chemical safety assessment (taking into account existing risk management measures) using the IUCLID5 tool. This includes the development of exposure scenarios and the derivation appropriate no effect level or minimal effect levels depending on exposure scenario (e.g., acute versus chronic) and hazard profile (e.g., threshold versus non-threshold) as well as the risk characterization process. The paper further discusses the possibilities for data waiving and the use of alternative methodologies such as in vitro testing, (Q)SARs (structural activity relationships) or read-across approaches.

983 INTEGRATION OF LIFE-STAGE AND EXPOSURE DURATION ASSESSMENTS INTO DERIVATION OF STANDARDS.

H. Goeden, P. Moyer and C. Greene. *Minnesota Department of Health, St. Paul, MN.*

The Minnesota Department of Health (MDH) establishes human health protection values called "Health Risk Limits" (HRLs). HRLs are expressed as micrograms of contaminant per liter of groundwater (ug/L) and represent a concentration that is without appreciable risk to human health whether ingested only once or daily for a lifetime. Historically, HRLs were thought of as protecting against adverse health effects from chronic exposure and combined an adult intake rate (2 L/day and 70 kilogram body weight or approximately 29 mL/kg-day) with a chronic reference dose. As part of the current rule revision MDH incorporated a variety of risk characterization approaches as recommended by the EPA Review of the Reference Dose/Reference Concentration Processes report. The evaluation for deriving non-cancer HRLs included: 1) evidence of life stage sensitivity; 2) assessing the relationship between the effects observed and duration of exposure; 3) selecting endpoints based on characterization of the entire database rather than the "critical" study; 4) incorporation of water intake rates based on age and duration considerations; and 5) evaluating the range of potential HRL values for different duration reference values and exposure durations before selecting a final value. The evaluations demonstrated that the historic reliance on chronic assessments may not be protective of less-than-chronic exposures. The result was a range of HRL values that ensure protection of sensitive life-stages and periods of high exposure. Evaluation of shorter durations lead to the identification of precursor events for chronic effects as well as endpoints attributed to shorter exposure periods. The major challenge to employing these methods was insufficient data for many of the chemicals of concern. Current testing protocols are typically not designed with a focus on assessing different life stages (timing of exposure) or different durations of exposure, therefore, these factors are often not well characterized. Examples of evaluations for specific PFCs, VOCs and pesticides will be presented.

984 TOXICOLOGY CONSIDERATIONS FOR PRECLINICAL DEVELOPMENT OF ANTICANCER DRUGS.

P. Colombo, M. Cattoni, R. Pulci and M. Brughera. *Accelera, Preclinical Development, Nerviano Medical Sciences, Nerviano, Milano, Italy.*

There is no universally accepted approach in the development of anticancer drugs. This is the consequence of the lack of a specific guideline as only regional ones or recommendations are followed in different geographical areas. If on the one hand, this may suggest some freedom to operate, on the other this lack of harmonization creates difficulties in having programmes accepted worldwide without potentially unnecessary use of resources and laboratory animals.
Additionally, the approach to the pre-clinical development of anticancer drugs is also depending on the class of drugs under investigation e.g. small molecules versus biological drugs. Furthermore, the approach within a given class of compounds is dependent from their respective mechanism of action. As an example, the pre-clinical development of a small molecule having cytotoxic properties requires different strategies with respect to a non-cytotoxic compound (e.g. anti-angiogenic compounds, hormonal drugs). Considering the high unmet medical need in the field of oncology drugs, it becomes more and more important to ensure a harmonized approach in order to make available new therapies to patients with shorter development programs, well-defined study typologies allowing minimization of animal use. With this aim, the International Conference of Harmonization (ICH) has initiated the process of preparing a guideline (ICHS9) that aims to address all the main points. This guideline should become effective from 2010.
Working for years in the pre-clinical development of anticancer drugs, Accelera has acquired a wide expertise in this field. Specific approaches used for the pre-clinical development of cytotoxic and non-cytotoxic compounds are exemplified on the basis of general toxicology, safety pharmacology and other in vitro/in vivo tests.
New perspectives and scenarios based on current trends and on the forthcoming ICH guideline are also mentioned.
Reference:
- "S9 Preclinical Guideline on Oncology Therapeutic Development" Final Concept Paper; April 30, 2007

985 PROGRESSING FROM THE MOUSE BIOASSAY FOR SHELLFISH TOXIN TESTING IN CANADA.

A. Guy and G. Griffin. *Canadian Council on Animal Care, Ottawa, ON, Canada.*
Sponsor: A. Goldberg.

Bivalve mollusks are filter-feeders that accumulate marine biotoxins which can severely affect the health of those who ingest them. To ensure the safety of its shellfish, the Canadian Food Inspection Agency manages a marine biotoxin monitoring program that relies on a mouse bioassay. While Canadians expect the government to protect public health, they rely on the Canadian Council on Animal Care, Canada's oversight body for the care and use of animals in science, to ensure that the use of animals in testing employs optimal physical and psychological care without compromising scientific integrity. The continued use of the mouse bioassay is ethically challenging because of the potential for extreme pain and distress. Canadian research has led to the development of non-animal test methods that are more sensitive and more reliable than the mouse bioassay, but these have not yet been adopted by Canadian regulators despite international validation studies. This research study used a policy stream model to characterize the problems and the solutions involved in the adoption of alternative methods for shellfish toxin testing. An ethnography study of stakeholders in shellfish toxin testing revealed that Canadian regulators still use the mouse bioassay because none of the alternative methods have been accepted as standards for international trade. Problems identified include: the incomplete set of certified reference standards; the insufficient throughput of liquid chromatography-based methods; and the high cost of the equipment for developing countries. Solutions identified include: research to develop more reference standards; improvement in the throughput of alternative methods; and the adoption of a two-tiered testing system for First World and Third World countries. Looking for opportunities to act where the problem stream and the solution stream converge, this study points to a need for more focus to be placed on validation of existing methods, rather than on further research on the development of new instrument-based methods, in order to balance protection of public health and ethical animal use.

986 EXTRAPOLATING HUMAN EFFECT THRESHOLDS FROM ANIMAL TOXICITY DATA FOR THE DERIVATION OF IMMEDIATELY DANGEROUS TO LIFE AND HEALTH VALUES.

A. Parker[1], A. Maier[1], G. Dotson[2] and C. L. Geraci[2]. *[1]Toxicology Excellence for Risk Assessment, Cincinnati, OH and [2]EID, CDC/NIOSH, Cincinnati, OH.*

Immediately Dangerous to Life or Health (IDLH) values have a long history of use in industrial settings in defining work practice and respiratory protection requirements for entry into potential high exposure environments. The National Institute for Occupational Safety and Health (NIOSH) defines the IDLH values as "airborne concentrations of a substance that may, in an occupational inhalation exposure of 30 minutes or less, pose an immediate threat to life, or cause irreversible adverse health effects, or interfere with the capability of a worker to escape should respiratory protection fail." This study was conducted to 1) critically assess the current strategy for the derivation of new IDLH values, 2) compare IDLH values derived from non-lethal toxicity data versus those derived from acute lethality data, and 3) examine the differences in the ratios of animal-to-human effect levels for various modes of action. As an update to a prior analysis (Weinrich et al., 2005), the acute toxicity data for 20 new high priority compounds (i.e., chemical terrorism agents, industrial or agriculture chemicals agents, or other agents that cause serious health effects from acute exposures) was assembled and provisional IDLH values were derived using alternative approaches. Alternative methods for extrapolating from acute lethality data in animal studies (LC50, LC10, and lowest lethal concentrations) to human exposure thresholds were compared. The findings indicate mixed results with a significant mode of action effect observed for some of the 20 chemicals. Overall, this work further enhances the transparency of the underlying rationale for the methods used to derive IDLH concentrations and provides a basis for updated safety factor selection. Lessons learned from this research were used in the derivation of new IDLH values for chemicals of interest to homeland security applications.

987 DEVELOPMENT OF AN IMPROVED STRATEGY FOR THE DERIVATION OF SKIN NOTATIONS.

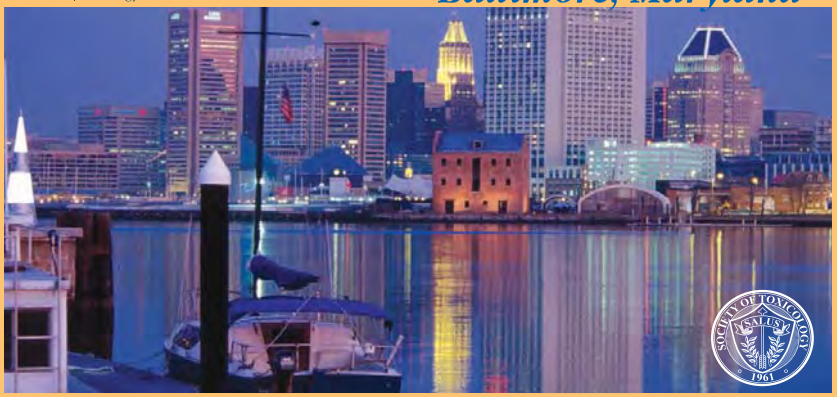
G. Dotson[1], A. Maier[2], B. Gadagbui[2] and C. L. Geraci[1]. *[1]EID, CDC/NIOSH, Cincinnati, OH and [2]Toxicology Excellence for Risk Assessment, Cincinnati, OH.*

Contact of the skin with chemical substances represents a significant route of exposure within workplace settings. The occupational safety and health community has relied on skin notations to identify and communicate the health hazards associated with dermal chemical exposures since the 1950s. These skin hazard designations have traditionally been used to indicate that a chemical has the potential to be ab-

SOT | Society of Toxicology

48th Annual Meeting and ToxExpo™

Baltimore, Maryland



March 15–19, 2009

Baltimore Convention Center

Photos courtesy of Baltimore Area Convention and Visitors Association

47th Annual Meeting and ToxExpo™

March 16–20, 2008

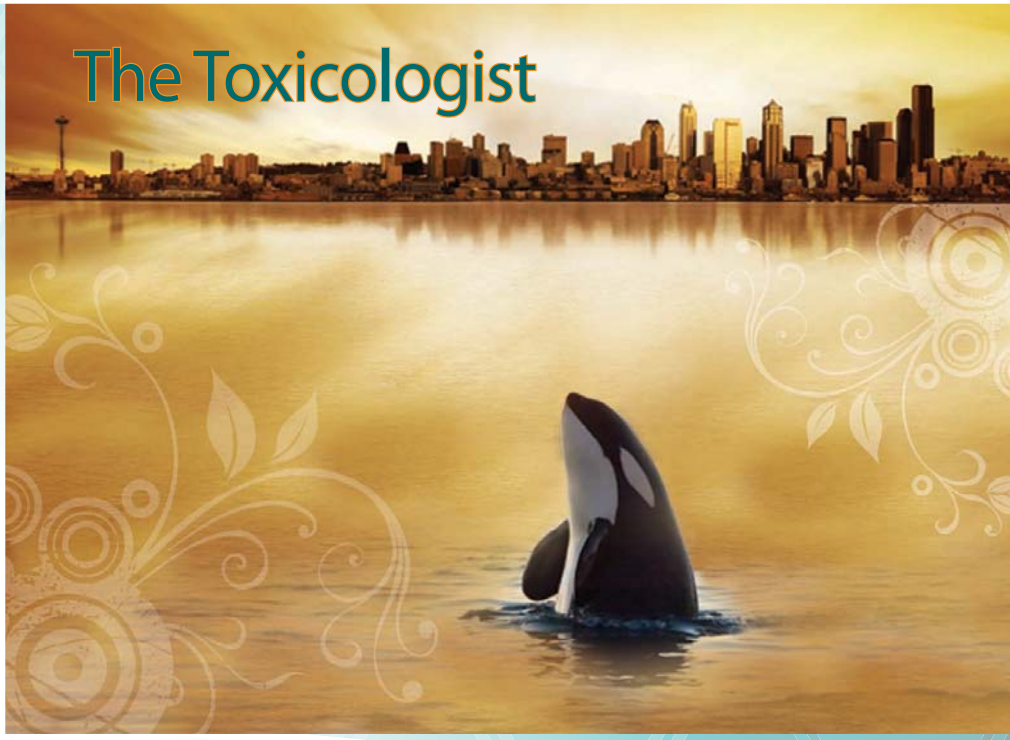
Society of Toxicology
1821 Michael Faraday Drive, Suite 300 • Reston, VA 20190
T: (703) 438-3115 • F: (703) 438-3113 • E-mail: sothq@toxicology.org
www.toxicology.org

SOT | Society of Toxicology

The Toxicologist

March 2008

The Toxicologist



47th Annual Meeting and ToxExpo™

Seattle, Washington

Supplement to Toxicological Sciences
An Official Journal of the Society of Toxicology

SOT | Society of Toxicology

www.toxsci.oxfordjournals.org
OXFORD UNIVERSITY PRESS ISSN 1096-6080 Volume 102, Number 1, March 2008