of REPs required a complex mixed-effects Hill model that assumed DLC partial agonism. The accuracy of 50% effective concentration (EC50)-derived REPs in the presence of uncertain maximal effects of differing magnitudes is questionable. However, the responses observed at low agonist concentrations appeared to be extremely consistent across NHEK donor cultures. To capitalize on this feature, responses and concentrations were first log10-transformed, revealing a donor-invariant dose at which a minimally significant response (MSR) was first achieved. After removal of high concentration data at which the responses showed evidence of saturation, a simple linear regression model of log relative response against log concentration (a power law model) was used to directly estimate the "minimally significant" dose (MSD), using only data from the remaining doses at which statistically significant responses were observed. The resulting MSDs and the related low-dose REPs were largely invariant, regardless of whether or not the response slopes (Hill coefficients) were assumed equal across the different AHR agonists. By simultaneously modeling all three compounds, low-dose REPs were derived. Overall, this power law modeling procedure for REP derivation can likely be applied to in vitro systems where donor variability in response and/or the presence of partial agonists may pose problems for EC50 estimation.

PS 475 NON-THRESHOLD BIOLOGICAL PROCESSES AND THE ASSUMPTION OF LOW-DOSE LINEARITY: CONSIDERATION OF RECEPTOR-MEDIATED EVENTS IN RISK ASSESSMENT.

P. D. White, M. A. Spassova, R. P. Subramaniam and L. Kopylev. *U.S. EPA, Washington, DC.* Sponsor: S. Vulimiri.

Important classes of toxic substances act through biological processes that modify the function of nuclear receptors. The shape of dose-response relationships for these processes continues to be contentious. A brief review is presented of scientific arguments for non-threshold and for low-dose linear behavior and their relevance for receptor-mediated toxicity. Dose-response inferences based upon mechanistic arguments, dose-additivity to background biological processes, and the impact of population variability are discussed. Secondly, a focused review and statistical analysis of examples of empirical data on dose-response relationships for receptor mediated biological responses is presented. Misimpressions regarding the shape of such relationships due to plotting of observed data on semi-log plots are elucidated. For example, a low-dose linear curve, such as a Michaelis-Menten relationship, will appear "sigmoidal" when plotted on a semi-log scale, yet one can easily see that a Michaelis-Menten relationship is linear at low doses when the plots are presented on linear scales. Datasets illustrating receptor mediated effects including induction of P450 enzymes, epidermal growth factor receptor regulation, and observed damage to DNA are statistically analyzed. The data analyzed are generally consistent with low-dose linearity, (e.g., are acceptably fit using Michaelis-Menten relationships) and generally do not show evidence of steep (non-proportional) decrease within the studied dose ranges. In specific cases where steeper than linear dose-response relationships are observed for apical toxicological responses at high dose, limits on the magnitude of a low-dose linear component of the risk relationship are examined.
Disclaimers: The views expressed in this paper are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA.

PS 476 THE HUMAN-RELEVANT-POTENCY-THRESHOLD: UNCERTAINTY ANALYSIS AND HUMAN CALIBRATION FOR CUMULATIVE RISK ASSESSMENTS.

E. Sargent[2], R. Golden[4], D. Dietrich[3], G. Casella[5] and C. Borgert[1]. *[1]Applied Pharmacology & Toxicology, Inc., Gainesville, FL, [2]EV Sargent LLC, Clearwater, FL, [3]Faculty of Biology, University of Konstanz, Konstanz, Germany, [4]ToxLogic, Potomac, MD and [5]Department of Statistics, University of Florida, Gainesville, FL.*

Cumulative effect models based on concentration addition (CA), e.g., relative potency, TEF/TEQ, Hazard Index, are the defaults for toxicological health risk assessments of chemical mixtures with constituents presumed to have similar modes of action or to produce similar toxic effects. CA models predict toxic effects according to the relative potencies of mixture constituents summed by dose, extrapolating the prediction irrespective of the potency of the chemicals or the concentrations to which humans may be exposed. Methods to assess uncertainties inherent in this extrapolation are seldom employed and methods for calibrating the extrapolation to potencies and concentrations relevant for humans have yet to be devised. Using anti-androgens (phthalates, procymidone, finasteride, DES) as a test dataset, we demonstrate that uncertainties in cumulative effects data for the observable toxicity range in rodent studies may be 2-fold or more, and may be orders of magnitude greater when extrapolated to lower, human-relevant doses. We present a novel Human-Relevant-Potency-Threshold approach that can improve application of the concentration addition model and obviate a need to use default uncertainty factors in deriving human-protective point-of-departure doses (e.g., RfDs) for estimating cumulative toxicity and projecting human risk. The HRPT approach uses data for hormonally active pharmaceutical chemicals or natural receptor ligands, prioritizing human clinical data and relating the human observable effect range to those from animal toxicology studies. We discuss how an HRPT for anti-androgens might be developed and how it could be used to improve the application of CA models in cumulative risk extrapolation.

PS 477 THRESHOLD ANALYSES FOR ACRYLONITRILE AND BRAIN TUMORS IN RATS.

D. E. Strother[1] and C. R. Kirman[2]. *[1]ToxSolve LLC, Manassas, VA and [2]Summit Toxicology LLP, Orange, OH.*

The potential risks from exposures to acrylonitrile (AN) have historically been assessed based upon its potential carcinogenicity, primarily driven by brain tumor response in rats. Analyses were performed to evaluate the presence of a threshold for brain tumor response in rats based upon pooled data, which includes twelve data sets (six oral and six inhalation), spanning 34 nonzero dose groups and 12 control groups, expressed in terms of an internal dose measure (peak 2-cyanoethylene oxide or CEO in brain). Stepwise addition of the nonzero dose groups indicates no evidence of a dose-response relationship below 0.012 mg/L (peak CEO in brain). The slope of the dose-response relationship above 0.012 mg/L is significantly different from zero, and is significantly different from the slope of the dose-response relationship predicted below 0.012 mg/L. Inclusion of a threshold term did not result in a significant improvement of the fit of a Weibull dose-response model to the pooled rat brain tumor data, demonstrating the difficulty in proving the existence of a threshold based solely upon changes in goodness of fit tests. The dose-response relationship for AN and rat brain tumors is well correlated with published measures for oxidative stress (8-oxo-dG, oxidative DNA damage), while showing a lack of correlation with direct DNA damage. Together the statistical and biological approaches provide support for adopting a nonlinear dose-response assessment (i.e., cancer reference values) when assessing risks to human populations exposed to AN.

PS 478 EFFICIENT DESIGN OF BIOLOGICAL EXPERIMENTS FOR DOSE-RESPONSE MODELING IN TOXICOLOGY STUDIES.

F. Yang[1] and D. Porter[2]. *[1]West Virginia University, Morgantown, WV and [2]NIOSH, Morgantown, WV.*

This work is concerned with the efficient design of biological experiments to quantify the dose-response relationship of a substance, which is one of the most fundamental steps in risk assessment. To obtain such relationships, biological experiments need to be performed at different dose levels to observe the corresponding bioactivity responses of animals. Because of costs, ethics, or other limitations, sample sizes are usually restricted and efficient use of resources is critical. Thus, the design of experiments, i.e., the selection of experimental doses and the allocation of animals, plays an important role in the estimation of dose-response relationships. Efficient design for dose-response modeling is challenging due to the special features of toxicity data, i.e., the possibly nonlinear nature of dose-response curves and the typical variance heterogeneity (non-constant variance) involved. In this work, an experimental design procedure particularly suitable to toxicity data collection is developed to guide the dose selection and animal allocation in experiments. The design procedure is built in a two-stage Bayesian paradigm, which provides a statistically valid mechanism to utilize prior information for the design of future experiments. Most appropriate dose-response and variance models are identified to describe the toxicity data. Bootstrapping, a computationally intensive resampling method as opposed to conventional statistical inference methods, are used to derive important information from the preliminary data required by the subsequent experimental design. To achieve practically useful designs, multiple design criteria are considered simultaneously, and multi-objective metaheuristics are adapted to search for a set of Pareto optimum designs, which allow for the evaluation of various trade-offs in practical experimental settings. The efficiency of the proposed design methods over conventional designs is demonstrated through extensive simulation experiments as well as the toxicology study of a series of engineering nanomaterials.

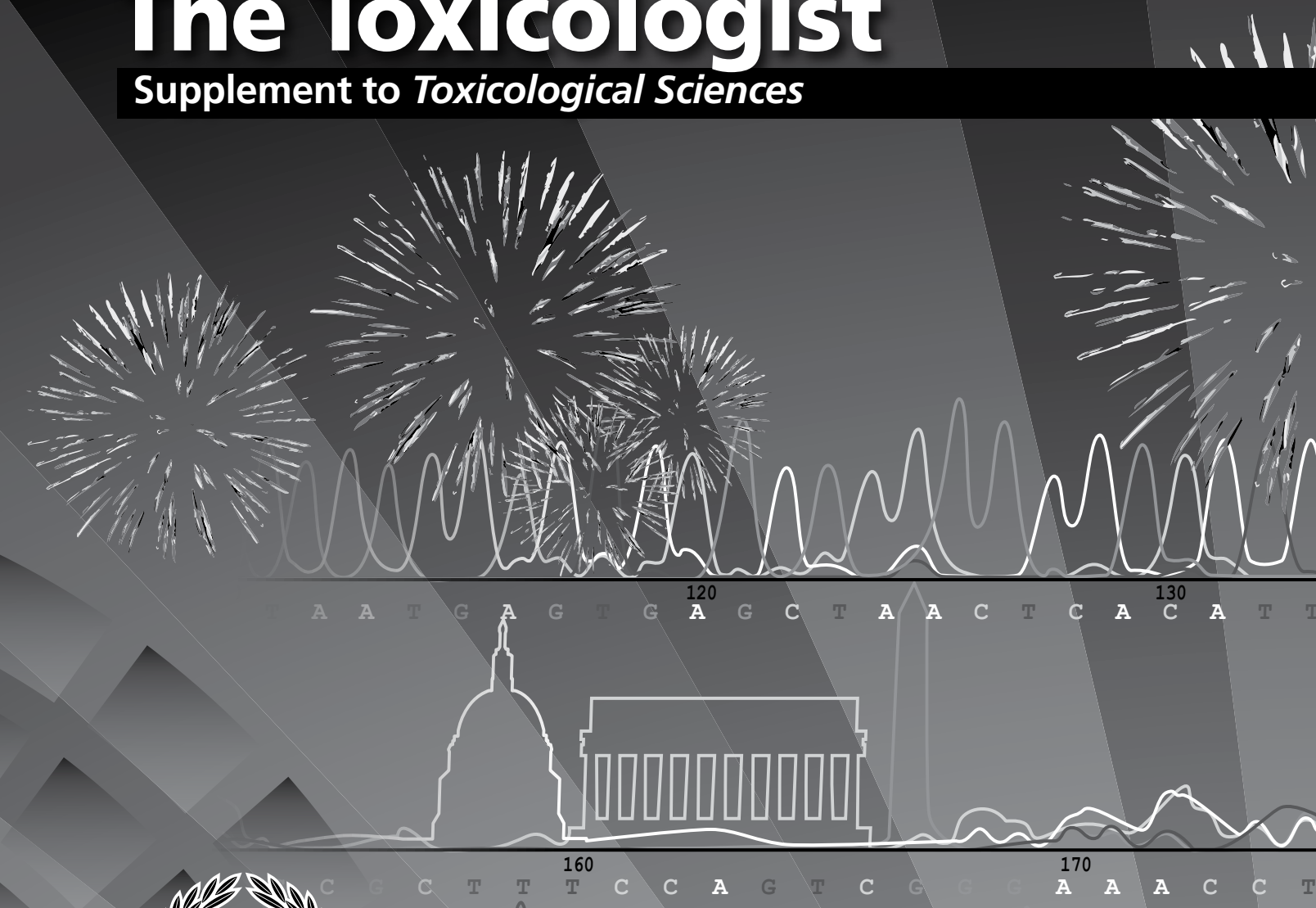
PS 479 PHARMACOKINETIC AND TOXICOLOGICAL PROFILING OF NATURAL PRODUCTS AND DRUGS.

C. Hasselgren[1], H. Chen[2], Y. Yang[2], S. Boyer[1], T. I. Oprea[3] and S. Muresan[2]. *[1]Global Safety Assessment, AstraZeneca, Mölndal, Sweden, [2]DECS, AstraZeneca, Mölndal, Sweden and [3]Division of Biocomputing, University of New Mexico, Albuquerque, NM.*

Natural products are often considered relevant starting points in drug discovery projects due to their diversity, novelty and intrinsic biological activity. In addition to being complex structures and difficult to synthesize, a major challenge when working with libraries based on scaffolds derived from natural products is their

The Toxicologist

Supplement to *Toxicological Sciences*



SOCIETY OF TOXICOLOGY
50th Anniversary
1961–2011

Celebrating 50 Years of Service in Science

50th Anniversary Annual Meeting and ToxExpo™ Washington, D.C.

An Official Journal of the Society of Toxicology

OXFORD UNIVERSITY PRESS

ISSN 1096-6080
Volume 120, Supplement 2
March 2011

www.toxsci.oxfordjournals.org

SOT | Society of Toxicology

Creating a Safer and Healthier World by Advancing the Science of Toxicology

www.toxicology.org

Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 50th Annual Meeting of the Society of Toxicology, held at the Walter E. Washington Convention Center, March 6–10, 2011.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 578.

The issue also contains a Key Word Index (by subject or chemical) of all the presentations, beginning on page 606.

The abstracts are reproduced as accepted by the Scientific Program Committee of the Society of Toxicology and appear in numerical sequence.

Copies of *The Toxicologist* are available at $45 each plus $5 postage and handling (U.S. funds) from:

Society of Toxicology
1821 Michael Faraday Drive, Suite 300
Reston, VA 20190

www.toxicology.org