VOC Cancer Risk Simulation Model

A new model that integrates pharmacokinetic, cytotoxicity, cell proliferation, and stochastic carcinogenicity components into a unified framework is available to download here.

The Cyclophosphamide Hematotoxicity BBRA Model

To experiment with this model, there are three items to download:

1. The free run time version of ITHINK 5.0 (download here) from High Performance Systems. This is a continuous simulation modeling environment that will enable you to run and use simulation models created in ITHINK 5.0. You will not be able to save changes that you make in the models, however, unless you buy a full version of ITHINK 5.0 from High Performance Systems.

2. The Cyclophosphamide Hematotoxicity BBRA Model (download here ~ 140KB) developed for the American Petroleum Institute by Cox Associates. This is a specialized tool that simulates the effects of the drug cyclophosphamide on blood cells, especially CFU-GM stem cells and both earlier and later blood cells in the granulocyte- macrophage (GM) lineage. The model takes a biologically based risk assessment (BBRA) approach, meaning that it simulates the flows of cells among physiologically important compartments in response to user-specified dosing scenarios. The model is intended primarily to simulate responses to low to moderate doses that are small enough so that full recovery can occur after cessation of dosing. Long-term irreversible poisoning of the stromal microenvironment is not modeled, but cell kinetics are described in enough detail to make a variety of testable predictions.

3. A document (download here ~1MB) describing the Cyclophosphamide Hematotoxicity BBRA Model and how to use it. This is an electronic document written in MS Word for Office 97. The current version contains some hyperlinks to key references and web resources; others will be added over time.

The detailed technical background for the model and document, including a tutorial review of normal and perturbed hematopoiesis, is contained in reports to the American Petroleum Institute prepared by Cox Associates since 1993. Click here for a summary overview of the model and its validation to date using experimental and clinical data.

Bayesian methods for assessing uncertain exposures
Click **here** to download presentation

Marketers and biostatisticians must often try to estimate a statistical relation between "exposure" and the probability of a "response" when the true exposure values are unknown and only rough estimates are available. Applying standard text-book methods that ignore errors in the estimated values of the independent variables may yield misleading or meaningless results. Moreover, the conventional wisdom that ignoring such errors attenuates estimated relations between exposure and response does not hold when more than one independent variable is involved. This presentation summarizes recent progress in numerical Bayesian methods for estimating correct exposure- response relations even when the correct values of exposure are highly uncertain.

MOLECULAR BIOLOGY OF CHEMICAL LEUKEMOGENESIS FOR BENZENE

In February, 1999, Cox Associates delivered to Exxon Biomedical Sciences, Inc., a review of the detailed biological mechanisms by which benzene can cause hematotoxic damage and induce secondary Acute Myeloid Leukemia in humans. A key finding from this study is that many of the mechanisms of benzene-induced health effects are sub-linear at low doses, helping to explain why recent epidemiological studies do not find the excess leukemias and health damage at low exposure concentrations (e.g., 1 ppm or less) predicted from older benzene health risk assessment models.

CLINICAL APPLICATIONS OF CYCLOPHOSPHAMIDE MODEL?

On December 15th, 1998 a Hematoxicity Modeling Workshop was held at the University of Ottawa Institute of Population Health (Professor Dan Krewski, host), in conjunction with the Benzene State of the Science Workshop, 1998. The topic of the one-day Hematotoxicity Modeling Workshop was a review of the simulation model of cyclophosphamide hematotoxicity developed by Cox Associates for the American Petroleum Institute. Reviewers included government scientists from EPA and NIEHS, biomathematical modelers from the Fred Hutchison Cancer Research Center and the University of Ottawa, and experts in clinical hematology and research from the University of Ottawa and the University of Colorado. Workshop papers will be submitted for publication in 1999. The main finding, reported to the Benzene State of the Science Workshop, was that the model appeared to offer useful, apparently realistic predictions. An unexpected finding was that several of the expert hematologists felt that the model might be useful in clinical practice, in refining dose regimens for chemotherapy patients.

PREDICTING CHEMICAL CARCINOGENS BY COMBINING MULTIPLE PREDICTIONS

Cox Associates' ongoing applied research in data mining technologies has recently led to a promising new application: using data mining algorithms to combine predictions from different expert systems for predicting which chemicals are carcinogenic without undertaking expensive experiments to find out. We discovered that the new prediction-combination technique, which is based on classification trees, can produce "hybrid" predictions than are more accurate than any individual expert system's prediction and also than the predictions from previous combination methods. Click here to download a technical paper describing the new approach and results.

FINDING BURIED HAZARDS

In September of 1998, Cox Associates completed a new approach to finding the probable locations of greatest soil concentrations of contaminants based on soil samples. Traditional geostatistical and sampling and estimation methods such as kriging do not fully address the problem of efficient search for buried hazards when the spatial distribution of yield is highly uncertain. Our new approach adaptively optimizes the search process so as to continually maximize its expected yield. This can

dramatically cut the sampling costs needed to show that spatial hazards have been adequately reduced by sampling and remediation efforts. Details may be found in the attached technical paper. Click here to download the paper.

SIMULATING HEMATOTOXICITY

Since 1986, Cox Associates has developed biologically-based risk assessment (BBRA) simulation models and methods for understanding the human health risks from chemical exposures. A program developed for the American Petroleum Institute (API) to predict the effects on blood cells of dosing with the immunosuppressive drug cyclophosphamide is now available to other researchers from our web site. Click here to download the required modeling software and documentation.

CAUSAL ANALYSIS AND PUBLIC POLICY: THE CASE OF DIESEL EXHAUST

In early June 1998, Cox Associates delivered written comments on behalf of the Engine Manufacturer's Association to the Clean Air Science Advisory Committee (CASAC) on EPA's recent (2-98) Draft Risk Assessment for diesel exhaust health risks. The comments address causation (as opposed to statistical associations) in epidemiological literature on health risks of diesel exhaust. It concludes that no causal link between diesel exhaust and human lung cancer has been found.

METHODS: The document provides references and web links to statistical resources that help untangle causation from statistical association. This is a novel application of insights and methods from our data mining and causal forecasting practice areas.

IMPACT: CASAC has directed EPA to rework its draft risk assessment to address issues identified in public comments by Cox Associates and others. The comments document identifies current methods for overcoming modeling challenges in this area.

For information, please see the attached report.

CLIENT CONTACT: Glenn Keller, Engine Manufacturer's Association, 312-644-6610