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.

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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.

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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.

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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-

sorbed through the skin and contribute substantially to systemic toxicity. Despite their importance as a risk management tool, several shortcomings have been identified with their continued use in their current form. The primary limitations are 1) the failure of the warnings to be assigned based on a standardized methodology, and 2) their inability to provide a warning for localized and sensitizing effects of chemical exposures. The National Institute for Occupational Safety Health (NIOSH) has developed a new strategy for the assignment of improved skin notations designed to address these issues. This process is a form of health hazard identification that provides the scientific rationale and framework for the derivation of multiple skin notations that clearly distinguish systemic, direct, and sensitizing effects caused by dermal exposures to chemical substances. This method relies on a critical evaluation of reports of human exposure and health effects, empirical data from animal toxicity studies, considerations based on mathematical models, and the application of a weight-of-evidence approach to assess the health risks associated with chemical contact with the skin. Issues encountered during the derivation of skin notations for 48 chemicals are presented. Special emphasis is placed on the application of the scientific rationale, the use of toxicological cut off values to determine systemic toxicity, and data quality.

988 THE NICEATM-ICCVAM FIVE YEAR PLAN: CREATING A PATH FORWARD TO REDUCE, REFINE AND REPLACE ANIMAL TESTING.

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NICEATM and ICCVAM have developed a five-year plan that builds on the mission, vision, and strategic priorities in the 2004 ICCVAM Strategic Plan. Implementing the five-year plan involves four key challenges. The first is to identify priority toxicity testing areas for the next five years, and to conduct and facilitate activities in those areas. Currently, the four highest-priority areas are ocular, dermal, acute, and biologics testing. Other priority areas include immunotoxicity, endocrine disruptors, pyrogenicity, reproductive and developmental, and chronic toxicity/carcinogenicity testing. The second challenge is to identify and promote research initiatives that are expected to support future development of innovative alternative test methods. These new methods might incorporate techniques such as high throughput screening, computer modeling, informatics, and biomarkers. The third challenge is for NICEATM and ICCVAM to foster the acceptance and appropriate use of alternative test methods through outreach and communication. This will be accomplished by sponsoring and participating in workshops, NICEATM-ICCVAM website communications, and the development and publication of standardized test method protocols. Finally, ICCVAM and NICEATM will develop partnerships and strengthen interactions with stakeholders to facilitate meaningful progress. These efforts are expected to facilitate research, development, translation, validation and regulatory acceptance of alternative methods that will reduce, refine, and replace animal use while maintaining scientific quality and the protection of human health, animal health, and the environment. Contract support provided by NIEHS contract N01-ES-35504.

989 CREATION AND IMPLEMENTATION OF DATA RESOURCES SUPPORTING INTEGRATED SCIENCE ASSESSMENTS OF CRITERIA AIR POLLUTANTS.

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Under the Clean Air Act (CAA) as amended in 1990, the US Environmental Protection Agency (EPA) is charged with establishing and periodically reviewing National Ambient Air Quality Standards (NAAQS) for six criteria pollutants: carbon monoxide, ozone, nitrogen dioxide, particulate matter, sulfur dioxide, and lead. The CAA requires EPA to review and, if appropriate, revise the NAAQS for each pollutant at five year intervals. A high level of effort is needed to adequately review and integrate the science (e.g., air quality analyses, quantitative risk/exposure assessments, risk characterization) that informs the Agency decision-making process. EPA recently decided to change the process of revising the NAAQS to help meet the mandated 5-year schedule. Included in this set of revisions is development of integrated science assessment (ISA) documents to address the most policy-relevant science. Timely development of the ISA will be facilitated by the use of a continuous process for identifying, compiling, characterizing, and prioritizing relevant new scientific studies into a database to store, organize and allow analysis of the scientific basis for each NAAQS. This "evergreen" database would encompass the entire breadth of information used in assessing the state of the science on exposure, ecological effects and health effects (epidemiologic, clinical, and toxicologic). This effort is also anticipated to enhance other data sharing activities within the EPA and in collaborations with other agencies and organizations. Examples of analyses, reports, queries and graphics created using the database thus far developed, and their relationship to the ISA documents will also be presented.
[The views expressed in this abstract are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.]

990 THE USE OF HEALTH-BASED OCCUPATIONAL EXPOSURE LIMITS AS REACH DERIVED NO EFFECT LEVELS.

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Under the European Union's new Registration, Evaluation, and Authorization of Chemicals (REACH) regulation, Derived No Effect Levels (DNELs) represent a level of exposure above which humans (e.g. consumers, workers, etc.) should not be exposed. In risk characterization of REACH-regulated chemicals, known and/or potential exposures are compared to the appropriately derived DNEL. The health risk is considered adequately controlled if the exposure does not exceed the DNEL. Compliance with traditional health-based occupational exposure limits (OELs) has been one of the most significant and useful methods for ensuring worker health and safety. As REACH stands right now, even though there may be an authoritative health-based OEL(s) (e.g. ACGIH TLVs, AIHA WEELs, German MAK, SCOEL, etc.) for a particular REACH chemical, a DNEL still needs to be derived (i.e. for long-term occupational exposure via inhalation) as the "benchmark" for exposure comparison. Because of current differences in the methodologies for deriving DNELs and OELs (e.g. in the use of professional judgment and experience, assessment, uncertainty/safety factors, etc.) it is generally anticipated that for any particular chemical, the health-based OEL will differ from that of the REACH-derived DNEL. Moreover, some experts believe that the workplace inhalation DNEL will be lower than its corresponding health-based OEL. Therefore, it is possible that workers, health and safety personnel (e.g. toxicologists, industrial hygienists, etc.), and managers will be confronted with both a DNEL and an OEL for the same chemical on which they need to make risk management (e.g. exposure reduction) decision. This poster will present background on the development of both DNELs and health-based OELs, discuss some of the potential regulatory and health & safety issues/consequences regarding the concurrent development and use of a DNEL and OEL for the same chemical in the occupational setting, and provide an overview of any updates regarding the REACH regulation (e.g. to the RIP 3.2-2 TGD) as it applies to the use of OELs as DNELs for workplace exposures.

991 SYSTEMIC TESTING BY THE DERMAL ROUTE CAN BE PRECLUDED BY *IN VITRO* OR *IN SILICO* PERCUTANEOUS ABSORPTION STRATEGIES.

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Recent developments in percutaneous absorption testing now make it possible to determine, using either in silico or in vitro prediction methods, to what degree a specific chemical will be absorbed through the skin. If there is concern for exposure by the dermal route but chemicals have little or no dermal penetration potential, systemic toxicity tests can be avoided. Within programs such as the US EPA's High Production Volume chemical challenge, this approach can be particularly rewarding. Here we present data generated using the QSAR model EPA DERMWIN for the mixture Commercial Hydroxyethyl Piperazine (CHEP), sponsored in the HPV program by The Dow Chemical Company. To check the applicability of the model experimental and modeled absorption data for ten analogous amines were compared; the ratio of experimental to modeled data was of acceptable concordance (values ranged from 0.1 to 10.5) and the absorption of CHEP was modeled. The components were predicted to minimally absorb through the skin, with estimated average total absorption at 1.99 mg/kg/day. When considered together with other factors such as production and use, protective equipment, and available data on piperazine (the component predicted to penetrate in the largest amount), this estimation supported the conclusion not to conduct a stand-alone dermal reproductive and developmental toxicity study. This approach protects public and worker health while avoiding resource- and animal-intensive tests such as dermal developmental or reproductive toxicity.

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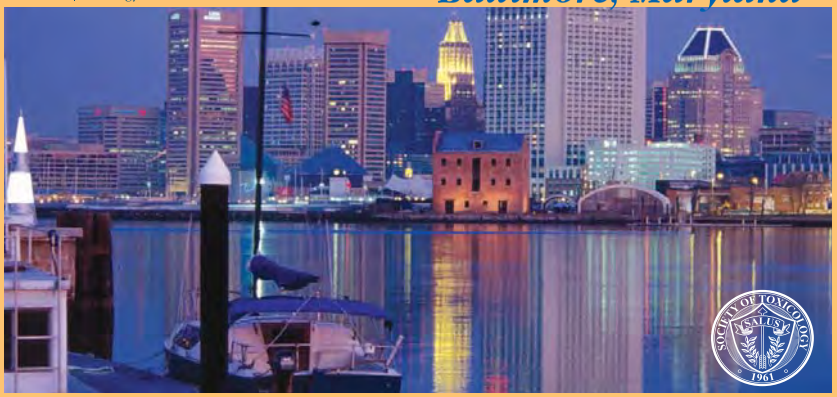

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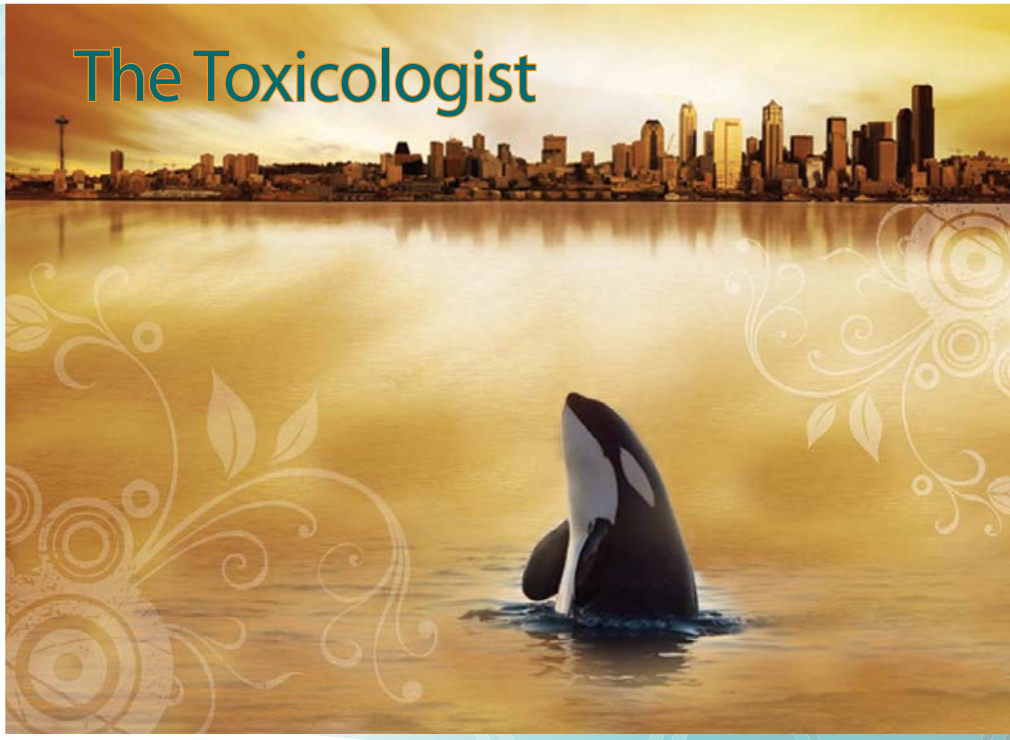

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