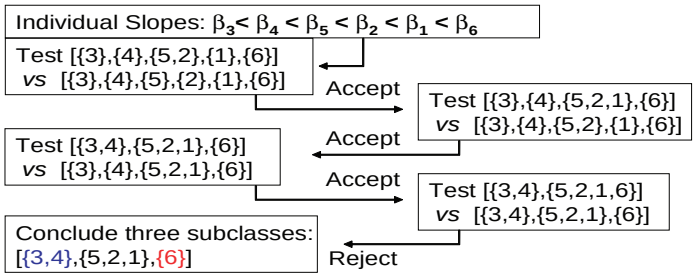
Mechanism-Based Model for Cancer



Risks from Chemical Mixtures

Frequently, the human population is exposed simultaneously to multiple chemicals. Assessing the dose-response relationship for a mixture of chemicals generally requires a determination of whether the chemicals act through a similar mode of action or act independently. Through an interagency agreement with the U.S. Environmental Protection Agency (EPA), Division mathematical statisticians have collaborated with EPA scientists to extend the relative potency factor (RPF) approach for assessing risks from mixtures. They have developed algorithms to determine classes of chemicals in mixtures having similar dose-responses and to combine dose-responses to assess the cumulative risk or set exposure levels.

Top-Down Tree-Classification Algorithm to form Subclasses of Similar Chemicals in Mixtures

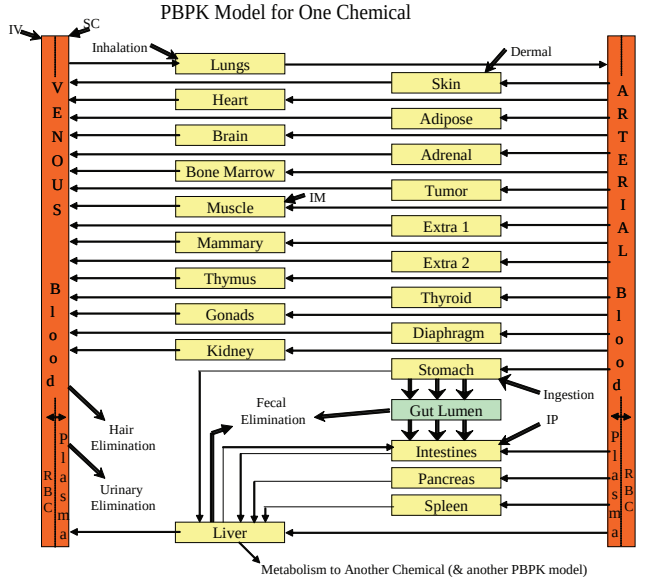


Exposure Assessment:

Software for Complex PBPK Models of Tissue Dosimetry

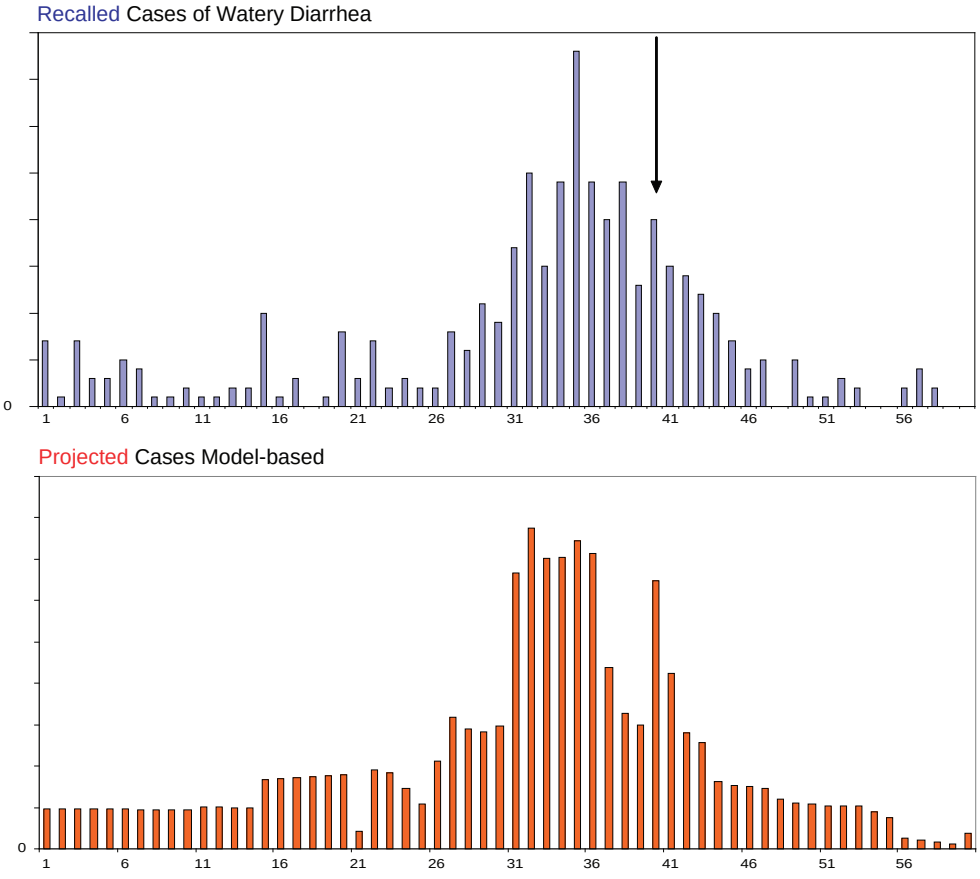
Human health risk assessment most often involves the use of experimental results in animals to infer risks to humans. The best cross-species extrapolations are done with physiologically based pharmacokinetic (PBPK) models, which can provide comparable biologically effective doses of toxic substances. NCTR research biologists have developed novel PBPK models for the simultaneous modeling of parent compound and metabolites (e.g., acrylamide and its chief metabolite, glycidamide). These species-independent models are flexible enough to incorporate both growth and dynamics. The models are validated by accurately predicting measured levels of a chemical in various tissues of a variety of species.

PBPK Model for One Chemical



Models and Data for the Transmission Dynamics of Microbial Pathogens

Sensitive subpopulations are recognized as a key factor in the spread of microbial infections among individuals in a population. Through an interagency agreement with the U.S. EPA, Division research biologists have formulated novel models for disease spread based on sensitive subpopulations, and have conducted animal experiments to acquire data for characterizing sensitivities to infection and illness. These models have been validated by accurately mimicking epidemiology data on actual outbreaks, in particular, the outbreak of cryptosporidiosis in Milwaukee due to contamination of the city's water supply by *Cryptosporidium parvum*.



Application of Susceptible-Subpopulation Model to a 1993 Waterborne Outbreak of Cryptosporidiosis in Milwaukee

Risk Characterization:

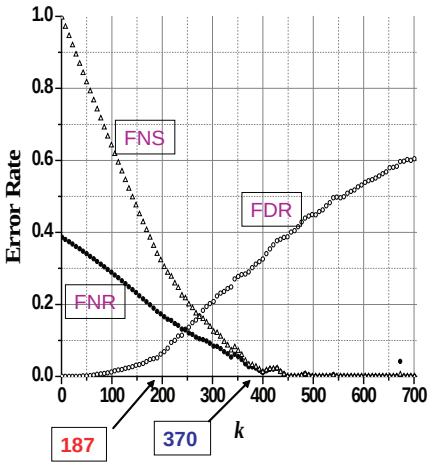
Statistical Techniques for Identifying Genomic Risk Profiles

Microarray experiments conducted to measure the expression of thousands of genes simultaneously require novel statistical methods to ascertain which genes are differentially expressed between risk groups. NCTR mathematical statisticians have developed theory and methods for determining the number of differentially expressed genes, which enable selection of optimal cutoffs for declaring statistical significance and estimation of the associated false discovery rate and false nondiscovery rate. Because the methods allow hazards to be identified in terms of their effects on gene expression, they facilitate the development of genomic risk profiles.

Statistical Methods for Classification and Prediction

As new biotechnologies, like microarray platforms for genomic profiling, have been developed, the need for novel algorithms to process the resulting high-dimensional data has become critical. NCTR mathematical statisticians are developing statistical algorithms for biomedical decision making that can enhance the accuracy of classification in areas ranging from personalized medicine to chemical carcinogenesis. A strategy for building ensembles of classifiers indicates how subject-specific data of various types can be combined to increase accuracy. These algorithms show promise for enhancing the assignment of treatment therapies as well as streamlining the testing of new drugs and chemicals.

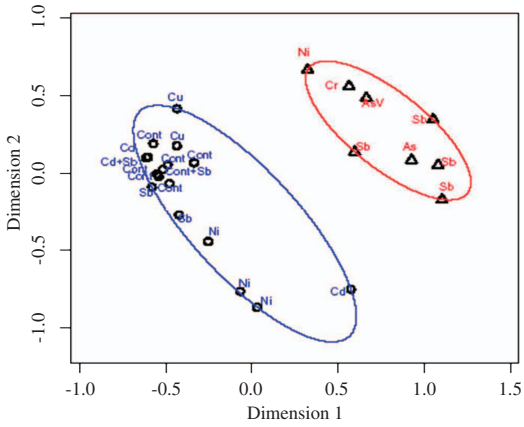
False Discovery Rate (FDR), False Nondiscovery Rate (FNR), Fraction Not Significant (FNS)



Cost Function:
FN$=3FP$
Select **370** genes
FDR=0.284
FNR=0.024
FNS=0.030

Cost Function:
3FN$=FP$
Select **187** genes
FDR=0.051
FNR=0.184
FNS=0.350

Using Cluster Analysis with a 2-MDS Plot for Classifying 25 Compound-Specific Marker Genes. Each gene is labeled with the compound to which it gives unique expression.



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