Southern California Chapter of the Society of Toxicology (SCCSOT) Meeting

Emerging Topics in Computational, Drug Discovery, Neuro-, and Environmental Toxicology

Green Acre Campus Pointe, San Diego, CA

November 7th, 2019
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<td>8:55-9:00 AM</td>
<td>Welcome Address and Introduction</td>
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<td>Giovanna Pozuelos PhD Candidate, UC-Riverside</td>
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<td>1:10-1:50 PM</td>
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<td>35 min talk/ 5 min Q/A – “Comparison of Atomizer Design and Concentration of Metals/Elements in Aerosols from Three Generations of Electronic Cigarettes”</td>
<td>Monique T. Williams, PhD UC-Riverside</td>
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<td>10 min talk/5 min Q/A – “mRNA-Sequencing Identifies Liver as a Potential Target Organ for Triphenyl Phosphate in Embryonic Zebrafish”</td>
<td>Aalekhya Reddam Graduate Student, UC-Riverside</td>
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<td>2:45-3:00 PM</td>
<td>10 min talk/5 min Q/A – “Analyzing the effect of perfluorobutanesulfonic acid on pancreatic organogenesis in zebrafish using automated image segmentation”</td>
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Sincere thanks to all the SCCSOT meeting sponsors!

Be sure to visit each sponsor table during breaks and reception and get your ‘passport’ stamped. All attendees who receive stamps from every sponsor can enter a raffle for a prize to be awarded at approximately 4:30 pm during the reception.

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Early Human Insights
## 2019-2020 SCCSOT Chapter Officers

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**FOR MORE ABOUT SCCSOT:**
[https://www.toxicology.org/groups/rc/SouthernCal/index.asp](https://www.toxicology.org/groups/rc/SouthernCal/index.asp)
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Chemical Elements and Metals in Aerosols from Three Generations of Electronic Cigarettes: Does it Cause VAPI?

Monique Williams¹, Krassimir Bozhilov², Jun Li³, Amanda Villarreal¹, Shane Sakamaki-Ching¹, My Hua¹, Sabrina Lin¹, Steve Bates⁴, Andrew Robinson⁴, Maciej Goniewicz⁵, Timothy Lyons⁴, and Prue Talbot¹

¹Department of Molecular, Cell, and Systems Biology, University of California, Riverside, CA. ²Central Facility for Advanced Microscopy and Microanalysis, University of California, Riverside, CA. ³Department of Statistics, University of California, Riverside, CA. ⁴Department of Earth Sciences, University of California, Riverside, CA. ⁵Department of Health Behavior, Roswell Park Cancer Institute, Buffalo, NY

Since their introduction in 2004, electronic cigarettes (EC) have evolved into three distinct generations of devices, which include the cig-a-likes, clearomizers, and mods. The atomizer, which heat the e-fluid, contains various metal components and is important as it affects the performance of ECs and what transfers into the aerosol. The purpose of this study was to examine the elements/metals in EC atomizers and the elements/metals in EC aerosols as a function of evolution, puffing topography, and collection method. Data were consolidated on atomizers from 32 brands representing three generations of ECs (cig-a-likes including cartomizers and disposables, clearomizers, and mods). The atomizers were dissected and photographed using a stereoscopic microscope, then elements in atomizer components were analyzed using scanning electron microscopy and energy dispersive spectroscopy. The concentration of 19-37 elements/metals in aerosols was determined using inductively coupled plasma optical emission spectroscopy. EC atomizers across all generations contained a filament(s) (usually nichrome) and wicks (silicon, cotton). Other major components were: a thick wire (copper, nickel), joints between wires (tin/lead solder, brass clamps, brazing of wires, a sheath(s) (fiberglass), and Polyfil fibers. Some third-generation models of EC lacked several of these components in their atomizers. Of 37 elements studied, 12 (aluminum, calcium, chromium, copper, iron, lead, magnesium, nickel, silicon, sodium, tin and zinc) were frequently present in EC aerosols across all three generations. Calcium, silicon, and tin often had the highest concentrations (0.012-1.124 mg/L, 0.021-5.581 mg/L, and 0.001-2.645 mg/L, respectively). For some elements, such as arsenic, copper, iron, nickel, lead, tin, the concentration increased in aerosols as voltage/power increased with the introduction of clearomizers and mods. Many of the elements detected in the aerosols originated from components in the atomizers. Concentrations of some elements, such as chromium, lead, and nickel, were higher in aerosols of the later generation ECs and may present a health risk, such as vaping-associated pulmonary injury or VAPI.
mRNA-Sequencing Identifies Liver as a Potential Target Organ for Triphenyl Phosphate in Embryonic Zebrafish

Aalekhya Reddam, Constance A. Mitchell, Subham Dasgupta, David C. Volz
Department of Environmental Sciences, University of California, Riverside, CA, USA

Triphenyl phosphate (TPHP) is a commonly used organophosphate flame retardant and plasticizer in the United States. Over the past decade, there has been a marked increase in the use of TPHP due to the phase-out of certain brominated flame retardants. Using zebrafish as a model, previous studies have shown that TPHP exposure from 24 to 72 hours post fertilization (hpf) results in severe cardiac looping defects by 72 hpf – a phenotype that is dependent on exposure during pharyngula (24-48 hpf) and mitigated by pre-treatment with non-toxic concentrations of a pan-retinoic acid receptor (RAR) agonist (fenretinide). Therefore, the objectives of this study were to 1) rely on mRNA-sequencing to identify pathways before and after cardiac looping (30 and 48 hpf, respectively) that may be impacted following exposure to 10 µM TPHP from 24-48 hpf and 2) determine whether pre-treatment with 2 µM fenretinide from 24-30 hpf mitigates cardiotoxicity-related pathways within embryos exposed to TPHP from 30-48 hpf. Based on mRNA-sequencing, TPHP exposure from 24 to 30 hpf and 24 to 48 hpf significantly affected the abundance of 305 and 274 transcripts, respectively, relative to vehicle (0.1% DMSO) controls. In addition to minor effects on cardiotoxicity- and nephrotoxicity-related pathways, Ingenuity Pathway Analysis (IPA) of significantly affected transcripts from 30- and 48-hpf embryos revealed that hepatotoxicity-related pathways were strongly affected following exposure to TPHP alone. Moreover, while pre-treatment with fenretinide mitigated TPHP-induced cardiac looping defects at 72 hpf, IPA revealed that fenretinide was unable to block TPHP-induced effects on hepatotoxicity-related pathways at 30 and 48 hpf, suggesting that, unlike the heart, TPHP-induced hepatotoxicity may be RAR-independent. Overall, our mRNA-sequencing-based data suggest that, in addition to the heart, the embryonic liver may be highly susceptible to TPHP exposure during early development. Therefore, our ongoing studies are focused on 1) confirming that TPHP exposure alters the normal trajectory of liver development (based on phenotypic data) within zebrafish embryos and 2) identifying the mechanism of action that leads to potential TPHP-induced effects on hepatocytes within zebrafish and human cell-based systems.
Analyzing the effect of perfluorobutanesulfonic acid on pancreatic organogenesis in zebrafish using automated image segmentation

Ashley Schwartz
San Diego State University

Increased levels of perfluorobutanesulfonic acid (PFBS) in environmental and human samples is a recent area of concern for the potential negative health effects. This study aims to identify the hazard posed by embryonic PFBS exposure on pancreatic development in zebrafish embryos (Danio rerio) by creating an algorithm for automated detection and image segmentation of the exocrine pancreas. Embryos of the transgenic fishline Tg(ptf1a-GFP), which fluoresce in the exocrine pancreas, were exposed to 0 (0.01% DMSO) 16, or 32 μM PFBS beginning at 1 day post fertilization (dpf) until 4 and 7 when fluorescent microscopy images were captured. Image analysis was performed using a novel automated MATLAB algorithm to accurately segment and quantify the area of the fluorescent exocrine pancreas in the images captured. From this quantification, we found that PFBS significantly decreased exocrine pancreas size in exposed samples both 4 and 7 dpf. The results of study show that PFBS exposure can perturb embryonic development and the image segmentation algorithm outlines a framework for efficient and accurate screening of embryonic organs in microscopy.
Automated Mining of Vaping-Associated Health Effects Reported in Online Forums

My Hua1,3, Shouq Sadah2, Vagelis Hristidis2, and Prue Talbot1,3
1Environmental Toxicology Graduate Program, 2Department of Computer Science and Engineering, 3Department of Molecular, Cell and Systems Biology, University of California, Riverside, Riverside, CA, United States 92521

Background: Vaping-associated pulmonary illness (VAPI) has reached epidemic proportions in the United States. To better understand this epidemic, we have used computer automated methods to extract and analyze over 41,000 posts from a major EC online forum. The posts spanned 7.5 years and were used to identify the health effects associated with EC use. Methods: Extracted data were annotated with a set of medical concepts from the Unified Medical Language System (UMLS), using a modified version of the MetaMap tool. Posts were used to analyze symptoms (undiagnosed conditions) and disorders (physician diagnosed terminology) associated with EC use. Health effect data were annotated as symptoms or disorders and then categorized into 12 organ systems/anatomical regions. Data were further analyzed for: (1) frequency of symptoms and disorders, (2) sentiment, (3) changes in reported health effects between 2008 and 2015, (4) linkage between symptoms, and (5) similarities between existing VAPI case report symptoms to the mined dataset. Results: Symptoms and disorders were most often reported in the neurological, respiratory, digestive, integumentary, and mouth/throat systems, over the 7.5-year period studied. The most common symptoms were: headaches (N=939), coughing (N=852), pain in throat (N=643), dermatitis (N=565), and heartburn (N=327). The most commonly reported disorders were asthma (N=916), pharyngitis (N=565), chronic obstructive pulmonary disorder (N=471), dehydration (N=403), aptyalism (N=377), and pneumonia (N=367). Overall, most symptom and disorder posts contained negative sentiment across all years. Several symptoms were linked (e.g., coughing and headache). Additionally, many commonly reported symptoms in this dataset are present in the current VAPI epidemic cases. Conclusions: Online forums are a unique repository of data that can track health effects over time. This is the first study to use automated methods to retrieve EC health data online and it demonstrates the importance of medical internet surveillance. Our data agree well with the symptoms of reported VAPI cases and others in peer reviewed literature. This suggests that health problems have existed among vapers for at least 7.5 years, although this has not been widely recognized by the medical community until now. Our data also suggest that there are many other EC users with pulmonary illness due to vaping who are not yet part of the of the statistical data reported by the Centers for Disease Control. The genotoxic risks associated with low dose exposure to clastogenic agents are thought to decrease linearly into the very low.
Thirdhand smoke (THS) consists of residual tobacco smoke that settles and remains on indoor surfaces after smoking has ceased. Remediation of these chemicals is important in reducing exposure to THS. In this study, we investigated the affinity of THS chemicals to common household fabrics that are not washed frequently (e.g. draperies and upholstery) and could act as chemical reservoirs. Cotton, terry cloth, polyester, and wool carpet fabrics were washed four times before being placed in a chamber designed for THS exposure smoke exposure. They were then exposed for 1, 6, 12 or 18 months to 696, 1569, 1795, 3617mg of smoke, respectively. THS was extracted from each fabric at a concentration of 0.1g of fabric/mL of PBS, DMSO, or cell culture medium. Extraction media were examined using fluorescence spectroscopy at various wave lengths. Nicotine, nicotine alkaloid and tobacco specific nitrosamine (TSNA) concentrations in extracts were quantified using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Affinity of nicotine to terry cloth and polyester was compared by exposing each fabric to 10 mg/ml of nicotine, and quantifying the amount of nicotine recovered after extraction using high performance liquid chromatography (HPLC). Our results showed that THS chemicals in fabric extracts autofluorescence, and fluorescence was proportional to the time and amount of THS exposure received by the fabrics. THS autofluorescence was not detected in extracts from polyester and wool carpet at any of the excitations tested. Nicotine, nicotine alkaloid, and TSNA concentrations were higher in THS extracts from cotton and terry cloth than in polyester and wool carpet. Using fabrics spiked with 10 mg of nicotine, we showed that extraction efficiency was much higher from terry cloth (7mg) than from to polyester (0.11mg). The absorption into and release of THS from fabrics varied with the type of fabric. Human exposure to THS could be influenced by fabric type, and remediation techniques may need to vary depending on the fabrics reservoirs being treated.
Evaluation of serotonin-modifying toxicants using a standardized tracking and behavioral model in C. elegans

Courtney McClure and Patrick Allard
University of California, Los Angeles

CPF is a commonly used organophosphate pesticide in the US despite evidence that it can cause life-long, persistent changes in the serotonergic system of mammals. Serotonin is responsible for modulating behavior and plays an important role in behavioral plasticity, memory, and learning. Here, we use the model system C. elegans as it shows a high degree of conservation of the serotonergic system with mammals including serotonin receptor, transporter, and synthesis and shows alterations in behavior in response to serotonin deficiency. We will evaluate this pesticide, CPF, using a self-designed and standardized behavioral model for serotonin-mediated behaviors, and monitor its effects on behaviors and alterations to the serotonergic system. We will also evaluate how this exposure can influence gene expression and epigenetic mechanisms transgenerationally. We hypothesize that CPF will alter serotonin-controlled behaviors and the serotonergic system, and that this will be seen transgenerationally and is influenced by changes in gene expression and epigenetic mechanisms. We have characterized the serotonin-controlled behaviors of enhanced slowing responses (ESR) via food deprivation, and basal slowing responses (BSR) under normal conditions for both wild type worms and mutant strains deficient in serotonin, dopamine, or both. Wild type worms display a significantly slower locomotion rate in their (P < 0.0001) when compared with their BSR by measuring either center point speed (fold change= 1.9) or absolute peristaltic speed (fold change 1.5). Other new insights into the behavior of mutants such as mod-5 (deficient in serotonin) and cat-2 (deficient in dopamine) reveal that mod-5 wavelength shows no difference when compared to wild type for the BSR, while cat-2 shows significantly (ESR = 1.27 fold change, BSR= 2.6 fold change) higher wavelength in both ESR and BSR(P < 0.0001). This in-depth individual behavioral analysis and subsequent dose response study using our behavioral model we have developed is the first of its kind and will address a significant gap of knowledge into the transgenerational effects of serotonin modifying agents on behavior.
Chlorpyrifos-Induced Transgenerational Modifications on Serotonin-Mediated Behaviors in C. elegans

Maria Blumenkrantz, Courtney McClure, and Patrick Allard
University of California, Los Angeles

Although chlorpyrifos (CPF) is a frequently used organophosphate insecticide in the US, and has been shown to modify serotonergic mechanisms. The insecticide has also been correlated with a significantly higher rate of suicide, depression, and other neurologic symptoms among farmers and their families (Lee et al. 2007). However, a knowledge gap about the transgenerational and neurotoxic effects of CPF still exists. Since serotonin and dopamine are neurotransmitters implicated in these disorders, we aim to characterize the impacts of CPF on serotonin and dopamine-mediated behaviors by exposing the nematode C. elegans to the insecticide and analyzing its behavior on the WormLab tracker. Our hypothesis is that serotonin and dopamine mediated behaviors in C. elegans will be altered as a result of exposure to CPF and that these changes will be passed down transgenerationally. We have created a standardized model for serotonin/dopamine-related phenotypes by analyzing both wild-type, serotonin-mediated, and dopamine-mediated behaviors on WormLab. The first of these serotonin-mediated behaviors is termed the enhanced slowing response, which has so far been analyzed in the context of several of the mutants, such as tph-1 (defective in serotonin). This strain shows significantly center point speed (P value= 0.008, fold change = 2.7) , aligning with previous examples in literature and showing its evident loss of the serotonin-mediated enhanced slowing response (Sawin et al., 2000). Also among these behaviors is swimming, which is composed of four stages: swim onset, swimming, emergence, and dragging. Previous studies have shown that dopamine is necessary for the swim-to-crawl transition, and serotonin is necessary for swimming and the crawl-to-swim transition (Vidal-Gadea et al. 2011). After standardization of this assay, dose response of CPF will be performed on wild-type worms to analyze its effects on behaviors regulated by serotonin. Because the role of serotonin is conserved across nearly all animal phyla, understanding the effects of CPF on behavioral phenotypes and transgenerational mechanisms would increase our ability to evaluate its risk to the nervous system and overall public health.
Identifying the genetic determinants of physiological response to combinatorial environmental exposures

Misaki Kobayashi, Manali Ghadiali, Justin Nguyen, Courtney McClure, and Patrick Allard
University of California, Los Angeles

C. elegans behavior is conditioned by the cumulative interaction of many factors, such as natural environmental stimuli and manufactured toxicants (Anderson et al., 2004). Specifically, we are interested in how deleterious environmental exposures, alone or in combination, can modulate behaviors mediated by serotonin, an important neurotransmitter conserved across nearly all animal phyla. We focus on two exposures that are known to affect serotonin-dependent behaviors: (1) high temperature as a model for warmer climate and (2) the common pesticide chlorpyrifos. We aim to use genetic methods to identify genetic loci that convey resistance of the serotonergic system when under environmental stress by either temperature, chlorpyrifos, or both. We hypothesize that specific gene networks control the function and resilience of the nervous system, and that combinatorial exposures may uncover new nodes of stress response and resilience. For this, we will use of a resource available in the common genetic model system C. elegans where several, genetically-distinct wild isolates are available using a natural diversity resource, (Cook et al., 2016). This will address a key gap, as behavior has been assessed only in the wild type isolated from Bristol, England. By using a model for serotonin-mediated behaviors developed by the Allard lab and an added heat stimulus model, the behavioral profile of each wild isolate will be investigated across temperature ranges and chlorpyrifos concentrations to assess which wild type isolates are able to convey enhanced thermotolerance through survivability. Preliminary data from the seven strains which are from diverse regions, including the Bristol, England strain as a control were compared at several temperatures, focusing on the critical temperature of 33°C for percent of worms surviving (40 worms per replicate, 1 trial each). Fold change for strain with the origin of Israel, between control was 13.84% and for strain with the origin of Peru was 4.33%, indicating enhanced survivability. When survival and behavior have been measured, we will use Quantitative Trait Loci (QTL) analyses to identify the loci responsible for increased or decreased sensitivity to these exposures alone or in combination. We therefore hypothesize that this synergistic exposure will adversely impact the serotonergic system and conveyed thermotolerance, evident in altered serotonin-mediated behaviors. Genetic analysis of specific gene networks will uncover how animals from different environmental conditions and that are exposed to varied environmental stimuli can differ in terms of behavior, and what key genetic differences can contribute to this.
A Single Nuclei Analysis of Changes in Epigenetic Sensitivity to Chemical Exposure with Age

University of California, Los Angeles, Los Angeles, CA.

It is well-known that the epigenome in early development is particularly vulnerable to chemical exposure. There is relatively little known, however, about periods of sensitivity during the aging process. Understanding how sensitivity to chemical exposure changes with age is crucial for designing thorough risk assessments. To map epigenetic sensitivity with age we are performing single nuclei RNA sequencing in adult C. elegans. C. elegans’ short lifespan facilitates aging experiments and many fundamental age-related pathways are conserved between C. elegans and humans. Previously, we used immunofluorescence to show that regulation of certain histone marks becomes more variable with age, suggesting that older organisms may be more vulnerable to epigenetic perturbations. Single nuclei sequencing will help us further understand gene expression changes with age and chemical exposure. To assess the quality of our nuclei dissociations we used fluorescent activated cell sorting on nuclei dissociated from transgenic C. elegans containing GFP tagged germline nuclei. We obtain about 30% germline nuclei, suggesting we will be able to detect changes in the germline transcriptome with age and chemical exposure. After performing sequencing on day two adult C. elegans, we obtained 32,099 reads per cell, 1,515 genes per cell, and 10,810 nuclei sequenced, indicating that we had the sequencing depth to gain a comprehensive view of adult C. elegans transcriptomic changes and communication between tissues. The breadth of our sequencing enabled us to obtain rare cell types, for example roughly 5% of our nuclei were neurons. However, we had a low sequencing saturation of 31%, suggesting our samples were overly concentrated. Next, we will expose C. elegans to two chemicals pervasive in the environment, bisphenol A and perfluorooctanesulfonic acid, at different ages and then perform single nuclei sequencing. Subsequent chromatin immunoprecipitation sequencing will identify the upstream epigenetic changes associated with the observed gene expression changes. We will compare perturbations to the transcriptome and epitranscriptome at different ages to identify changes in chemical sensitivity with age. One benefit of our approach is that we can evaluate transcriptomic changes in specialized cell types, such as neurons, whose expression patterns are usually masked in bulk RNA sequencing. Furthermore, our research will help fuel dialogue on how to account for age when designing chemical safety assessments.
Examining the transgenerational effects of environmental cues in C. elegans

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In sexually reproducing organisms, germ cell development is vital for the faithful transmission of the genome and epigenome across generations. Recent studies have shown that germ cell development is affected by different environmental toxicants, resulting in a decrease in germ cell health and number. Here, we examine and compare the transgenerational impact and mechanisms of two prevalent toxicants, the plastic chemical Bisphenol A and ethanol. Both have well-described impacts on the developing fetus; however, their effects on developing germ cells and subsequent generations are less explored. We analyze the transgenerational effects of both compounds in Caenorhabditis elegans. We hypothesize that exposure disrupts the epigenetic machinery in germ cells, causing changes in histone modifications, fertility defects, and germline dysfunction in a transgenerational manner. First, we show that BPA exposure causes a transgenerational two-fold increase in germline chromatin desilencing with \( p \leq 0.01 \) coupled with a reduction and redistribution of histone H3K9me3 and H3K27me3. We show that the alteration of repressive histone levels is required for the observed transgenerational 43% increase in germline apoptosis with \( p \leq 0.01 \) and 85% increase in embryonic lethality with \( p \leq 0.001 \). An increase in apoptosis suggest possible perturbations in the germline checkpoint machinery. We show that BPA exposure transgenerationally induces untimely single-stranded DNA invasion with \( p \leq 0.001 \), 2.5-fold increase in incorrect crossover formation with \( p \leq 0.001 \), and 67% increase in missgregation of the X chromosome. To understand which checkpoint BPA perturbs to cause the increase in apoptosis, we used mutants of each checkpoint to rescue the effect. This revealed that BPA perturbs the synapsis checkpoint because a \( pch-2 \) mutant decreased BPA induced apoptosis by two-fold with \( p \leq 0.0001 \) but not the DNA damage checkpoint. Similar to that of BPA, ethanol exposure at human-relevant doses also causes transgenerational chromatin desilencing and germline dysfunction, although to a lesser extent than BPA's. This project identified BPA's and ethanol's transgenerational effect on the germline machinery and reproductive health. We hope to further understand how it induces germline dysfunction, carrying important implications for human reproductive health in the context of environmental exposures.
Active bacterial copper-efflux response contributes to environmental toxicity in *Caenorhabditis elegans*

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Environmentally ubiquitous transition metals challenge prokaryotic and eukaryotic species through uncontrolled redox cycling. When these ions are overly abundant, all extant organisms contain largely conserved mechanisms (chelation, sequestration or excretion) to minimize damage and increase chances for survival. However, organismal toxicity is not only dependent on absolute abundance, but also speciation, complexation, and other environmental factors that contribute to overall ion availability. For instance, lower concentrations of copper (Cu) are more toxic to *Caenorhabditis elegans* (*C. elegans*), a free-living nematode, when grown on a diet of dead *Escherichia coli* (*E. coli*), as opposed to *E. coli* that is alive. The cause of this discrepancy goes beyond passive metabolic functions because cadmium (Cd), another transition metal, is equally toxic to *C. elegans* regardless of the bacterial status. From these observations, we hypothesize that an active and specific bacterial response mediates Cu toxicity in higher organisms. To test this hypothesis, we took advantage of the *C. elegans/E. coli* model system to examine bacterial factors that contribute to the environmental toxicity of Cu. Using *E. coli* knockouts with 100%, 50% and 25% of wildtype Cu-efflux capacity, we discovered a significant relationship between this active bacterial response and the severity of metal toxicity in *C. elegans*. Comparing defined Cu-toxicity endpoints in *C. elegans* fed *E. coli* with wildtype Cu-efflux capacity (100%) to those fed *E. coli* with reduced efflux capacity (25 to 50%), we observed 1) reduced lethality from 8.5 days of median survival up to 14.5 days (*p > 0.0001*), 2) a 7.6% (*p=0.0001*) increase in length independent of dauer arrest, 3) a 10-fold (*p=0.0008*) reduction in cumulative risk for egg-laying defects comparable to no-exposure control risk levels, and 4) reduced transcription of a known *C. elegans* metal-response marker. Conversely, overall body burden of the metal in *C. elegans* appeared unaffected by bacterial Cu-efflux capacity and entirely dependent on CuSO₄ supplementation in growth media. Current results support the bacterial Cu-response as an important contributor to the severity of metal toxicity in higher organisms. Ongoing work seeks to better define the *C. elegans* transcriptional activity during these conditional Cu exposures.
Multigenerational effects of perfluorooctane sulfonic acid (PFOS) in *Daphnia magna*

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Perfluorooctane sulfonic acid (PFOS) is a widespread environmental contaminant routinely detected in drinking water and human serum samples across the US. Since PFOS has also been detected in human follicular and amniotic fluids, female germ cells and developing embryos are particularly subject to PFOS exposure. To test the hypothesis that germ cell and early developmental exposure to PFOS produce negative reproductive effects across multiple generations, age-matched, sexually mature *Daphnia magna* were individually exposed to 10μg/L PFOS, 100μg/L PFOS, or standard culture medium for 10 days. These exposure concentrations were designed to produce internal PFOS concentrations relevant to human levels. The exposure period was long enough internal concentrations to stabilize and for at least one cycle of oocyte maturation to be completed. After this time, F1 neonate (<24 hours) offspring were pooled within treatments and twelve offspring per treatment randomly selected and maintained individually in standard culture conditions for 21 days. The third broods of the F1 generation were used to establish the F2 generation. Each generation was monitored daily with counting and removal of live and dead offspring, as well as aborted embryos. PFOS exposure to the P0 generation caused an insignificant decrease in total live offspring produced at 100μg/L. However, using a generalized linear model, the total number of nonviable (i.e. sum of dead neonates and aborted embryos per adult) was significantly increased at 100μg/L PFOS. In the F1 generation, prenatal/neonatal PFOS exposure resulted in a significant increase in nonviable offspring produced at both 10μg/L and 100μg/L. In the F2 generation, the rate of survival to adulthood was decreased in both PFOS treatment groups. These preliminary results suggest that early life exposure to PFOS may negatively impact adult reproductive health.
An Interactive Online Database for Mining Information on Tobacco Products

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Our lab has obtained large amounts of data on flavor chemicals and metals in electronic cigarette fluids and aerosols, the cytotoxicity of these products, and the specific ingredients that cause cytotoxicity using various assays and cell types, including stem cells. In order to manage, search, and work with these data and make them available to others in a useful form, we have developed a searchable online database. The centralized database is being created using Microsoft SQL Server 2017, which is an intelligent relational database management system that runs on the SQL programming language. The SQL Server was chosen since it optimizes the storage of data and ensures security, integrity, and consistency. SQL also gives various ways to present the data analytically, making it convenient for a user to mine and extract useful information. A layout of the database was designed to store data in tabular form with appropriate naming conventions and necessary columns. The master tables are formed by identifying and assembling subjects from experiments and each tabular row is assigned a unique ID. These unique IDs help distinguish subjects across the database and serve as foreign keys to join related tables to retrieve complex information. The database has an interactive web interface that can be leveraged by users worldwide to perform various functions that include searching on keywords (e.g. specific metals and elements, specific flavor chemicals, product names, cell types), visualizing graphs, constructing statistical tables, and navigating to the published papers. Multiple cell types have been used in the cytotoxicity experiments enabling direct comparisons between the responses of stem cells and differentiated cells. The database is scalable and additional information can be added to the database as it becomes available, by conveniently importing and exporting data and modifying the database schema to add new columns and constraints.
Effects in Cell Fate following Exposure to Tobacco Chemicals: A Combinatorial Study

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According to a report by the U.S. Department of Health and Human Services, cigarette smoking is the cause of upwards of 480,000 deaths per year. Additionally, exposure to second-hand smoke results in more than 41,000 deaths annually. While numerous studies demonstrate the adverse effects of tobacco-related products towards health and developing embryos, the ramifications towards embryonic skeletal development remain unclear. Our laboratory has previously shown that in vivo exposure to cigarette smoke caused metabolic bone disease characterized by hypomineralized bones. However, it is not known whether the resulting phenotype can be attributed to an individual chemical or a combination of chemicals that prevent osteogenic differentiation. Following a ToxPI analysis, the 10 likely chemicals to produce the effect were identified as acetaldehyde, benzopyrene, catechol, coumarin, nicotelline, nicotine, NNA, quinoline, NNN, and acrolein. The obtained ID50 values were used to make comparisons between calcium content and cell viability related to a double combination, a triple combination containing acrolein, and total combination exposure using a human embryonic stem cell osteogenesis model. Most notably, the double and triple combination exposures containing the flavoring chemical coumarin showed both a decrease in cell viability and calcium content. However, in the triple combination exposure, the addition of acrolein showed to either rescue calcification or have the same effect as the double combination. Together, these experiments suggest that different combinations of chemicals have additive effects and that others cancelled out the effects of individual chemicals. To further validate this point, a next set of experiments was conducted in which cells were dosed with all 10 chemicals together, at the ID50 concentration as well as three 10-fold dilutions thereof. At the ID50 concentration of the chemicals, the MTT data showed a severely toxic response. As the concentration of those chemicals actually found in tobacco smoke extract is lower than the identified ID50, the additional dilutions were next evaluated. Indeed, the toxic effect lessened considerably with a 10-fold dilution (0.1x ID50) and were almost negligible at the 100-fold dilution (0.01x ID50). However, and more concerningly, the associated calcium data showed that even at the lowest concentrations of chemicals (0.001x ID50) calcification was still affected. These findings let us conclude that it may be difficult to isolate single chemicals as the primary drivers of embryotoxicity and that rather the full combination of chemicals in tobacco smoke may produce the hypomineralization phenotype. Further mechanistic investigation of how tobacco-related products affect signaling pathways that mediate adverse outcome could lead to new treatments to reverse the inhibition in osteogenic differentiation from exposure to tobacco-related products.
Proteomic Analysis of Normal Human Bronchial Epithelial Cells After IQOS Aerosol Exposure

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Background: IQOS devices deliver nicotine and flavor by heating tobacco heatsticks rather than by combustion. There is a need for independent research to understand the potential health consequences of IQOS usage. This study was done to determine the effects of acute IQOS aerosol exposure on the proteome of normal human bronchial epithelial cells (NHBE) and to compare the proteome when using different device cleaning protocols. Methods: IQOS aerosol solutions were generated using two cleanliness conditions, C1 (holder cleaned after every heatstick) and C20 (holder cleaned after 20th heatstick). NHBE cells (nonsmoker) were treated with IQOS aerosol solutions for 24 hours, then proteins were isolated and identified using multidimensional protein identification technology (MudPIT) analysis. Non-statistically significant data were removed, and the remaining data were evaluated using Database for Annotation, Visualization and Integrated Discovery 6.8 (DAVID) and Ingenuity Pathway Analysis (IPA) software. Results: A total of 5237 proteins were detected with a false discovery rate (FDR) controlled at 1% for control, C1, and C20 treated cells. Of these, 439 and 384 proteins were differentially expressed in C1 versus control (C1vC) and C20 versus control (C20vC), respectively. IPA disease and function annotations found 11 common categories in both groups and one additional category in C20vC. DAVID analysis showed five annotation clusters exclusive to C1vC, four to C20vC only, and four clusters common to both groups. IPA analysis identified five pathways for C1vC and three for C20vC that had 2 < z-scores and z-scores< -2 with p < 0.05. The three pathways identified in C20vC (NRF2-mediated Oxidative Stress (z-score = 3.317); Adrenomedullin Signaling (z-score = 2.646); NF-κB Signaling (z-score = 2.236)) were among the five identified in C1vC. These results indicate that relatively brief exposure to IQOS aerosol activates pathways associated with inflammation and oxidative stress and may not be as benign as previously suggested, emphasizing the need for more extensive testing.
Ziram, a Pesticide Associated with Parkinson’s Disease, Increases Neuronal Excitability and Synaptic Vesicle Release through Distinct Cellular Mechanisms

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Exposure to environmental toxins, including the dithiocarbamate fungicide ziram, is linked to an increased risk of Parkinson’s Disease (PD). We hypothesize that molecular targets of ziram could serve as novel entry points into disease associated pathways. Using calcium indicators, we previously observed that ziram increases excitability in aminergic processes at the Drosophila neuromuscular junction (NMJ). We now extend these findings to show that ziram also increases calcium signals at the level of abdominal ganglion aminergic cell-bodies. However, the cells do not exhibit the ziram-triggered calcium response when the processes are severed, indicating that ziram targets distal portions of aminergic processes. Using electrophysiological measurements, we find that ziram affects glutamatergic neurons through two distinct mechanisms. First, it increases vesicle release probability at the NMJ and second it increases excitability of glutamatergic and aminergic cells. It was previously reported that disruption of protein ubiquitination increases vesicle release in mammalian neurons. Since ziram inhibits the first step of this pathway, we tested ubiquitination inhibitors at the NMJ. Pharmacological disruption of this pathway phenocopied ziram and increased vesicle release probability indicating that ziram may act through this pathway. Interestingly, these compounds did not change excitability. To investigate ziram’s excitability targets, we used channel mutants to show that the ether-a-go-go family of potassium channels phenocopies ziram-induced excitability, but does not exhibit increased release probability. Ziram thus increases both vesicle release and excitability via separate molecular mechanisms in multiple cell types. We are currently investigating how either pathway might contribute to idiopathic PD.
Electronic cigarettes (ECs) are often recommended to pregnant women as an alternative to smoking. However, their effects on embryonic and fetal health have not been rigorously assessed. Recently, vaping-associated pulmonary illness (VAPI) has raised awareness regarding possible harm that ECs may cause. ECs expose the user and conceptus to nicotine, flavor chemicals, solvents, metals and reaction products. This project examined the effect of fluid from two popular ECs and pure nicotine on early development using H9 human embryonic stem cells (hESC) taking a “toxicology in a dish” approach. hESC were cultured on Matrigel and maintained in mTeSR Plus medium. To examine the effect of e-liquids on attachment, cells were plated into 1% dilutions of JUUL Virginia Tobacco, JUUL Classic Menthol, Vuse Original and Vuse Menthol e-liquids, allowed to attach for 24 hours, then the number of attached colonies was determined in micrographs of nine fields of view/treatment. Attachment of hESC was inhibited in both JUUL and Vuse treatments. The impact of the e-liquids and nicotine on cell proliferation was also studied. hESCs were plated on 24-well plates, and after a 24-hour attachment period, treated with various concentrations of nicotine or e-liquids. Time-lapse images were collected over 48 hours in a BioStation CT. MTT assays were performed to determine the effects of treatment on mitochondrial reductases. Images were analyzed using CL-Quant to obtain growth rates. Proliferation of cells exposed to e-liquids was not affected in the 0.1% and 0.3% e-liquid treatments, but was impaired in the 1.0% treatments, and cell death was seen in the 3% treatment groups. Cells exposed to the nicotine concentrations in 0.1%-1% e-liquids (0.034-0.160 mg/ml) showed growth rates like the control. Exposure to 1.01-1.83mg/ml nicotine (found in 3% e-liquids) resulted in cell death. The MTT assay results showed that 1% e-liquid impaired mitochondrial reductase for each flavor. Nicotine MTT results showed that lower concentrations stimulated mitochondrial reductase but higher concentrations were toxic. Failure to attach to substrates and reduced proliferation could have detrimental effects during early human development. Based on these data, women should avoid using ECs during early pregnancy when the embryo is most susceptible to toxicants.
Comparison of Flavor Chemicals and Cytotoxicity of Authentic and Counterfeit Refill Fluids Purchased Worldwide

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Electronic cigarettes (ECs) expose consumers to nicotine, flavor chemicals, metals and reaction products that can negatively impact the health of users. The purpose of this study was to examine the flavor chemicals and cytotoxicity of LIQUA electronic cigarette refill fluids that were purchased in the US, Nigeria, England, and China and to determine if users in different countries receive similar exposures. Additionally, counterfeit products were compared to authentic LIQUA products. Flavor chemicals were quantified in 135 LIQUA products by gas chromatography-mass spectrometry. Cytotoxic refill fluids were identified using the MTT assay, and cell dynamics were analyzed using live cell imaging. Total flavor chemical concentration was ≥ 1 mg/ml in 76% of the refill fluids, and ≥ 10 mg/ml in 34% of these. Of 130 flavor chemicals identified, 28 were ≥ 1 mg/ml in at least one sample and 6 of these were ≥ 10 mg/ml. Total number of flavor chemicals in each product ranged from 0 – 50. For specific refill fluid flavor categories, products purchased in different countries were similar in type and concentration of flavor chemicals. However, counterfeit “Menthol” and “Bright Tobacco” products contained twice the concentration of flavor chemicals than their authentic counterparts. Identical authentic products purchased in different countries induced similar cytotoxic responses, and cell growth inhibition patterns in the MTT and live cell imaging assays, respectively. However, the effects of “Bright Tobacco” on cell growth were greater with the counterfeit products. Ethyl maltol, furaneol, and eugenol were identified as flavor chemicals that contributed to the toxicity of refill fluids. Except for counterfeit products, refill fluids purchased in four different countries were similar with respect to flavor chemical composition, concentration, and cytotoxicity. Cytotoxicity could be attributed to specific flavor chemicals that were high in concentration. Some refill fluids have concentrations of flavor chemicals that exceed those in other consumer products and were high enough to produce cytotoxicity. Safety of these products could be improved by regulation of their flavor chemicals.
In order to survive in nature, animals must quickly adapt to and modulate their behavior in response to environmental cues. With a well-characterized nervous system, C. elegans proves to be a robust model to study behavioral plasticity in response to chemical exposures. In normal conditions, C. elegans display an indifference to ethanol. However, previous C. elegans studies have shown that pre-exposure to ethanol results in an increased preference to ethanol later in life (McIntire et. al., 2010). Here, we explore the effects of ethanol exposure in L1 C. elegans larvae on their overall development and behavior toward ethanol as adults. In this study, we expose L1 larvae to 600mM of ethanol for 16 hours, allow them to grow on OP50 bacteria-seeded recovery plates for 36-48 hours, and perform a chemotaxis assay in order to test for ethanol preference. So far, we have demonstrated a proof of concept that C. elegans show preference toward the positive control 3-methyl-1-butanol (3M1B) with a chemotaxis index (CI) of 0.926. Next, we will confirm that C. elegans exposed to ethanol early in life have a higher preference toward ethanol later in life compared to those not pre-exposed to ethanol. In the future, we hope to investigate whether ethanol pre-exposure and later observed ethanol preference in mature C. elegans can be passed on transgenerationally to subsequent generations. Our research hopes to explore whether ethanol preference can be passed down through multiple generations via the germline, which could have great implications for alcohol preference in various other organisms, including humans.
Predicting Cardiotoxicity of Cancer Tyrosine Kinase Inhibitors with Adult Human Primary Cardiomyocytes

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Background: Tyrosine kinase inhibitors (TKIs) provide effective cancer treatments, but they are often associated with cardiotoxicity ranging from heart failure, left ventricular systolic dysfunction and hypertension to arrhythmia. Objectives: In order to enable the development of a new generation of safer TKIs, it is therefore critical to establish novel strategies that can help rank, early in the discovery process, the cardiotoxicity of molecules in this drug class. Methods: Adult human primary cardiomyocytes isolated from ethically consented donor hearts were used to measure contractility transients using an imaging-based platform. Changes in contractility parameters were used to infer both TKI-induced inotropic (sarcomere shortening) and pro-arrhythmia (after contraction, AC) risk. We addressed the clinical relevance of this approach using a panel of 8 FDA-approved TKIs and one experimental TKI. Each TKI was tested separately at multiple concentrations. Using clinical reference data, we have assessed the ability of non-invasive measurement of cardiomyocyte contractility to predict the cardiac safety risk associated with each one of the TKIs. Results: The data demonstrate that isolated adult human primary cardiomyocytes are differentially affected by non-cardiotoxic (Afatinib, Dasatinib, Erlotinib, Gefitinib) and cardiotoxic (AZD7762, Imatinib, Sorafenib, Sunitinib, Vandetanib) TKIs. For example, while AZD7762, Imatinib, Sorafenib, Sunitinib and Vandetanib inhibited sarcomere shortening with IC₅₀ values of 0.8µM, 44µM, 1.2µM, 3.6µM and 4.6µM, respectively, which closely match the therapeutic plasma concentrations (C_max), Afatinib, Dasatinib, Erlotinib and Gefitinib had no effects on this parameter up to concentrations equivalent to 30-fold the C_max at therapeutic dose. Also, AC incidence demonstrates that human cardiomyocytes could identify TKIs associated with pro-arrhythmic risk. Next, we generated a “safety index” (IC₅₀/C_max) to express the cardiotoxicity of these 9 TKIs. We found that TKIs with low cardiac safety indices are associated with cardiotoxicity in patients. Conclusion: Adult human primary cardiomyocytes can provide a useful strategy for the early assessment of cardiac risk associated with anticancer TKIs. Furthermore, this study resulted in the unexpected finding that toxic TKIs can have an acute effect on human cardiomyocyte contractility, irrespective of the effects on the vasculature and chronic cardiac remodelling.
Southern California Chapter of the Society of Toxicology Council

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Dear Council and Fellow Members,

I am honored to serve as President of the Southern California Chapter of the Society of Toxicology (SCCSOT). When accepting the role of President, I designed to support communication objectives that foster strong and meaningful relationships between academics, industry, and pharma. I am not alone in recognizing our part in SCCSOT. President, as noted, the Executive Council is charged to host a successful 2019 Annual SCCSOT Meeting with the theme "Translational Research: an International Perspective." On June 20, the new SCCSOT Executive Council held its annual face-to-face meeting which served as an opportunity to forge new working relationships as well as to re-examine by our best to live up to the standards for professionalism set in our field day by day.

President's Message

2019 SCCSOT Meeting: Emerging Topics in Computational, Drug Discovery, Neuro, and Environmental Toxicology

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- Edible Nanoparticles in the Aging C. elegans Germline

Second Prize ($250): David Herman, UC Irvine
- Seasonal Effects of PM2.5 on the Cardiovascular System in Adult Hyperlipidemic Mice

Third Prize ($100): Rajpat (George) Phanadhron, UC Irvine
- Biophysical Methods for Extracting Information from Soy and Video Imaging

Photographs from the 2019 SCCSOT Annual Meeting Reception

Southern California, Northeast and Mountain West Regional Chapters’ Joint SCCSOT Reception at Ripley’s Believe it or Not in Baltimore, MD

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- The SCCSOT is one of the most active SCT regional chapters, with a nice blend of members from industry and academia.
- Keeping membership at the level of a group effort. Our membership committee works hard to attract new members, but you can help by encouraging your colleagues to join.
- Annual membership dues are FREE! Membership application forms may be downloaded from our website.
- Questions regarding membership can be addressed to jmccollester@johnson.com

Voting for Council is ongoing:

- SCCSOT is currently seeking a Postdoctoral Representative
- Being engaged in your regional chapter council is a brilliant opportunity to network, learn more about SCT, enhance your leadership skills, and serve your chapter.

2019 SCCSOT Meeting: Emerging Topics in Computational, Drug Discovery, Neuro, and Environmental Toxicology

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