2710 Evaluation of Chemically Induced Cytotoxicity of Read Across Compounds in Rat and Human Lung Tissue

O. Danov[1], S. Escher[1], K. Schröder[1], J. Koschmann[3], M. Niehof[1], D. Vorgrimmler[2], P. Braubach[4], D. Jonigk[4], T. Hansen[1], A. Braun[1] and K. Sewald[1]. *[1]Fraunhofer ITEM, Biomedical Research in Endstage and Obstructive Lung Disease Hannover (BREATH), Member of the German Centre for Lung Research (DZL), Hannover, Germany; [2]Freiburg Center for Data Analysis and Modeling (FDM), Freiburg, Germany; [3]geneXplain GmbH, Wolfenbüttel, Germany and [4]Hannover Medical School, Hannover, Germany.* Sponsor: C. Dasenbrock.

Read across (RAX) is an alternative approach to evaluate chemicals for human risk assessment. Toxicity of untested chemical(s) should be predicted by tested compounds based on their structural and physico-chemical similarity. Three RAX-categories have been selected based on shared structural properties and similar toxicological effects in repeated dose toxicity studies and were evaluated in rat and human precision-cut lung slices (PCLS). Exposure of PCLS was performed on three days for three hours daily. The cytotoxicity was assessed by WST-1 assay in the dose-dependent manner. A concentration showing 10-20 % cytotoxicity was used for gene expression analysis. Vicinal halogenides showed decreasing cytotoxicity from 1,2-Dibromo-3-chloropropane (DBCP, IC50=0.3mM), to 1,2,3-Trichloropropane (IC50=4mM) followed by 1,2-Dichloropropane (1,2-DCP, IC50>10mM) in rat PCLS and 3.3mM, and over 10mM for both other chemicals in human PCLS, respectively. Aromatics showed decreasing cytotoxicity from 2-Naphtol, to 2-Methylnaphthalene with comparable IC50 values in both species: 0.4mM vs. 0.9mM (rat vs. human) and 0.5mM vs. 0.4mM, respectively. Naphthalene was non-toxic in human lung sections at the highest tested concentration of 1mM while showing 20 % vitality reduction in rat PCLS at the same concentration. Esters showed comparable IC50 values in both species. Differentially expressed genes (DEG) were analyzed in human tissue sections. Up- and down-regulated genes were assessed for all tested substances. The number of DEGs ranged from 16 for 1,2-DCP to over 600 DEGs for DBCP. DEGs could be mapped to biological processes such as regulation of cytokine secretion, neutrophil chemotaxis or apoptotic process. This evaluation of rat and human PCLS showed that *ex vivo* chemical testing results in a promising approach for toxicity profiling and assessment of interspecies diversity. Moreover, evaluation of chemically induced gene regulation can reveal similarities and differences within the groups. This work was supported by BMBF grant 031A269A.

2711 Toxicological Categorization of P- and E-Series Glycol Ethers Using High-Content Screening of Human Induced Pluripotent Stem Cell (iPSC)-Derived Cells

Y. Iwata[2], F. Grimm[2], M. Wilson[2], M. Bittner[2], O. Sirenko[3], J. C. Rowlands[1], N. Ball[1] and I. Rusyn[2]. *[1]The Dow Chemical Company, Midland, MI; [2]Engineering Experiment Station, Texas A&M University, College Station, TX and [3]Veterinary Integrative Biosciences, Molecular Devices, LLC, Sunnyvale, CA; [4]Veterinary Integrative Biosciences, Texas A&M University, College Station, TX.*

High-content screening (HCS) assays utilizing novel organotypic cell culture models are an attractive approach for predictive safety assessments of chemicals through biological data-based read across. To test the hypothesis that HCS represents a feasible approach to categorize chemicals based on similarities in their *in vitro* toxicity profiles, we screened eight propylene (P-series) and twelve ethylene (E-series) glycol ethers, structurally related yet toxicologically diverse group of prototypical industrial high production volume chemicals. We used two human induced pluripotent stem cell (iPSC)-derived cell types, cardiomyocytes and hepatocytes. Cells were exposed to glycol ethers in concentration-response over five (semi-)logs for up to 48 hours. Toxicity endpoints included effects on cardiomyocyte beating patterns. Cytotoxicity, mitochondrial and cytoskeletal integrity, and (in hepatocytes) reactive oxygen species formation and lipid accumulation were also assessed. Data were fit to a concentration-response to derive point-of-departure values that were used as quantitative descriptors for categorization in Toxicological Prioritization Index (ToxPi). We found that there is a correlation between the length of the alcohol group and induced effects such that glycol ethers can be categorized based on simple glycols, methyl-, ethyl-, propyl-, butyl-, and hexyl ethers. Within an alcohol group based category, in general there was increasing cytotoxicity between mono-, di-, and tri-substituted glycol ethers. A trend was observed with integrative ToxPi evaluation that combined all endpoints and cell-types, which was more prominent than when the data was expressed by individual cell-type. However, the trends in *in vitro* data did not align with the data trends in *in vivo* toxicity for these substances as there was no separation between E- and P- series glycol ethers in terms of biological activity. Future efforts should be directed towards correlating biological data and physico-chemical data sets and gene expression analysis as additional means to define biological similarity.

2712 Isomer-Specific Toxicity Profiles of Aminophenols

S. Perumal Kuppusamy[2] and J. Lipscomb[1]. *[1]National Center for Environmental Assessment, US EPA, Cincinnati, OH and [2]Risk Evaluation Branch, National Institute for Occupational Safety and Health/Centers for Disease Control and Prevention, Cincinnati, OH.*

Aminophenols are used in photographic processes, and in several fluorescent and hair dyes. Because the isomers differ in metabolism and the capabilities to cause toxicities in different organs, the repeated dose toxicity profiles for aminophenol isomers (ortho-, meta- and para-) are compared. Ortho aminophenol (OAP) is converted to 2-aminophenoxazine-3-one by cytochrome c and excreted as sulfate and glucuronide conjugates. The critical effect is increased relative liver weight in male rats at 83 mg/kg-day on 12 days oral exposure. No observed adverse effect level (NOAEL) could not be identified. For metaaminophenol (MAP), only glucuronidation and sulfation conjugation reactions are reported. The critical effect is reduced body weight, tremors, and increased serum bilirubin in newborn rats of both sexes at 240 mg/kg-day on postnatal days 4-21 oral exposure. NOAEL is 80 mg/kg-day. Paraminophenol (PAP) is oxidized to p-benzoquinoneimine by renal tissue cytochrome P-450 and binds to renal protein. PAP acetylates and conjugates with glutathione for excretion. The critical effect is brown urine, increased epithelial cells in the urine, and increased proximal basophilic tubule in the kidney of both sexes of rats at 100 mg/kg-day on 28 days oral exposure. NOAEL is 20 mg/kg-day. The severe nephrotoxic effect of PAP, among other isomers, may be due to para arrangement on the benzene ring of hydroxyl and amino groups. OAP and PAP produced dose-related increases in developmental toxicity in Syrian Golden Hamsters with intraperitoneal injection. Although both positive and negative genotoxicity results are reported for all isomers, there is inadequate information to assess the carcinogenic potential for all of them. No repeated dose inhalation studies for all aminophenols are located. Taken together, each isomer target different organs. These kind of studies improve our understanding of the different risks posed by different arrangement of atoms in the molecule. [The findings and conclusions in this presentation are those of the authors and do not necessarily represent the views of the NIOSH or the US EPA.]

2713 Multi-Dimensional Analysis of Mode of Action: Identifying the Critical Factors for Determining Risk

G. M. Woodall, A. K. Hotchkiss and A. M. Jarabek. *National Center for Environmental Assessment, US EPA, Research Triangle Park, NC.*

Human exposures to chemical pollutants are often not at uniform concentrations for constant, continuous periods of time; this represents a challenge to evaluation of risk and developing effective risk mitigation approaches based on real-world exposure scenarios. A simple, two-dimensional dose-response relationship (increasing response or severity versus increasing exposure levels) is typically used to describe toxicological data. Factors other than dose can affect an adverse outcome *in vivo*, and can be outcome- or chemical-specific, including: duration of exposure; nature of exposure (single or repeated peaks versus long-term average); recovery time between exposures; timing of exposure (time of day, life-stage, presence of other stressors); and many others. The dose-response relationship is also dependent on the mode of action (MOA) and choice of dose metric. A two-dimensional dose-response relationship is insufficient to comprehensively describe these relationships. Instead, we are using a multi-dimensional surface analysis with exposure concentration, duration, and timing as independent variables. To test this analytical approach, we reviewed the existing literature for several chemical classes (e.g., VOC, aldehyde, aromatic hydrocarbons, metals, anions) to characterize the relative contribution of each for explaining the surface response function for a spectrum of endpoints (e.g., respiratory, reproductive/developmental, liver). This type of information will be useful for making health risk decisions to mitigate risk based on the most critical factors (e.g., if repeated peak exposures are more relevant than long-term averages, an acute reference value may be more relevant than a chronic reference value). The results of this analyses are compared to existing health effect reference values, with recommendations on how best to derive relevant risk estimates for acute and episodic exposures based on chemical class and adverse outcome. (The views expressed in this abstract are those of the authors and do not necessarily represent the views or policies of the US EPA).

The Toxicologist

Supplement to *Toxicological Sciences*

55th Annual Meeting and ToxExpo™

SOT

New Orleans, Louisiana

March 13–17, 2016

OXFORD
UNIVERSITY PRESS

ISSN 1096-6080
Volume 150, Issue 1
March 2016

www.toxsci.oxfordjournals.org

The Official Journal of the Society of Toxicology

SOT | Society of Toxicology

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

www.toxicology.org

Preface

This issue is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 55th Annual Meeting of the Society of Toxicology, held at the New Orleans Ernest N. Morial Convention Center, March 13–17, 2016.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 603.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 629.

The abstracts are reproduced as accepted by the Scientific Program Committee of the Society of Toxicology and appear in numerical sequence. Author names which are underlined in the author block indicate the author is a member of the Society of Toxicology. For example, J. Smith.

Scientific Session Types:

- CE Continuing Education Courses
- EC Education-Career Development Sessions
- FS Featured Sessions
- HH Historical Highlights Sessions
- IS Informational Sessions
- PL Platform Sessions
- PS Poster Sessions
- RI Regional Interest Sessions
- R Roundtable Sessions
- S Symposium Sessions
- W Workshop Sessions

The 2016 SOT Mobile Event App and Online Planner

The Mobile Event App and Online Planner are available via the SOT website and app marketplaces. These mobile tools enable you, the attendee, to engage with organizers, exhibitors, and each other, and to manage your time and maximize your experience during the Annual Meeting. You also can access some ePosters electronically via the Mobile Event App until May 11, 2016.

To cite a 2016 SOT Annual Meeting Abstract, please format as follows: *The Toxicologist*, Supplement to *Toxicological Sciences*, 150 (1), Abstract #__, 2016, Title, First Author.

Copies of *The Toxicologist* are available at $40 each plus shipping ($15 shipping & handling in the USA and $50 for overseas shipments) from:

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

www.toxicology.org