HOW DOES CLEANER AIR AFFECT HUMAN HEALTH AND LONGEVITY?

Many expensive regulatory proposals are based on the belief that continuing to reduce levels of fine particulate matter in urban air and mineral dusts in occupational environments will further reduce the burden of lung diseases and promote longer and healthier lives. But is this true? In 2011, Cox Associates found that there is likely to be an exposure concentration threshold for exposure to crystalline silica duet below which further reductions in exposure have no effects on human health; conversely, exposures above this threshold can stimulate unresolved chronic inflammation of the lung, leading to increased risk of lung cancer and other diseases (www.ncbi.nlm.nih.gov/pubmed/21477084). Cox Associates also found that current regulatory proposals and benefits assessments for further reducing fine particulate matter (PM2.5) in urban air rest on questionable assumptions about causal impacts of exposures on human mortality rates, and on incomplete uncertainty analysis (www.ncbi.nlm.nih.gov/pubmed/22050234)

WHAT IS THE ECONOMIC VALUE OF INFORMATION FROM TRACKING CANADIAN CATTLE IMPORTED TO THE US?

Amid growing concern about the potential emergence of BSE in North America since the discovery of a BSE-positive cow of Canadian origin in Seattle in 2003, there has been debate and litigation over whether, when and how fully the US should re-open its borders to the import of Canadian cattle and beef products. In 2004, Cox Associates led a study for R-CALF (Ranchers-Cattlemen Action Legal Fund) to identify and apply decision and risk analysis frameworks to help inform the debate. One of the results is a Value-of-Information (VoI) framework that suggests that tracking Canadian-origin cattle in the US may have a high economic value if additional BSE cases are discovered. This framework and results can be downloaded here.

WHICH FOOD-BORNE MICROBIAL HAZARDS MATTER MOST?

In June of 2003, Cox Associates delivered to the Animal Health Institute (AHI) a new approach to quickly and accurately rate food-borne microbial hazards and risk management proposals. The new approach, called the Rapid Risk Rating Technique (RRRT), rates hazards and risk management interventions based on their probable human health impacts. These are estimated by multiplying several risk factors, including relative values for expected contamination exposure frequency, infectivity, dose-response, and health consequence. Data values are provided in the methodology.

The new rating methodology is intended to build upon and refine FDA's proposed Draft Guidance Document #152 while seeking to overcome some of #152's potential limitations (http://www.fda.gov/ohrms/dockets/ac/03/slides/3919OPH2_01_Cox.ppt http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3919T2.htm). Simulation-optimization is used to optimize and validate the performance of the proposed rating system in identifying the worst problems, taking into account realistic uncertainties.

The RRRT method can consider human health benefits as well as risks, account for projected changes in future antimicrobial resistance rates among multiple bacterial pathogens, and assess risks for specific human sub-populations. Applications to tetracyclines, macrolides, ionophores, and other classes of animal antimicrobials are ongoing.

ARE ANIMAL ANTIBIOTICS TIME BOMBS?

Concern over evolving resistance to antibiotics among human bacterial pathogens and commensals due to the use of similar drugs in food animals has been growing in the US, Japan, and the European Union. Biomathematical modeling of the evolution of resistance has added to this concern by suggesting that continued use even of drugs (such as virginiamycin) with long histories of safe use in animals and without apparent significant adverse effects on human resistance might lead to a sudden increase in human resistance in the future. An April 2003 draft report by Cox Associates, undertaken with partial support from Phibro Animal Health to understand and quantify the potential human health risks, has found that these mathematical models predict a very low probability of future resistance outbreaks and a vanishingly small probability of resistance epidemics triggered by continued use of animal antibiotics and antimicrobials if real, rather than hypothetical, parameters values are used. Using virginiamycin as a case study, the report applies techniques of Bayesian uncertainty analysis to a discrete-event dynamic simulation model with parameters estimated from data to show that the human health risks are small (much less than one excess statistical mortality in the whole US population expected over many years due to emerging resistance caused by animal drug use) with very high statistical confidence. This analysis based on dynamic simulation produces quantitative risk estimates similar to those previously obtained by simpler calculations (www.cox-associates.com/VIRGINIAMYCIN.ppt.)

WHEN ARE LARGER EXPOSURES LESS RISKY?

In May of 2003, as part of a research initiative supported by the American Chemistry Council, Cox Associates completed an initial version of an integrated pharmacokinetics-and-pharmacodynamics (PK-PD) simulation model of volatile organic chemical (VOC) interactions with hematopoietic (blood-forming) stem cell populations in the bone marrow. Building on an earlier biomathematical model of hematotoxicity (www.alceon.com/cp99pa2.pdf, http://ehpnet1.niehs.nih.gov/docs/1996/Suppl-6/cox.html), the new model integrates the homeostatically regulated responses of normal hematopoietic stem cell populations into a two-stage stochastic model of carcinogenesis and cytogenetic damage. It is able to quantitatively simulate, for the first time, the theoretical cancer-causing potential of different exposure patterns. Initial results show that cumulative exposures (ppm-years), the most widely used exposure metric in most epidemiological analyses and statistical risk models of VOC cancer risks, do not yield accurate risk predictions if exposure patterns are highly variable. Instead, in addition to the cumulative exposure, the average concentration within a day, hours-per-day of exposure, days between consecutive exposures, and length of post-exposure follow-up can all strongly affect predicted hematotoxic and leukemogenic risks. These factors combine non-linearly, and their interactions are so strong that they can easily lead to larger cumulative exposures posing smaller risks (essentially by allowing more time for the hematopoietic system to adapt to the stress of sustained exposure, reducing the extent of compensating proliferation and the number of initiated stem cells formed.) These initial results were presented at the 2003 BELLE conference on Non-Linear Dose-Response Relationships in Biology, Toxicology, and Medicine: An International Conference. (University of Massachusetts, Amherst, MA, May 28-30th, 2003 www.belleonline.com/abstracts/session6.html). They appear to be robust to many scientific and modeling and uncertainties. They suggest a new class of multivariate exposure metrics that can better explain past animal and human data and better describe the aspects of exposures that are most useful for predicting occupational and public health risks from exposures to hematotoxic VOCs. Slides describing these preliminary results can be downloaded here.

ANIMAL ANTIMICROBIAL RISK ASSESSMENT DO'S AND DONT'S

In February of 2003, Cox Associates in partnership with the Animal Health Institute prepared a report offering suggested technical guidance on how to assess human health risks from antimicrobial drugs used in animal feed additives. The report, entitled Animal Antimicrobial Feed Additives and Human Health: A Guide to Risk Analysis, reviews methods and principles for sound and practical risk analysis in this area, as well identifying practices that should be avoided. It can be downloaded here.

WHAT DO VOLATILE ORGANIC CHEMICAL (VOC) CARCINOGENS HAVE IN COMMON?

In January of 2003, Cox Associates completed a research report on data sources available to support integrated pharmacokinetics-and-pharmacodynamics (PK-PD) simulation modeling of cancer risks from mixtures of volatile organic chemicals (VOCs). This work suggests a framework for exploiting the common features of many VOC-induced carcinogenic responses - including Phase 1 and Phase 2 metabolism leading to reactive products causing cytotoxicity and regenerative hyperplasia, or other mechanisms of stem cell proliferation - to create a common template for streamlining the analysis of cancer risks from exposure to the most common VOCs and their mixtures. Data sources and technical modeling literature for PK and PD components available to support such an ambitious attempt at integrated risk modeling are surveyed and hyperlinks to relevant documents are provided. The report can be downloaded here.

SOCIETY FOR RISK ANALYSIS BEST PAPER AWARD, 2002

In December of 2002, a paper on "Quantifying human health impacts of antimicrobial risk management alternatives for enrofloxacin", by Drs. Tony Cox and Doug Popken of Cox Associates, received a Society for Risk Analysis Best Paper Award at the Society for Risk Analysis Annual Conference, New Orleans, LA. December 9-11, 2002 (www.sra.org/news0203.pdf, page 5). This paper presented the results of mathematical model validation and extension efforts originally recommended by Dr. Cox to the FDA in 1999 (http://www.fda.gov/cvm/antimicrobial/vm120999.htm#Anchor-MATHEMATICA-43816). It also presents initial results of a new simulation model suggesting how withdrawing an approved animal drug can increase human health risks by increasing the prevalence of a condition in chickens called airsacculitis that increases the microbial loads of campylobacter, salomonella, and other bacteria reaching humans. Finally, it reviews the evidence for and against the widely accepted hypothesis that chicken is a primary source of campylobacteriosis in humans - a piece of common wisdom that may have to be revised in light of data. The presentation slides can be downloaded here.

VIRGINIAMYCIN USE IN CHICKENS POSES MINIMAL HUMAN HEALTH RISKS

In May of 2002, Cox Associates completed a quantitative risk analysis of the human health risks that might plausibly be attributed to the use of Virginiamycin as a growth promoter in poultry. The risk

analysis makes use of a simulation model, based on extensive human and animal data, that quantifies the number of human treatment failures, early mortalities, and excess illness-days that could result from bacteria (vancomycin-resistant Enterococcus faecium, or VREFs) that also acquire resistance to the human drug quinupristin-dalfopristin due to selection pressures from use of Virginiamycin in poultry. The model uses recent genogroup and genotype data from amplified fragment-length polymorphism (Willems et al., 2000, 2001) to show that an extreme upper bound on the number of human lives saved by an immediate ban on Virginiamycin use in poultry is less that 1/3 of a statistical life for the entire US population over the next 5 years. The true number could be zero, if resistance gene transfer from poultry to humans does not occur.

NEW BOOK ON RISK ANALYSIS

Many theoretical advances and practical applications of health risk analysis developed at Cox Associates between 1986 and 2001 have been summarized in a recent book on Risk Analysis: Foundations, Models and Methods (http://kapis.www.wkap.nl/prod/b/0-7923-7615-3). This advanced text, published in the prestigious INTERNATIONAL SERIES IN OPERATIONS RESEARCH AND MANAGEMENT SCIENCE, makes full use of contemporary operations research methods in tackling some of the most difficult and rewarding problems of risk model creation, validation, and application needed in current health risk analysis applications. The attached presentation illustrates a few of the ideas explained in detail in the monograph.

BALANCING "REAL" VS. "THEORETICAL" RISKS TO CANADIAN BLOOD SUPPLY

Member of different communities of blood recipients, such as hemophiliacs and immunocompromised patients, often place different weights on the relative importance of availability and extremely high safety of blood supplies. This leads to potential conflicts over policies for addressing the potential risks from emerging threats, including prion-borne (vCJD, or mad cow disease related) contamination. Proposals to defer donations from blood donors who have visited the United Kingdom or who may otherwise have been exposed to vCJD may increase the theoretical safety of donated blood, but may do so by increasing the risks of shortages and/or contamination from new first-time donors. In March, 2002, Dr. Cox presented a decision-analytic approach to making risk-risk tradeoffs and optimizing decisions about blood supply in the face of large uncertainties about the underlying science and the reality and extent of threats from prion-related contamination. The approach calls for the use of simulation models that can be fit to available data to estimate the probable consequences of alternative risk management decisions. It provides a framework for defining and choosing the "best" risk management option even when there are realistically wide uncertainties about the probable consequences of different choices.

IS PERCHLORATE BAD FOR YOU?

Perchlorate, widely used in rocket fuel, is found as a drinking water contaminant in California, Nevada, and elsewhere. While high doses of perchlorate can cause thyroid tumors and other effects in rats by inhibiting iodine uptake into the thyroid gland, ultimately leading to compensating cell proliferation and increased cancer risk, there is no evidence of a comparable carcinogenic effect in humans. In March of 2002, Dr. Cox participated as an invited Expert Peer Reviewer at a two-day

public meeting in Sacramento to advise the US EPA on how to maximize the usefulness and validity of its recent Draft Risk Assessment document for human health effects of perchlorate. A key recommendation was that the EPA risk assessment needs to address pharmacodynamic differences between human and rat sequelae of iodine inhibition in order to realistically explain and predict human health impacts of perchlorate in drinking water.

WHAT REALLY CAUSES CAMPYLOBACTERIOSIS?

Campylobacter jejuni is the most frequent bacterial cause of gastroenteritis in the United States and frequently causes traveler's diarrhea in both developed and developing countries. Recently, the U.S. Food and Drug Administration (FDA) proposed to ban a therapeutic drug, enrofloxacin, from veterinary use in chickens in case such use might increase drug-resistant campylobacteriosis in humans. On March 1, 2002, Dr. Cox presented new data analyses in Boston, Massachusetts, indicating that eating chicken per se is not a risk factor for campylobacteriosis in the United States, contrary to widespread assumptions. Instead, it appears that restaurant dining is a risk factor, whether or not chicken is eaten, while chicken and other meats consumed at home are protective against campylobacteriosis. This finding has dramatic implications for how risks of campylobacteriosis should be managed. It suggests that banning enrofloxacin will have little or no human health benefit, but that better restaurant kitchen hygiene could be important.

Drs. Cox and Popken of Cox Associates are currently modeling the risks, costs, and benefits associated with different risk management strategies for campylobacter. Initial simulation results suggest that a ban on enrofloxacin may inadvertently increase the microbial load reaching consumers by reducing uniformity of chickens at the processing plant. In March, this and other insights from "farm-to-fork" simulation modeling of risks associated with chicken-borne campylobacter were submitted to the World Health Organization (see attached link).

ARE PLAYGROUNDS POISONING OUR CHILDREN?

In April, 2002, the Detroit News ran a story in which Dr. Cox helped to debunk claims by the Environmental Working Group (EWG) that pressure-treated wood is putting children at risk of cancer due to the preservative chromated copper arsenate (CCA). The EWG's conclusions were extrapolated from a statistically non-valid study in which EWG invited environmental activists to collect samples without using any standard or reliable sampling plan and then interpreted the results as representing realistic exposures. In Dr. Cox's opinion, the EWG study did not fulfill the requirements for a scientifically credible or useful risk assessment.
http://www.detnews.com/2002/editorial/0204/09/a11-460152.htm

CAUSAL MODELING FOR WORKSHOP ON ANTIMICROBIAL RESISTANCE

In October, 2001, Cox Associates presented initial findings at the Second OIE Workshop on Antimicrobial Resistance (http://www.oie.int/eng/press/a_051001.htm) from a new causal model and analysis of case-control data from the Centers for Disease Control (CDC). Causal modeling indicates that improper restaurant food preparation, rather than microbial load of Campylobacter in chickens per se, as has previously been supposed, is likely to be the main driver of campylobacteriosis

risks in the US. Indeed, our independent analysis confirmed and extended previous findings suggesting that chicken prepared and eaten at home protects against campylobacter risk.

RISK ANALYSIS FOR WORLD HEALTH ORGANIZATION

In July, 2001, Dr. Tony Cox participated as an independent expert in the World Health Organization's Consultation on human health risks
from campylobacter (http://www.fao.org/es/ESN/pagerisk/reportCV.pdf).

DO ANIMAL ANTIBIOTICS INCREASE THE RISK OF HUMAN RESISTANCE?

In February 2001, Cox Associates delivered to the Animal Health Institute a risk analysis report on the relation between use of fluoroquinolones (FQ) to treat critically ill chicken flocks and potential excess illness-days in the US population due to increased resistance of Campylobacter jejuni (CP), a chicken-borne pathogen, to FQ treatments. This report breaks new ground by applying a dynamic discrete-event simulation model to quantify the probable health impacts of different risk management interventions. Its main conclusion is that the potential health benefits from tighter control of FQ use on farms is less than 1% of the potential health benefits from relatively modest changes in processing of chickens. In addition, the report finds little evidence of a causal relation between FQ use on farms and excess illnesses or illness-days in humans.

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.

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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.

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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.

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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.

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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.

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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.

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