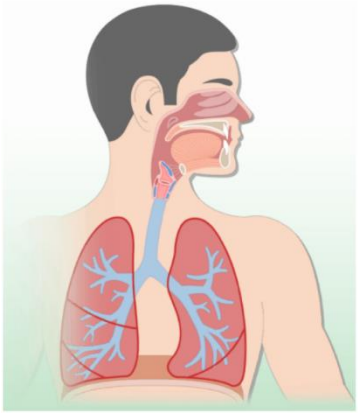
Genetic and Environmental Toxicology Association of Northern California (GETA)

2019 Spring Symposium

Monday, April 22nd, 1-5 PM

California EPA Building, Sierra Hearing Room, 2nd Floor
1001 I Street, Sacramento, CA 95812

Advances in Inhalation Toxicology: Experiment Models and Dosimetric Approaches



Speakers:

- **Dr. Annie Jarabek,** Senior Science Advisor, Office of Research and Development, US EPA, Research Triangle Park, NC. "*Inspiration for Inhalation Risk Assessment Applications: What a Difference the Dose Makes!*"
- **Dr. Laura Van Winkle,** Center for Health and Environment, University of California, Davis CA. "*In Vivo, Ex Vivo and In Vitro Approaches to Lung Toxicology*"
- **Dr. April Si,** Department of Aerospace, Industrial and Mechanical Engineering, California Baptist University, Riverside, CA. "*New Nasal Delivery Systems for Olfactory Targeting: Addressing the Bottleneck Issue of Nose-to-Brain Delivery*"

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Program

12:00 - 1:00	Registration
1:00 - 1:15	Welcome
1:15 - 2:00	**Inspiration for Inhalation Risk Assessment Applications: What a Difference the Dose Makes!**, Annie Jarabek, PhD, DABT
2:00 – 2:45	**In Vivo, Ex Vivo and In Vitro Approaches to Lung Toxicology**, Laura Van Winkle, PhD, DABT
2:45 – 3:45	Coffee Break and Poster Session
3:45 – 4:30	**New Nasal Delivery Systems for Olfactory Targeting: Addressing the Bottleneck Issue of Nose-to-Brain Delivery,** April Si, PhD
4:30 – 5:00	Wrap-up
5:00 – 6:30	No-Host Happy Hour at Pizza Rock (1020 K St, Sacramento, CA 95814)

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Keynote Speaker Abstracts

Inspiration for Inhalation Risk Assessment Applications: What a Difference the Dose Makes!

Dr. Annie Jarabek,
Senior Science Advisor, Office of Research and Development,
US EPA, Research Triangle Park, NC

Biography

Annie M. Jarabek currently serves as the Senior Science Advisor in the immediate office of the National Center for Environmental Assessment (NCEA) at its Research Triangle Park (RTP) Division, within the U.S. Environmental Protection Agency's Office of Research and Development (ORD), following recent service as the Deputy Director of the Human Health Risk Assessment (HHRA) national research program in ORD. Dr. Jarabek has significant experience and training in inhalation toxicology in both laboratory and clinical environments, dosimetry modeling, risk assessment, and decision analysis. She was principal author of the Agency's Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Dr. Jarabek has worked on risk assessments, dosimetry models or analysis methods across all media and routes of exposure. She was the lead for the Agency's risk assessment of ingested perchlorate. Some of her other work addressed several priority, interdisciplinary Agency assessments including inhaled particulate matter, vinyl acetate, manganese, and asbestos. Her current research efforts focus on multi-scale dosimetry modeling, including approaches for *in vitro* to *in vivo* extrapolation (IVIVE) of inhalation exposures to advance the application of emerging methods for translation and evidence integration across various experimental platforms. Dr. Jarabek has received three awards for best manuscript in risk assessment application from the Risk Assessment Specialty Section (RASS) of the Society of Toxicology, along with several best abstract presentation awards. A manuscript on her IVIVE work received an honorable mention as the best 2018 paper from the Biological Modeling Specialty Section (BMSS) at the SOT in Baltimore. She has also received a Lifetime Achievement Award from the University of Massachusetts, the Risk Practitioner of the Year award from the Society of Risk Analysis, the Superfund National Notable Achievement Award, and several award medals (gold, silver and bronze) and technical or special service awards from the Agency.

Abstract

Inhalation is a major route of human exposure to airborne substances. Resultant toxicity may manifest as portal-of-entry effects in the respiratory tract or remote tissue effects subsequent uptake and systemic distribution. Airway architecture and various physiological properties underlie the critical processes of absorption, distribution, metabolism, and elimination (ADME) that dictate the disposition of inhaled materials. These ADME processes integrate with physicochemical properties as determinants of the inhaled dose for a range of inhaled agents including various particles (including nanomaterials and fibers) and different types of gases (e.g., volatile organics versus reactive). To improve dose-response analysis by utilizing internal tissue doses instead of external exposures, address issues of interspecies extrapolation, and to better understand human variability due to age and activities, the US EPA has deployed dosimetry modeling since 1994. This presentation will describe the conceptual basis of the processes and

parameters included in dosimetry modeling approaches and highlight how available data, physicochemical properties, and observed toxicity can be used to guide the choice of appropriate models in a hierarchical strategy from default approaches to more sophisticated mechanistic structures. Efforts to modernize computational approaches will be briefly described with examples of how adverse outcome pathways (AOPs) can be used to describe the mechanisms through which a substance causes toxicity and inform the design and selection of *in silico* and *in vitro* methods to include in integrated approaches to testing and assessment (IATAs). A recently published decision strategy to aid development of novel approach methodologies (NAMs) that utilizes AOP to identify key events of pathogenesis and to organize data on adverse effects coupled with computational dosimetry models to provide quantitative descriptions of the interactions will also be described to reinforce the roles of key anatomical and physiological features, major ADME mechanisms, and physicochemical properties as critical to both informing testing requirements and to mechanistic interpretation and synthesis of results. *(The views expressed in this abstract are those of the author and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency.)*

***In Vivo, Ex Vivo* and *In Vitro* Approaches to Lung Toxicology**

Dr. Laura Van Winkle
Center for Health and Environment,
University of California, Davis CA

Biography

Laura S. Van Winkle, PhD is a Professor of Respiratory Toxicology at UC Davis in the School of Veterinary Medicine, Department of Anatomy, Physiology and Cell Biology and has a research appointment in the UC Davis John Muir Institute - Center for Health and the Environment. She received her PhD in Pharmacology and Toxicology in 1995 at UC Davis and has been a faculty member at UC Davis since 1997. Dr. Van Winkle is active in environmental health research as part of the leadership group of UC Davis' Environmental Health Sciences P30 Core Center at UC Davis and as a member PI of the NIEHS consortium on nanomaterials health effects (NHIR). Dr. Van Winkle has been active in the Society of Toxicology serving the SOT Inhalation and Respiratory specialty section as a Councilor and Secretary and is currently a standing member of the NIH study section Systemic Injury from Environmental Exposures (SIEE) as well as an associate editor of Toxicological Sciences. Her research is in the area of lung toxicopathology with a special focus on exposures that target the distal conducting airways of the lung. She is known for her expertise in lung epithelial injury and repair as well as for her

work on the respiratory toxicology of indoor and outdoor air pollutants. She is on the leadership group of the long running T32 training grant at UC Davis in Comparative Lung Biology and Medicine. She has authored over 90 research publications, 8 book chapters and has been board certified in General Toxicology (DABT) since 2002.

Abstract

While dose and route of administration of toxic agents are important, another key factor in determining susceptibility to toxic agents is the architecture and cell biology of the lung. The lung contains over 40 cell types and they are distributed unevenly throughout the respiratory tract. Further, some cell types, by virtue of their location or their cellular functions, are uniquely susceptible to toxicity. The epithelium of the respiratory system is the primary first point of contact for inhaled chemicals, but epithelial cells populations vary by location within the lung. Toxicity can vary by location within the lung due to region specific delivered dose, cellular susceptibility and resistance factors (including phase I and phase II metabolism) and the differential distribution of susceptible cells. In this presentation, we will summarize approaches to define site and cell specific toxicity in the lung during in vivo, ex vivo and in vitro approaches. Methods for the study of distal conducting airway epithelial toxicity will be emphasized.

New Nasal Delivery Systems for Olfactory Targeting: Addressing the Bottleneck Issue of Nose-to-Brain Delivery

Dr. April Si
Department of Aerospace, Industrial and Mechanical Engineering,
California Baptist University, Riverside, CA

Biography

Dr. Si is the department chair and Associate Professor of Aerospace, Industrial and Mechanical Engineering Department at California Baptist University. She worked as a research associate in Rice University and Assistant professor at Calvin College before joining CBU.

She received her B.S. in Environmental Engineering, M.S. in Chemical engineering, and Ph.D.in Aerospace Engineering from Texas A&M University. She has broad research interests including drug delivery through computational simulations, medical devices, heat transfer enhancement

and single crystalline actuator. She has more than ten years' research experience in inhalation dosimetry and drug delivery. Dr. Si has published more than forty scientific papers.

Abstract

The complex structure of the nasal cavity filters most of the nasally administered aerosols and prevents effective drug delivery to the olfactory region. Different methods were explored to improve drug targeting to the olfactory region. These include pointed drug release, bi-directional intranasal delivery, and aerosols with electric charges. Both *in vitro* experiments and computational modeling were used to quantify the deposition rate to the olfactory region. A Sar-Gel based method was used to visualize the deposition distribution inside the nasal cavity. Both the pointed drug release and bi-directional technique yielded improved deposition in the olfactory region. The vibrating mesh nebulizer was found to be more responsive to the bidirectional breathing and elicited more increase in the olfactory delivery than the jet nebulizer. For both types of nebulizers, reducing the inhalation flow rates increased the nasal dose, but decreased the olfactory dose, which was consistent between *in vitro* measurements and numerical simulations. Aerosols with electric charges can further improve olfactory targeting by applying an appropriate external electric field in the nose. The olfactory deposition was sensitive to the voltage of the electrode close to the nose. For both the normal and bi-directional deliveries, electric field guidance resulted in a significant increase (~3 times) in the olfactory deposition.

Poster Presentation Abstracts

Poster #1

Public Health Advisory Statements for Pesticides Regulated by the Bureau of Cannabis Control

Brittany A. Boerstra, Shelley DuTeaux, Rachel Kubiak, Maxwell Leung and Anna Kalashnikova

Department of Pesticide Regulation, CalEPA, Sacramento, CA

The Department of Pesticide Regulation (DPR) enforces laws that govern the sale and use of pesticides in California, including use on cannabis. Since passage of the 2016 Medicinal and Adult-Use Cannabis Regulation and Safety Act (MAUCRSA), DPR is required to provide recommendations and guidelines on safe pesticide use for cannabis products. As a result, products manufactured from California-grown cannabis are tested for 66 different pesticides. These pesticides are designated as Category 1 or 2 based on their level of toxicity, impacts to groundwater, and their allowed use on food crops. Cannabis products that test positive for Category 1 pesticides are prohibited from being sold to the public while Category 2 pesticides must exist below pre-determined action levels. The public health advisory statements provide information on the human health impact that exposure to specific pesticide residue may have should a failed cannabis product make it into the marketplace. These statements summarize the risks of acute high-level and chronic low-level pesticide exposure that may occur via ingestion, inhalation, or dermal contact with contaminated cannabis products and can help government agencies warn consumers about potential risks.

Poster #2

Gene expression in whole blood of patients with ischemic stroke and cigarette smoking.

Xiyuan Cheng[1,2], Eva Ferino[1], Natasha Shroff[1], Heather Hull[1], Glen C Jickling[1], Bradley P Ander[1], Boryana Stamova[1] and Frank R Sharp[1,2].

[1]Department of Neurology and the M.I.N.D. Institute, [2]Toxicology and Pharmacology Graduate Program, and University of California at Davis, Sacramento, California.

Though previous studies suggested that cigarette smoking-related genes may be linked to ischemic stroke (IS), no specific biomarkers have been identified in whole blood for patients who suffer IS and also smoke. We performed whole genome mRNA expression study on Affymetrix HTA 2.0 microarrays using whole blood from 219 subjects (including 42 IS current smokers, 68 IS never smokers, 23 control smokers, 86 control never smokers). The significantly regulated genes were identified using ANOVA with p-value < 0.01 and fold change>|1.2|. The related functional pathway of identified genes was analyzed using Exploratory Gene Association Networks software. Our data showed 158 genes were significantly altered in IS smokers vs IS never smokers, and 100 genes significantly altered in control smokers vs control never smokers. We also found 10 genes associated with IS smokers were overlapped with non-IS control smokers. Based on 158 genes associated with smoking and IS, the significantly related functional pathways include T cell receptor, cytokine-cytokine receptor, chemokine, and adipocytokine signaling. In summary, we found that the alteration of inflammatory genes may provide direct

evidence for explanation of health hazard of smoking before and/or after IS and significance of smoking cessation, especially for people at high risk of IS.

Poster #3

Sulfuryl fluoride-induced neurotoxicity: potential direct brain access via the intranasal route

Qiaoxiang Dong*, Andrew Rubin, Svetlana Koshlukova, Stephen Rinkus, Carolyn Lewis, Puttappa Dodmane, Shelley DuTeaux, Marylou Verder-Carlos

Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA, USA.

Sulfuryl fluoride is a fumigant registered to control structural and commodity pests such as termites, bedbugs, and the saw-toothed grain beetle. It kills insects by depleting proteins and amino acid stores. As part of our ongoing evaluation of human health risks of fumigants, the California Department of Pesticide Regulation completed a risk assessment of sulfuryl fluoride in 2006 and an update to that risk assessment in 2018. The most current database includes registrant-submitted studies, open literature studies, and a physiologically based pharmacokinetic model. In humans, acute inhalation exposure to high levels of sulfuryl fluoride causes respiratory irritation, pulmonary edema, renal injury, central nervous system depression, brain necrosis, and even death. Short-term or chronic inhalation exposures result in brain, respiratory system, dental, and kidney effects in both humans and laboratory animals. Fluoride is considered the active principal in sulfuryl fluoride-induced toxicity and it is commonly thought to work through either a systemic or portal of entry mode of action (MOA). Common neurotoxic effects in mice, rats, rabbits, and dogs were malacia (necrosis) and vacuole formation in the basal ganglia, also generally considered to have a systemic MOA. However, from our analysis of the updated toxicity database, we suggest that neurotoxicity may instead be mediated via direct entry through the nasal cavity, bypassing the blood-brain barrier. This novel MOA for sulfuryl fluoride neurotoxicity is supported by the following: 1) a fluoride brain-to-plasma (T/P) ratio for acute inhalation studies that is approximately 20-fold higher than T/P ratios from oral, intravenous, or intraperitoneal studies with sodium fluoride (NaF); 2) sulfuryl fluoride-induced brain lesions that are confined to the basal ganglia after inhalation exposure, but not after oral NaF exposure; and, 3) evidence of direct intranasal absorption for other chemicals. In conclusion, future studies should explore the possibility of a direct access to brain via the nasal epithelium, which would influence the calculation of reference concentrations.

Poster #4

Application of ToxCast, ToxPi and Read-across for Analyzing the Potential Carcinogenicity and Mutagenicity of Some Di- and Tri-phenylmethanes

J Hsieh, M Sun, J Chang, MS Sandy

Office of Environmental Health Hazard Assessment, CalEPA

Di-phenylmethanes are commonly used as intermediates in the production of dyes and pigments, and tri-phenylmethanes are often used as food additives or to dye textiles. There are more than a hundred chemicals in this group and most have not been tested for carcinogenicity or

mutagenicity. To supplement the limited carcinogenicity and mutagenicity data for these chemicals, we took two approaches. First, we explored the use of high-throughput toxicity screening data available for chemicals in this group within the ToxCast Database (https://www.epa.gov/chemical-research/toxicity-forecasting), IARC's key characteristics of carcinogens, and Toxicological Prioritization index (ToxPi, http://toxpi.org/), a visual analytics tool, to predict carcinogenicity. Second, we applied a read-across tool, ToxRead (http://www.toxread.eu/index.php), to predict the mutagenicity of the chemicals in this group that had ToxCast data. We identified ToxCast data for 19 chemicals in this group. Six are diphenylmethanes, and all but one are intermediates in the production of dyes. Thirteen are triphenylmethanes, all are dyes, and four are approved as food additives in either the US or the EU. In order to predict carcinogenicity, we aligned the active ToxCast Assays for each chemical to the key characteristics of carcinogens. ToxPi was then used to rank each chemical, based on level of activity in cancer pathway-related assays. **C.I. Basic Red 9** and **Michler's ketone**, two known mutagens and carcinogens, served as positive comparison chemicals for tri- & diphenylmethanes, respectively. The results showed that several of the other chemicals share certain similarities in both ToxPi scores and slice patterns with the two comparison mutagenic carcinogens. In the analyses using ToxRead, which selects chemicals similar to the target compound based on molecular descriptors and structural alerts, and which uses modeling as well as experimental data, 17 of the 19 chemicals were predicted to be mutagenic. Several of the chemicals predicted to be mutagens were also predicted to be carcinogens. Our results suggest that alternative toxicity testing methods, such as high-throughput screening assays similar to ToxCast hold great promise for filling data gaps, and facilitating useful predictions for mutagenicity and carcinogenicity of structurally-related chemicals using read-across.

Poster #5

Assessing Acute Risks to Consumers from Pesticides on CannabisAnna A. Kalashnikova, Svetlana E. Koshlukova, Andrew L. Rubin, Rachel Kubiak, Shelley DuTeaux and Karen Morrison.

Department of Pesticide Regulation, CalEPA, Sacramento, CA

With recreational cannabis legalization in California and several other states, cannabis products have become readily available to the general public. Heightened public concern regarding pesticide contamination in cannabis products have resulted in an extensive testing regime. Cannabis sold in dispensaries should not contain pesticides at levels that might be dangerous to consumers. To reduce public health risks, in 2017 DPR established limits, referred to as action levels, on allowable pesticide residues on cannabis products. Cannabis products, such as foods, drinks, tinctures, cured flowers intended for smoking or cartridges intended for vaporization, cannot reach the marketplace if they contain pesticide residues that exceed these action levels. The main challenge in evaluating the risk from pesticide residues in cannabis stems from lack of residue and consumption data, both of which are necessary to compute exposure. DPR opted for a health-based approach to estimate the action levels of inhalable cannabis products, using guidance residue levels established for tobacco and used health-based approaches to estimate the protectiveness of the action levels.

Poster #6

Phytoplankton and cyanobacteria growth is inhibited by herbicides (fluridone >> glyphosate > imazamox toxicity)

Chelsea Lam[1], Tomofumi Kurobe[1], Peggy Lehman[2], and Swee J. Teh[1]

[1] Aquatic Health Program, Department of Anatomy, Physiology and Cell Biology, University of California, Davis, 1089 Veterinary Medicine Drive Davis, CA 95616
[2] California Department of Water Resources, Division of Environmental Services, Special Studies Section, 3500 Industrial Blvd West Sacramento, CA 95691

Herbicides are applied yearly to control invasive aquatic plants in the Sacramento-San Joaquin Delta. Phytoplankton and cyanobacteria are non-target species that could be sensitive to these chemicals. In this study, 96-well plate growth tests determined whether the herbicides: glyphosate, imazamox and fluridone would inhibit the growth of some of these non-target species, which naturally occur in the Delta. The three phytoplankton and cyanobacteria used were *Thalassiosira pseudonana* (nutrient rich diatom), *Microcystis aeruginosa* (dominant hazardous cyanobacteria), and *Chlamydomonas debaryana* (model green algae species). *M. aeruginosa* and *C. debaryana* were isolated from Delta waters. We found that glyphosate and imazamox inhibited growth of all species at concentrations higher than what would be found in the environment, inhibiting growth between 7,000 ppb to 70,000 ppb, and between 20,000 ppb to 200,000 ppb respectively. However, IC_{50} for fluridone shows it inhibits algal growth at environmentally relevant concentrations. The IC50 of fluridone was 46.9 ppb (95% CI: 40.5 – 53.4 ppb) for *M. aeruginosa*, 21.0 ppb (95% CI: 14.0 – 27.9 ppb) for *T. pseudonana* and 109 ppb (95% CI: 93.4 – 125 ppb) in *C. debaryana*. Sensitivity to fluridone from most to least was *T. pseudonana>M. aeruginosa>C. debaryana*. Additional growth inhibition tests with a variety of native algae species can help identify contaminants and contaminant levels that will negatively impact beneficial or harmful species present in the Delta. Of the three herbicides tested, fluridone was the only chemical that inhibited algal growth at concentrations that could potentially be applied in the environment. Fluridone treatments can decrease pelagic primary productivity in the Delta, although further experiments with field water are needed.

Poster #7

Air Quality: An interface between environment, climate change and public health

Savannah Mack, Keith Bein, Qi Zhang, Kent Pinkerton

Molecular, Cellular & Integrative Physiology, Center for Health and the Environment, University of California, Davis

RATIONALE: In recent years, Imperial County has consistently ranked as the top California County with the highest asthma rate in children. Community members are concerned their breathing problems are due to one or more of many sources of pollution that contaminate Imperial Valley (IV). Of particular interest is the potential toxicity of particles rising from the crusted lakebed of the Salton Sea. With polluted runoff as the only water source, the Salton Sea has become increasingly polluted and is rapidly shrinking. **PURPOSE:** No one has differentiated the sources of particulate matter (PM) in IV or their connection to asthmatic symptoms. Our goal is to investigate the differences between, and potential harmfulness of airborne particles to which

IV residents are exposed. **METHODS:** A state-of-the-art mobile sampling unit has been designed to collect (PM) particles of various size fractions, from ultrafine (<0.10 μm) to PM10. The geography and meteorological conditions in IV expose the community to a unique combination of natural and man-made pollutants. These sources include agriculture, industrial plants, and large cities across the border of Mexico, as well as the Salton Sea. In order to account for seasonal changes and source variation, our sampler collects particles from different wind directions over the course of an entire year. Each PM sample is chemically characterized and screened in an *in vitro* system to before moving into an *in vivo* model of asthma. Due to the high incidence of asthma in youth in IV, we are specifically interested in how this PM may modulate sensitization of the immune system to house dust mite (HDM) allergen, and in turn, how this impacts subsequent encounters with allergen (challenge). **RESULTS:** Our initial chemical characterization indicates organic species dominate IV particles (58%) followed by ammonium sulfate (37%). The chemical composition of the organic nanoparticles (ONP) from IV is highly complex and likely composed of hundreds of carbon-containing compounds. An *in vitro* screening in a human macrophage cell line demonstrates a significant increase in gene expression of COX-2, CYP1a1, IL-8 and IL-1B cytokines, as well as a similarity between IV PM and other agricultural regions in California. **CONCLUSION:** The high average degree of oxidation and the high organic nitrogen contents suggest that nanoparticles in IV are likely toxic and could a major culprit for the health problems in the region. The increase of inflammatory cytokines when exposed to IV PM *in vitro* suggests the need for further testing in a murine model of asthma.

Poster #8

Effects of Neonatal Inhalation Exposure to Ultrafine Carbon Particles and Diesel Particulate on Pathology and Behavioral Outcomes in C57Bl/6J

K. Morris-Schaffer[1,2], A. Merrill[2], M. Sobolewski[2], and D. Cory-Slechta[2]

[1]Exponent, Sacramento, CA, [2]University of Rochester Medical Center, Rochester, NY.

Epidemiological studies show that early-life exposure to anthropogenic fine particulate matter is associated with adverse neurodevelopmental outcomes in children. Complementary studies using rodent models have shown that developmental exposure to ambient nanoscale particulate matter can lead to sex-specific neuropathology and protracted learning deficits. However, it is still unclear about the direct sources and particulate matter constituents that contribute to these deleterious outcomes. To better evaluate potential particulate matter contributors to developmental neurotoxicity, two studies were conducted to assess the effects of pure ultrafine carbon particles (UFCP: median aerodynamic diameter: <40 nm) and nanoscale diesel particles (median aerodynamic diameter: <100 nm) on brain pathology and behavior in C57Bl/6J mice. The UFCP aerosol was generated from a spark-discharge setup and the diesel particles were generated from ultrasonic nebulization of dissolved National Institute of Standards and Technology Standard Reference Material 1650b (SRM 1650b). Separate inhalation exposure of each material with neonatal mice occurred on postnatal days 4-7 and 10-13 for 4hr/day, 4 days/week at a mass concentration of 50 $\mu g/m^3$ for UFCP and 100 $\mu g/m^3$ for SRM 1650b. Assessments of neuropathology 24 hours following exposure showed no gross inflammation or injury following pure ultrafine carbon exposure, while SRM 1650b exposure did increase glial

fibrillary acidic protein (GFAP) immunodensity in the corpus callosum and cortex, suggestive of inflammation. To assess learning deficits, behavior on a fixed-interval schedule of reinforcement, a paradigm that involves temporal learning and is historically effective at detecting the protracted effects of low-dose neurotoxicants such as lead, was investigated in adulthood. No significant treatment-related learning differences were found in either the UFCP or SRM 1650b exposed adult mice. The lack of extended effects from the developmental exposures, even at relatively high mass concentrations, suggests neither ultrafine elemental carbon nor diesel particle exposure alone are sufficient contributors to adverse developmental neurotoxicity. Further research on more reactive constituents of particulate matter, including volatile organic species, reactive metals, and gases, needs to be done to better clarify specific toxic contributors.

Poster #9

Hazard Identification for the Herbicide Propyzamide Silva, M.H., Koshlukova, S., Rubin, A., Lohstroh, P., Kalashnikova, A., Kwok, E., DuTeaux, S., and Verder-Carlos, M.

Department of Pesticide Regulation, California Environmental Protection Agency, Sacramento, CA, USA.

Propyzamide is an amide herbicide used primarily on lettuce in California. Plant cell division is halted by inhibiting microtubule polymerization during metaphase. Acute exposure to rodents affects motor activity, while repeated exposure interferes with the hypothalamic-pituitary-thyroid/gonadal axes (HPT/HPG). We evaluated registrant-submitted studies and peer-reviewed articles to compile a toxicology profile, identify target organs and establish dose-response relationships. Rodent data were used to characterize the risk of propyzamide exposure to human health by deriving critical points of departure (POD) for non-oncogenic effects. The critical acute POD was based on decreased motor activity in males and increased landing foot-splay in females on day-1 post-treatment in a rat neurotoxicity study. Because these effects occurred at all doses, a default factor of 10 was applied to the low dose (40 mg/kg/day) to generate an estimated POD of 4 mg/kg/day. A critical subchronic POD of 0.3 mg/kg/day was estimated based on decreased thyroxine (T_4) levels at the lowest-observed-effect-level (LOEL) of 3 mg/kg/day in a 15-week study in adult rats. This value was also used as the critical chronic POD since it was shown that early subchronic liver enzyme induction (p450) and endocrine effects on the target tissues (decreased T_4 and testosterone) lead to downstream effects such as tumors in liver, thyroid and testes in rodents. A non-genotoxic mode of action (MOA) for these tumors involves hepatocytic proliferation, enzyme induction and subsequent disruption of the HPT/HPG axes. However, propyzamide is carcinogenic only at doses 142-233-fold higher than the chronic POD of 0.3 mg/kg/day. The MOA for tumorigenesis in rodents is not considered relevant to humans due to quantitative differences in pharmacokinetics/pharmacodynamics. In rodent developmental/reproductive studies, effects were detected only at doses causing maternal toxicity. However, critical hormones were not measured in these pre-and/or postnatal exposures. One exception was a study in pubertal male rats treated on postnatal days 23-53 where decreased T_4 levels occurred at 10 mg/kg/day. Because the LOEL for T_4 decrements in adult rats was lower (3 mg/kg/day), concerns remain about *in utero* T_4 deficiencies affecting development. These concerns will be addressed in a comprehensive propyzamide human health risk assessment in California.

Poster #10

Exhaled Aerosol Fingerprinting for Early Detection of Respiratory Obstructive Diseases and Lung Cancer

Jinxiang Xi[1] and Xiuhua Si[2]

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Background: Accurate and early diagnosis of lung cancer is crucial to patient survivability. For instance, patients with non-small cell lung cancer have a cure rate of more than 70% when diagnosed at Stage I whereas less than 25% if diagnosed at Stage III. Conventional methods to diagnose lung diseases or cancers include pulmonary function tests using spirometer, chest X-ray for screening, CT/PET/SPET to examine abnormal structures, and sputum cytology or lung tissue biopsy to evaluate the type and extent of the lesion. These diagnostic techniques are generally reliable, but at the same time they are costly, time-consuming, and need professional operations. Some are invasive (biopsy) and pose radiation risks on patients (CT/PET/SPET). In recent years, a new type of lung diagnosis device that uses the exhaled breath is being developed. It has long been known that breath contains clues to many diseases. Metabolic changes of growing cancer cells cause changes in the production of certain chemicals and generate a unique breath '*fingerprint*', which can be used to determine whether a disease is present. Because breath tests provide a simple and noninvasive alternative to traditional testing, substantial research has been devoted to the analysis and identification of breath biomarkers. One critical limitation of the gas-signature based approaches is that they only measure the presence and concentration of exhaled gas chemicals. They cannot provide any information about the location where these chemicals are produced (i.e., the carcinogens site) or the level of the airway remodeling, both of which are critical in cancer treatment planning. Currently, this information can only be obtained with the help of radiological techniques such as CT or PET, which are accurate, but are also costly and have additional health risks. **Innovation:** We developed a new strategy that can detect subtle lesions in deep lungs using exhaled aerosol biomarkers. This method is also promising in identifying the locations of these lesions, thereby provide crucial information for targeted drug delivery. The method is based on the fact that each airway structure has a unique pattern of exhaled aerosols, and any deviation from the normal pattern may indicate an abnormality inside the lungs. The challenges are that these lesions are usually located in small airways, whose signals can be too weak to be detected in exhaled aerosol images due to the complex respiratory network and associated signal attenuation along its way to the mouth. It is not clear how much original information can be preserved in the exhaled AFPs, or how sensitive the exhaled AFPs are to lung abnormalities. The key issue is how to recover the lung structure information by decoding the exhaled AFPs in order to precisely detect and localize the underlying diseases. In our preliminary data, we have provided proofs to this concept in an idealized and an anatomically accurate lung model. **Significance:** The proposed concept of aerosol-fingerprint (AFP) based breath testing has two characteristics that are highly advantageous in the diagnosis and treatment of lung diseases: (1) detect and **locate the site of the disease**, and (2) achieve **precise, targeted drug delivery to the diseased site**. If proved feasible, a combined diagnosis-delivery device will be developed based on the outcomes of this proposed research. The device will be **non-invasive,** give **real-time diagnosis feedback,** be capable of **precise drug delivery** and at the same time, it will be **easy-to-use** and **low-cost** for lung disease patients. The vision is that the patient takes a breath test for diagnosis purpose, and

a patient-specific drug delivery protocol can be subsequently developed that target therapeutic aerosols at the diseased site only, thereby optimizing the medical outcome and minimizing side effects. The proposed AFP-based breath testing works best for abnormalities where the airway remodeling is not small, and therefore is suitable for diagnosis and treatment of diseases such as asthma, COPD, and non-small-cell lung cancer. This new breath test is particularly suitable for the screening of respiratory diseases for those with a high level of occupational exposures such as coal mine workers. Considering its advantages of being low-cost and easy-to-use, the coal mine workers can conduct the test more frequently to reduce the risk of respiratory diseases. Regular tests will develop a record of the patient's lung health condition. Disease localization with selective aerosol release approach will help to pinpoint the disease site and develop a patient-specific treatment protocol such as targeted pulmonary drug delivery.

Building Logistics

The CalEPA building (1001 "I" Street, Sacramento, CA 95814) entrance is at 10th and I streets. For more information, go to: https://calepa.ca.gov/headquarters-sacramento/location/

Check-in and obtain a badge from security in the main lobby of the building. The Sierra Hearing Room is on the second floor and is accessible via stairs or elevator.

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