34th Annual Virtual Meeting of the Allegheny-Erie Society of Toxicology Regional Chapter

October 13th, 16th and 19th 2020

Toxicology in the Real World

Session 1: October 13th (Starts at 1:00 PM EST)

1:00 Welcome Message and Announcements.

1:05 Speaker Introduction and Overview by Session Moderator.

1:10 **Keynote Speaker: Dr. Kent E Pinkerton, University of California, Davis; "Health Effects of Exposure to Particulate Matter: A Community, Student and Laboratory-Based Study."**

2:00 Rapid Fire Session (5 Min each, Q & A at the end of session)

Sarah Reppert, Lexy Mears, Kallie Schafner, Gul Mehnaz Mustafa, Boyce Gregory.

2:40 Young Investigator Presentation. "Maternal exposure to engineered nanomaterial during gestation diminishes fertility in F1 females", Elizabeth Bowdridge.

2:50 "Advancements in Inhalation and Exposure Research" by UV Shemesh, DSI Inc.

3:10 Undergraduate Student Award Announcement.

RJ Lee Inc Postdoctoral Researcher Award Announcement.

Moderator: Prof. Dr. Timothy R Nurkiewicz, Director, Center for Inhalation Toxicology, School of Medicine, West Virginia University.

Session 2: October 16th (Starts at 9:00 AM EST)

9:00 Speaker Introduction and Overview by Session Moderator.

9:05 **Keynote Speaker: Dr. Olivier Jolliet, University of Michigan, Ann Arbor; "High Throughput Risk and Impact Screening of Chemicals in Consumer Products."**

10:00 Rapid Fire Session (5 Min each, Q & A at the end of session)

Nicole Prince, Emily Burrage, Eiman Aboaziza, Heng Bai, Caroline Gillie, Todd Stueckle.

10:40 Young Investigator Presentation. “Cytotoxicity of Peracetic Acid Vapor Exposures on Human Bronchial Epithelial cells”, Nicole Olgun.

10:50 “Advancement in Electronic Cigarettes Research” by UV Shemesh, DSI Inc

11:10 PPG Industries Inc Graduate Student Award Announcement.

Moderator: Dr. Marisa Kreider, Principal Science Advisor, Cardno Chemrisk Inc.

Session 3: October 19th (Starts at 9:00 AM EST)

9:00 Speaker Introduction and Overview by Session Moderator.

9:05 **Keynote Speaker: Dr. Aleksandr Stefaniak, CDC-NIOSH, Morgantown.; “When Additive Manufacturing and Toxicology Cross Paths: Challenges and Opportunities.”**

10:00 Rapid Fire Session (5 Min each, Q & A at the end of session)

Mariana Farcas, Julie Griffith, Krista Garner, Nairrita Majumder, Janet Thompson, Todd Stueckle.

10:40 Young Investigator Presentation. “Telomeres in Toxicology: Occupational Health”, Mohammad Shoeb.

10:50 “Advancement in Whole-Body Plethysmography Systems” by UV Shemesh, DSI Inc.

11:10 PPG Industries, Inc Graduate Student Award Announcement.

RJ Lee Inc Young Investigator Award Announcement (3 sessions)

Moderator: Dr. Yong Qian, Senior Scientist, Health Effects Laboratory Division, NIOSH.

SOT | Society of Toxicology

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MEETING REGISTRATION

The 2020 AE-SOT Virtual Annual Meeting is Free but requires registration. You need to register for the three sessions separately. Registration confirmation and link to each session will be sent via email.

Links to Registration

Session 1:

https://aim-hq.webex.com/aim-hq/onstage/g.php?MTID=eaea660ab02b61fdcde4db7bea371249d

Session 2:

https://aim-hq.webex.com/aim-hq/onstage/g.php?MTID=ec071f48739fbbb9c3298c54832110d43

Session 3

https://aim-hq.webex.com/aim-hq/onstage/g.php?MTID=e2ed383b7ec1a46a74920a625b131c8a8

If you have any challenges or issues, you can reach out to Vamsi Kodali (ywu0@cdc.gov) or Ashley Black (ashley@toxicology.org) for help.

The Mentor-Mentee Matching Program

The Mentor-Mentee matching program is an effective way to provide professional guidance so that mentees can successfully navigate the career maze. It is a symbiotic relationship and helps mentors give back and expand their expertise.

Mentors and Mentees can sign up for this program by emailing the program coordinator William Mandler, Ph.D., (oex1@cdc.gov)

In order to effectively match mentee with a potential mentor, mentees must provide in their email

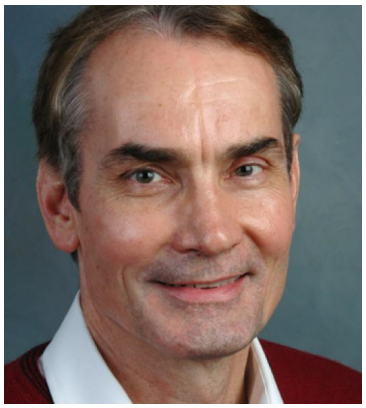
- Specific guidance that they are looking forward to, i.e. Job Document Review, Research Guidance, Career Outlook and Advice, Professional Development and Guidance etc.

- Are you looking forward to an Academic, Industry, Consulting or a Government Mentor?

  Based on availability although we cannot promise an exact match to your specific criteria, we will try to match you with a high-quality mentor close to your requested criteria.

Session 1

Dr. Kent Pinkerton.



Kent Pinkerton, MD, is professor of pediatrics, School of Medicine, and director of the Center for Health and the Environment at the University of California, Davis. His research focuses on the health effects of inhaled environmental air pollutants to alter respiratory, cardiovascular, and neurological structure and function. Special areas of interest include the interaction of gases and airborne particles to produce cellular and structural changes within site-specific regions and cells of the respiratory tract in both acute and chronic timeframes of exposure. Recent studies have focused on environmental and biological impacts of synthesized nanomaterials as well as the effects of environmental tobacco smoke and combustion particles on lung growth and development. He is associate director for the San Joaquin Aerosol Health Effects Research Center (SAHERC) to study airborne particles of the San Joaquin Valley. He is also the associate director for the Western Center for Agricultural Health and Safety (WCAHS) to study the health effects of airborne particles in an agricultural setting.

Keynote Presentation

Health Effects of Exposure to Particulate Matter: A Community, Student and Laboratory-Based Study.

Imperial Valley, located in Southern California next to the border with Mexico, experiences one of the highest rates of juvenile asthma in the state of California. Particulate matter (PM) in Imperial Valley comes from a variety of sources including, but not limited to agriculture, feedlots, vehicles at the border crossing, the megacity of Mexicali, and the dry lakebed of the evaporating Salton Sea. Residents in Imperial Valley have access to 24-hour air quality data from 50 different monitors that give real-time levels of PM2.5 and PM10 and recommendations on healthy practices, dependent on the current AQI (air quality index). However, no information is available on particle source or chemical composition. Working with the local community and high school students, studies were conducted to collect, characterize and examine the biological effects of PM of various size fractions in human immortalized cells and a mouse model of asthma. Students were involved in the collection of particles from a field station based at their school and spent one week at UC Davis to experience college life and to perform laboratory experiments on the particles they assisted in collecting. Such studies are increasingly more important to promote science and greater public health awareness.

Session 2

Dr. Olivier Jolliet.

Dr Olivier Jolliet is Professor in life cycle impact and risk modeling at the Department of Environmental Health Sciences in the School of Public Health, University of Michigan. His teaching and research aim to a) compare the life cycle human health risks and benefits of chemicals in consumer products and foods, and b) model population exposure, intake fractions and pharmacokinetics of chemicals at global level. He pioneered the incorporation of near-field exposure to consumer products, defining the product intake fraction as an adequate metrics to assess exposures, using large data bases for chemical screening in Alternatives Assessment, Life Cycle Assessment and Risk Assessment. He co-initiated the UN Life Cycle Initiative and is one of the lead authors of the UN Environment Global Chemical Outlook.

Keynote Presentation

High Throughput Risk and Impact Screening of Chemicals in Consumer Products.

The ubiquitous presence of 30,000 to 80,000 chemicals in thousands of consumer products used on a daily basis stresses the need for screening a broader set of chemicals than the traditional well-studied suspect chemicals. This study presents new High Throughput Screening method to assess exposure to chemicals in consumer products for both product users and the general population. It then compares exposure with toxicity data to assess risks and impacts of for 1000 chemicals in hundreds of personal care, cleaning, home maintenance products and toys, looking at potential impacts expressed in minutes of healthy life lost per person and per day.

Risks can be substantial for multiple home maintenance products, such as paints or paint strippers, for some home-applied pesticides, leave-on personal care products, and cleaning products. 57% of the chemical-product combinations have hazard quotients exceeding 1 (up to 10,000) and 8% of the combinations have lifetime cancer risks exceeding 10E-4 (up to 10E-2). Population-level impacts of household products ingredients can be substantial, representing 5 to 500 minutes of healthy life lost per day.

This screening study calls for more scrutiny, advancing the exposure and toxicity assessment of most impacting chemical-product combinations, fully ensuring from a regulatory perspective consumer product safety for high-end users, and using protective or exposure reduction measures for product users.

Session 3

Dr. Aleksandr Stefaniak.

Aleks Stefaniak is a Research Industrial Hygienist in the Respiratory Health Division at NIOSH. He conducts research on lung diseases related to inhalation of particulate. His current focus is emissions from various additive manufacturing processes with attention to asthmagenic compounds. He also supports the translation of additive manufacturing workplace exposure assessment data to the design of collaborative *in vitro* and *in vivo* toxicology studies with NIOSH colleagues.

Keynote Presentation

When Additive Manufacturing and Toxicology Cross Paths: Challenges and Opportunities

Additive manufacturing (AM) is an umbrella term that refers to various processes used to build objects from a computer file, often using layer-by-layer methodologies. AM has existed since the 1980s, though with the expiration of several key patents on technologies in the 1990s and the spawning of digital open-source initiatives in the 2000s, referred to as “democratization” of the technology, the prices of AM machines has decreased dramatically, making them available to the public. This rapid expansion in availability has gained the attention of the environmental, health, and safety community as some AM processes such as material extrusion 3-dimensional printers have become common fixtures in manufacturing environments as well as non-industrial settings such as small businesses, schools, libraries, and homes. AM has many potential benefits (reduced waste, decreased energy consumption, shorter lead-times, etc.) relative to traditional subtractive and formative manufacturing methods; however, there is little understanding of the health and safety implications from use of these processes. The purposes of this presentation are: 1) introduce toxicologist to the seven basic AM process categories, 2) provide an overview of challenges to evaluating the toxicity of AM process emissions and printed parts, and 3) explore opportunities to use AM as a tool for enabling toxicology experimentation.

ACUTE EFFECTS OF ELECTRONIC CIGARETTE AEROSOL ON CEREBRAL PERFUSION IN MICE.

SA Reppert, MS Smith, M Alvi, PD Chantler, and IM Olfert

West Virginia University School of Medicine, Center for Inhalation Toxicology, and West Virginia Clinical and Translational Science Institute, Morgantown, WV 26505.

Electronic cigarettes (E-cig) have become exceedingly popular with the campaigning notion of being more safe than tobacco cigarettes. However, it remains uncertain whether or not these products are less harmful than tobacco cigarettes.

We analyzed the cerebral perfusion flux (CPF) using a Moor Full-Field Laser Perfusion Imager (FLPI)-2 in wild-type C57BL/6 mice by collecting one image every minute for up to 2 hours after exposure. Mice were anesthetized with Isoflurane (5% induction/ 2-3% maintenance). Five baseline (pre-exposure) images were taken prior to exposure to either, French Vanilla flavored E-liquid with 18 mg/ml nicotine (E-cig18, n=4) or without nicotine (E-cig0, n=3), Univ. of Kentucky-reference tobacco cigarette (3R4F, n=2), or ambient air (Sham, n=4). Exposures were for ~5 minutes (total of 10 puffs, with 1 puff every 30 secs). Separate Harvard Apparatus Dual Phase Control Respirator Pumps were used to administer the E-cig aerosol (from 3rd generation tank-style device set at 17.5 W) and cigarette smoke (from one 3R4F cigarette). Baseline images obtained prior to E-cig exposure were averaged and used for comparison to post-vaping values (repeated measures ANOVA).

A rapid increase in whole-brain CPF was observed in E-cig0, E-cig18, and 3R4F immediately after vaping, showing peak responses of 13±9%, 12±1%, 9±7%, respectively (mean % change±SEM). CPF returned to baseline at 34 min, 16 min and 16 min in E-cig0, E-cig18, and 3R4F, respectively. There was no significant change in CPF in the Sham group (0 ± 2%) during the same time period as reported for the other exposure groups.

The immediate increase in CPF was similar between E-cig (with or without nicotine) and tobacco cigarette, indicating that the cerebral vascular response to vaping is similar to smoking. These data suggest that the cerebral vasculature may not be able to differentiate between E-cig aerosol and cigarette smoke, and therefore is likely to lead to the same cerebral pathologies known to occur with smoking.

THE BETA-CATENIN-INDUCED EXPRESSION OF ITGA7 AND ITGAV DURING LIVER REGENERATION AFTER PARTIAL HEPATECTOMY IN MICE.

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[3] *Department of Medicine, University of Pittsburgh, Pittsburgh, PA*

The liver has an intrinsic regenerative capacity and this unique characteristic is the science behind living donor liver transplantations. Partial hepatectomy (PH) has been widely used to study liver regeneration. Both Wnt/β-catenin pathway and Osteopontin, which is also a Wnt-target gene, play a role in liver regeneration following partial hepatectomy. Furthermore, interaction with integrins such as integrin alpha 7 (ITGA7) and integrin alpha V (ITGAV) is one of the mechanisms through which osteopontin mediates its biological functions which includes proliferation and regeneration. Preliminary data from our laboratory suggested that osteopontin plays a role in β-catenin induced liver regeneration at 40 hours after PH.

The objective of this study is to determine whether ITGA7 and ITGAV expression is induced by β-catenin during liver regeneration after PH. Liver samples from transgenic mice overexpressing β-catenin (TG mice), wild type (WT) control mice, and β-catenin knock out (KO) mice were used in this study at various time intervals, 6 hours (on day 0) and 40 hours after PH. ITGA7 and ITGAV protein expression were assessed on theses slides by immunohistochemistry techniques. Stained slides were imaged using brightfield microscopy to demonstrate the expression of ITGA7 and ITGAV. Images were analyzed using Nikon Element Analysis software. Our result showed that there is no significant difference in liver ITGA7 protein expression between TG mice and WT control at both 6 hours and 40 hours after PH. There is also no significant difference in ITGA7 protein expression between the WT control and the β-catenin KO mice after PH. However, ITGAV expression is significantly increased in the in TG compared to WT mice for both timepoints. Similarly, ITGAV protein expression is significantly increased in WT control compared to KO mice after PH. These findings suggest that ITGAV and not ITGA7 may be important in β-catenin-induced liver regeneration after PH in mice. Finally, exploring other integrins and ITGAV associated pathways will contribute significantly to the field of liver transplantation and regenerative medicine.

Key words: Partial hepatectomy; β-catenin; ITGA7; ITGAV; Regeneration

Funding: Start up grant from College of Health, Engineering and Science (CHES)

VAPING INHALATION CONSEQUENCES ON PLACENTAL AND PUP WEIGHT TO DETERMINE THE HEALTH EFFECTS OF EXPOSURE IN MATERNAL GESTATION.

KJ Schafner, EC Bowdridge, TR Nurkiewicz

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With the increase in popularity of electronic cigarette (e-cig) use, especially the JUUL, there has been a corresponding increase of use during pregnancy. This increase is associated with the marketing strategy that e-cigs are safer than regular cigarettes. While advertisements for e-cigs promote them as healthier than regular cigarettes, research has shown that e-cigs still carry significant health risks. Therefore, there is a critical need to understand the effects of vaping during pregnancy. The aim of this research was to demonstrate the health consequences of vaping during gestation on placental and pup weight. Dams were exposed 6 times between gestational day (GD) 10-19 through a chamber resulting in $1.54x10^{10}$ cumulative deposited particle burden in the lungs. One puff was released every 120 s for a total of 30 puffs to the dams. The vape juice contained 30% propylene glycol/60% vegetable glycerin. The mean chamber concentration was $3.49x10^{6}$ #/cc with a count median diameter of 3.49 nm per particle. Dams were sacrificed 24 hours after the last exposure on GD 20. Average pup weight was lower in JUUL exposed dams (3.61±0.11 g; n=5 litters; n=44 pups) compared to sham-air control group (5.72±0.10 g; n=11 litters; n=81 pups). Placental weight was not different between the JUUL exposed dams and control group (0.72±0.02 g and 0.87±0.03 g, respectively). Placental efficiency was lower in the exposed than the control group (5.11±0.16 vs. 7.10±0.26 respectively). There was also an average increase in reabsorption sites within the JUUL exposed dams compared to the control (1.33±0.33 and 0.67±0.67 respectively). At this time, we conclude that the use of e-cigs during pregnancy has adverse maternal and fetal health effects that may contribute to the developmental origins of health and disease.

Support: ES015022 (TRN)

SPATIALLY-DEPENDENT CYTOKINE PROFILES IN RESPONSE TO CHRONIC *STAPHYLOCOCCUS AUREUS* INFECTION.

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Chronic joint infections are an unfortunate complication following total knee arthroplasty procedures and are often difficult to treat by standard antibiotic therapies. Management requires a complex strategy of multiple surgical interventions, imposing high emotional and economic burdens on patients. Debridement decisions are complicated, as it is difficult to distinguish inflammation caused by implants from inflammation due to presence of infection, and incomplete removal of infected tissue leads to infection recurrence. Currently, there are no objective measures to assess infected tissue vs. healthy tissue in these scenarios, and surgeons must rely solely on subjective criteria. Several cytokines have been noted for their diagnostic utility through measurements in plasma or serum, but none have been investigated for their ability to serve as intra-operative debridement markers to distinguish infected tissue from healthy tissue. This study defined the spatial gradients of these cytokines in a rodent model of chronic joint infection with *Staphylococcus aureus,* the most commonly implicated pathogen, to understand the disparate tissue profiles associated with inflammation due to implants vs. inflammation due to chronic infection. Two-way ANOVA comparisons revealed that eight cytokines had higher concentrations due to presence of foreign body implant alone ($p<0.05$), and three cytokines showed infection-specific increases in concentration at a statistically significant level ($p<0.05$). Comparison of the joint tissues to proximal and distal sites revealed that ten cytokines showed spatially-dependent profiles dependent on proximity to the joint ($p<0.05$), highlighting the importance of these spatial gradients in the response to infection. The infection-specific cytokines may hold potential as quantitative, intra-operative debridement markers, paving the way for improved strategies for the surgical management of chronic *S. aureus* joint infection.

(NIH K08 AR073921)

CEREBROVASCULAR IMPAIRMENT DUE TO MATERNAL ELECTRONIC CIGARETTE USAGE DURING PREGNANCY IS NOT DOSE DEPENDENT.

EN Burrage[1], E Aboaziza,[1,2], SA Reppert[3], J O'Reilly[3], PD Chantler[1,2,4], and IM Olfert[2,3,4]

West Virginia University School of Medicine, Division of Neuroscience[1], West Virginia Clinical and Translational Science Institute[2], Center of Inhalation Toxicology[3], Division of Exercise Physiology[4], Morgantown, WV

Developmental harm to offspring from maternal exposure to electronic cigarettes (Ecig) during pregnancy is still poorly understood. Similar to cigarettes, we hypothesized the even low-level Ecig exposure would produce similar evidence of cerebral vascular dysfunction compared to a higher exposure dose.

We examined the effects of maternal E-cig exposure (Joyetech eGrip OLED using 5-sec puffs @17.5 W) on cerebrovascular function in offspring (n=2-4 from each dam) from Sprague-Dawley rat dams exposed to air (Control), Ecig with 18 mg/ml nicotine (Ecig18) and without nicotine (Ecig0). Dams were exposed to low (20 puffs) or high (60 puffs) dose for 1-hour each day, 5 days/week, starting on gestational day 2 and continued until pups were weaned. Pups themselves we never directly exposed to Ecig aerosol. Middle cerebral arteries (MCA) were obtained from pups at 3-months of age, isolated and positioned in a pressurized myobath, and exposed to increasing concentrations of acetylcholine (ACh), serotonin (5-HT), and sodium nitroprusside (SNP).

At the lower dose, MCA dilation to ACh was impaired by 60±1% and 50±0.1% in Ecig0 and Ecig18 groups, respectively, compared to controls ($p<0.05$). At the higher dose, MCA dilation to ACh was similarly impaired by 63±1% and 60±0.2% in Ecig0 and Ecig18 groups, respectively ($p<0.05$). At both low and high doses, the response to 5-HT and SNP were similar across all groups.

These data show that maternal Ecig usage results in similar cerebrovasculature impairment with either 20 or 60 puffs/day during pregnancy and lactation in adolescent offspring with prior *in utero* exposure from maternal vaping at suggesting that even low-levels of maternal Ecig use confers significant post-natal vascular health risks for the offspring.

Support: WVU Cancer Institute Philip R Dino Innovative Research Grant (IMO); NIHGMS 5U54GM104942-03 (PDC)

DOSE EFFECT OF MATERNAL ELECTRONIC CIGARETTE AEROSOL EXPOSURE ON AORTIC ENDOTHELIAL FUNCTION IN OFFSPRING.

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West Virginia University School of Medicine[1], West Virginia Clinical and Translational Science Institute[2], Center of Inhalation Toxicology[3], WVU Division of Neuroscience[4], Morgantown, WV 26506

There is growing evidence of cardiovascular risks of vaping; whether risks are conferred from vaping mothers to offspring is unknown. Here, we test two different exposure paradigms (20 vs 60 puffs) of daily Ecig exposure in a rodent model. We **hypothesize** that a higher dose of Ecig exposure during pregnancy would result in a greater impairment in aortic endothelial function in the offspring.

Pregnant Sprague-Dawley rats were exposed to either nicotine-free (Ecig0) or nicotine-containing Ecig aerosol (18 mg/ml, Ecig18) or ambient air (control). Ecig exposed dams received either 20 puffs or 60 puffs/day over 1hr, 5d/w using Joyetech eGrip OLED (with 5-sec puffs @17.5 W). Dam exposure began on GD2 and continued until PND21. Pups were never directly exposed. 2mm segments of thoracic aorta were obtained from 3-month old pups (n=8 per group) and mounted on a wire myograph system (DMT, AD Instruments). Preconstricted vessels (using U46619 10^{-8}M) were exposed to methacholine (Mch;10^{-9}M to 10^{-4}M) to assess endothelial-dependent relaxation.

At both 20 and 60 puffs exposure, significant impairment in aortic relaxation to Mch was observed in Ecig0 and Ecig18 groups (20 puff: 78±10% and 73±15%; 60-puff: 72±9% and 69±16%, respectively) vs controls (95±9%, $p<0.05$). Incubation with tempol reversed the dysfunction seen in both Ecig groups at 60 puffs, suggesting the superoxide pathway is involved.

Ecig vapor exposure to a pregnant dam elicited an impairment in aortic reactivity of adolescent offspring, a significant dysfunction at both 20 and 60 puff doses. This suggests that vaping mothers who wish to reduce risk by cutting back without actually quitting Ecig use during pregnancy would still be putting their child in danger of cardiovascular harm.

Support: WVU Cancer Institute Philip R Dino Innovative Research Grant (IMO); APS STRIDE Fellowship (JO); NIHGMS 5U54GM104942-03 (PDC)

ASSOCIATION OF ARSENIC EXPOSURE METABOLISM WITH BODY COMPOSITION: THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS (MESA).

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Exposure to arsenic in water and food increases the risk of cardiovascular and metabolic (cardiometabolic) diseases. However, pathogenic mechanisms that underlie this increased risk remain unresolved. Decreased muscle mass and increased ectopic adiposity in muscle have also been associated with cardiometabolic disease risk, and arsenic exposures have increasingly been shown to be associated with altered body mass and nutritional status. Thus, we hypothesized that arsenic is associated with lower abdominal muscle quality and altered abdominal adipose tissue distribution. We designed a cross-sectional pilot study using urinary arsenical and body composition measures in 283 participants (age 45-80) in the Multi-Ethnic Study of Atherosclerosis (MESA). Ingested inorganic arsenic (iAs) is metabolized to monomethylarsonic acid (MMA) and dimethylarsonic acid (DMA), and iAs. All metabolites were measured using HPLC separation and ICPMS quantification. We evaluated the health effects of total urinary arsenicals (ΣAs) and the proportion of each arsenic metabolite over Σas (i.e. iAs%, MMA% and DMA%) separately. Abdominal muscle quality was measured by muscle area and density in an abdominal CT scan slice at the L4-45 vertebral space. Other body composition variables were abdominal adipose tissue, body mass index (BMI) and waist circumference. We built linear regression models for each body composition indicator with urinary arsenic measurements adjusted for age, sex, race, region and other metabolic variables. We found that Σas was associated with a slight increase of BMI. However, MMA% was associated with decreased BMI, waist circumference and abdominal fat area, but importantly with decreased abdominal muscle area. DMA% was associated with opposite results. The data suggests that poor arsenic metabolism (high MMA%) may underlie body compositional changes that lead to increased risk of cardiometabolic diseases.

ACRYLONITRILE BUTADIENE STYRENE (ABS) 3D PRINTER EMISSION-INDUCED *IN VITRO* AND *IN VIVO* TOXICITY.

MT Farcas[1,2], AB Stefaniak[1], W McKinney[1], AK Knepp[1], L Bowers[1], WK Mandler[1], M Kashon[1], L Battelli[1], TA Stueckle[1,2], M Orandle[1], A Winn[1], SA Friend[1], SR Jackson[1], C Qi[1], DR Hammond[1], R LeBouf[1], D Burns[1], A Ranpara[1], TA Thomas[3], J Matheson[3], V Castranova[2], Y Qian[1,2]

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[3]US Consumer Product Safety Commission, Rockville MD, 20814 USA

Rationale: Fused filament fabrication 3D printing with acrylonitrile butadiene styrene (ABS) filament emits billions of particles and numerous volatile organic compounds (VOCs). However, their toxicological effects have not been elucidated.

Methods: For the *in vitro* study, human small airway epithelial cells (SAEC) were exposed to ABS particles and VOCs collected into serum-free cell culture medium using an impinger sampler inside a chamber while printing for 1.5 h. For the *in vivo* studies, Sprague Dawley rats were exposed to real-time ABS printing emissions or air (negative control) for 4 hours/day, 4 days/week for 1, 4, 8, 15, and 30 days.

Results and Discussion: For the *in vitro* studies, the ABS emission particle dose range was $1.42 \times 10^6 – 4.72 \times 10^6$ particles/cm^2, which induced significant dose-dependent cytotoxicity, oxidative stress, and cytokine production in SAEC. For the *in vivo* studies, the average aerosolized particle concentration was 0.24 ± 0.09 mg/m^3, which caused only elevated IL-10 and IFN-γ levels in bronchoalveolar lavage fluid. Neither adverse pulmonary oxidative stress responses nor histopathological changes in the lungs were observed.

Conclusion and Implications: Our *in vitro* studies indicated that the emissions from 3D printing with ABS filament induced pronounced toxicological effects in SAEC but minimal responses in rats, which is perhaps attributable to the low inhalation exposure dose used in this study. Thus, more *in vivo* studies with higher emission inhalation doses are needed to establish whether *in vivo* responses are similar to the *in vitro* findings.

Funding: U.S. Consumer Product Safety Commission (CPSC) and the National Institute for Occupational Safety and Health (NIOSH), Project [093909NF].

MATERNAL NANOPARTICLE INHALATION INFLUENCE ON CYCLOOXYGENASE-2 METABOLITES IN UTERINE MICROCIRCULATION.

JA Griffith, KL Garner, E DeVallance, EC Bowdridge, WT Goldsmith, TP Batchelor, TR Nurkiewicz

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Center for Inhalation Toxicology
West Virginia University School of Medicine, Morgantown, WV

A thriving nanotechnology market widely utilizes nano-titanium dioxide (nano-TiO_2) in products ranging from air filters to medical devices. Exposure of female workers and consumers in their child-bearing years creates the problem of maternal and fetal health consequences of gestational nano-TiO_2 inhalation. Meeting nutritional needs of a growing fetus requires uterine microvascular growth and adaptation plasticity. Alterations in uterine blood flow are mediated largely through endothelial impacts on vascular tone. Evidence exists prostacyclin (PGI_2) and thromboxane (TXA_2) are important mediators of the uterine microcirculation. Thus, altered PGI_2 and TXA_2 responsiveness may impair fetal development. We hypothesize *maternal nano-TiO_2 inhalation during gestation alters uterine microvascular PGI_2 and TXA_2 reactivity.* Pregnant, Sprague-Dawley rats were assigned to three groups: naïve, sham- filtered air, or nano-TiO_2 exposed. Rats were exposed 6 hrs/d for 6 days on gestational day (GD) 10-19 to nano-TiO_2 aerosols generated with Evonik-P25 (concentration= 12±0.5 mg/m^3; cumulative lung burden= 525±16 µg; primary particle size= 21 nm; zeta potential= -57 mV). An electrical low-pressure impactor determined the nano-TiO_2 count mean aerodynamic diameter (182±2 nm). On GD 20 (24-hours post final exposure) rats were euthanized. There was no difference in age, body mass, or litter size between groups. Placental efficiency for the nano-TiO_2 group was significantly increased (6.3±0.2 vs 4.7±0.1 air control group). Uterine arteriole responsiveness (pressure myography) to PGI_2 was not different among groups. The nano-TiO_2 exposed group trended toward an exaggerated constrictive response to TXA_2. Given these results, our preliminary position is that gestational nanomaterial inhalation exposures alter COX metabolites on pregnancy adaptations. Future work will delineate specific contributions of PGI_2 and TXA_2 in this mechanism.

Support: NIH ES015022 (TRN)

CRITICAL WINDOW OF GESTATIONAL EXPOSURE: UTERINE MICROVASCULAR AND FETAL CONSEQUENCES.

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Engineered nanomaterials are utilized in diverse applications yet microvascular ramifications of gestational exposure are poorly understood. It has been suggested that microvascular sensitivity is most volatile during early gestation. This study aimed to assess microvascular and reproductive consequences of gestational inhalation exposure to nano-titanium dioxide (nano-TiO_2) during distinct trimesters. We hypothesized that maternal exposure during early pregnancy, a period of rapid microvascular growth, implantation and trophoblast invasion, results in microvascular dysfunction and poor fetal outcomes. Uterine microvascular angiotensin II (ang II) reactivity was assessed as it is a vasoactive hormone involved in microvascular pregnancy adaptations. Sprague Dawley rats were assigned to 6 exposure groups (early gestational days (GD) 2-6, mid GD 8-12, late GD 15-19, or control groups). Nano-TiO_2 Evonik-P25 (primary diameter=21 nm) was utilized. Whole-body exposure (12±0.5 mg/m^3) was performed for 6 hrs/d for 3 d (cumulative calculated lung burden ~336 µg). Rats were euthanized on GD 20 to assess pup characteristics and pressure myography was performed on isolated uterine radial arteries. Dry pup mass of early exposed group was 0.43±0.01 g, dry placental mass was 0.13±0.01 g and placental efficiency was 3.50±0.15. Early exposed pups were significantly larger, had smaller placentas and reduced placental efficiency. Ang II ($1x10^{-13-4}$ M) reactivity only within the early exposed group was significantly altered compared to the control. These results suggest early gestation is a period of increased sensitivity to nano-TiO_2 exposure that leads to altered microvascular reactivity and fetal consequences. Experiments are ongoing to assess microvascular reactivity and ang II receptor distributions within uterine attachment sites. This may account for altered ang II sensitivity and pinpoint a mechanism of dysfunction.

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LUNG FUNCTION DECLINE AND PULMONARY INFLAMMATION AFTER INHALATION CO-EXPOSURE TO ULTRAFINE PARTICLES AND OZONE.

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Air pollution is among the five leading causes of premature deaths and increased cardiopulmonary hospitalizations. Air pollution is a complex mixture of gases and particulate matter. Recent epidemiological studies indicate that these components synergistically interact to induce adverse cardiopulmonary outcomes. However, most of the studies done till date are limited to single exposure system. We hypothesized carbon black (CB) and ozone (O_3) co-exposure significantly alter lung inflammation and lung function compared to individual exposure. We exposed C57Bl/6J mice to air, O_3 (2ppm) and/or ultrafine CB particles (10mg/m^3) 3 hours daily for up to four days and sacrificed mice 24 hours post exposure. We performed real time monitoring of aerosol mass and diameters (aerodynamic, count median and mass median) in our state of the art WVU Inhalation Facility. Bronchoalveolar lavage fluid (BALF) and lung tissue were collected to measure real time PCR based gene and proteins expression related to airway barrier leakage, airway injury, and inflammation. Particle deposition analyses revealed 18±0.3µg deposited particles in the lungs for both CB and CB+O_3. The Fourier Transformed Infrared (FTIR) indicated significant alteration in the surface characteristics of the CB particles after interaction with O_3. The studies demonstrated 1) significantly greater biological activity (Inflammation, LDH release, BALF proteins, lung function decline) of co-exposure compared with individual exposures, and 2) significantly greater increase in inflammation (cells in BALF, gene and protein expression) in repeated exposure compared to single exposure. Additionally, we demonstrated that induction of inflammatory response was mediated through reactive oxygen species and NF-κβ signaling pathway. In conclusion, utilizing a more realistic particle and gas co-exposure inhalation, we demonstrate that increased biological activity of co-exposures is mediated through oxidative stress-NF-κβ pathway. Further studies are ongoing to mechanistically elaborate the impacts of co-exposures in pulmonary and metabolic diseases utilizing animal models and organoid cultures.

WESTERN DIET ALTERS BLOOD FLOW AND EXACERBATES SILICA-INDUCED LUNG INFLAMMATION IN THE F344 RAT

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Obesity affects over 30% of adults in the United and leads to metabolic changes in adipose function also known as metabolic dysfunction (MetDys). MetDys is a risk factor for lung function impairment, pulmonary hypertension and asthma. Inhalation of respirable crystalline silica causes significant respiratory morbidity and mortality in exposed workers due to silicosis. Silicosis is an incurable restrictive lung disease associated with inflammation and fibrosis. The question addressed by this study is, “does pre-existing metabolic dysfunction increase a worker’s risk to pulmonary inflammation and silicosis?”

In previous studies, F334 rats developed metabolic dysfunction (MetDys)(weight gain, dyslipidemia, altered adipose function, and insulin resistance) after consuming a Western diet (WD) for 16 wk. For this study, 6 wk old male F344 rats were fed either a WD [40.6% fat (19.5% lard), 40.6% total carbohydrate (20% sucrose), 14.8 % protein] or standard rat chow (STD)[6.2 % fat, 44.2 % carbohydrate (grain sources), 18.6 % protein] for 16 weeks before inhalation exposure to respirable crystalline silica (Min-U-Sil 5®, 15 mg/m3) or filtered air 6 h per day, 5 d per week, for 39 d. Endpoints were measured at 0, 4, and 8 wk post-exposure. Rats were maintained on their assigned diet throughout the study.

Body mass, abdominal girth, and abdominal posterior fat pad weight were greater in rats fed a WD compared to the STD. Arterial blood flow increased in the WD air group compared to the STD air group at pre-exposure, 0, and 8 wk post-silica exposure. Silica inhalation increased arterial pulse frequency in both STD and WD at 8 wk compared to pre-inhalation levels. WD increased mean blood flow arterial pulse frequency at 0 wk post-exposure compared to pre-inhalation levels. Silica increased total cell count (TCC) and elevated lactate dehydrogenase (LDH) levels in bronchoalveolar lavage in both diet groups at all time points; however, combined WD and silica-exposure significantly increased TCC and LDH compared to STD silica-exposed groups. The results indicate that consumption of a WD induces weight gain and alters blood flow and arterial function. Silica exposure does not affect weight gain but alters arterial function at 8 wk post-exposure. Combination of WD and silica exposure exacerbates pulmonary inflammation compared to silica exposure alone.

COMPARATIVE ASSESSMENT OF *IN VITRO* TOXICITY INDUCED BY CRYSTALLINE SILICA AND MULTI-WALLED CARBON NANOTUBES IN HUMAN AND MOUSE MACROPHAGES.

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Pulmonary exposure to particles like crystalline silica (CS) and multi-walled carbon nanotubes (MWCNTs) are known occupational hazards. Once in the lung, these particles activate alveolar macrophages (AM), a first step in the development of diseases. To study the mechanisms involved in particle induced inflammation, THP-1 and RAW 264.7 cells were used and toxicity of CS and MWCNTs was tested. Cytotoxic dose-responses of each particle were determined for 24-hrs. Both particles caused a dose-dependent response. Concentrations pertaining to 0%, 10%, 30% and 60% toxicity for each cell and particle type were chosen for cytokine analysis: 41 markers in THP-1 and 32 markers in RAW 264.7 were measured. Activation of inflammasome cascade (IL18), pro-inflammatory markers (TNF-α), dysregulation (IL6) and fibrotic markers were observed. Cytokines involved in inflammation (IL1-B, IL18) and cell recruitment (MCP-1, MIP) were found to be elevated. Based on TH1/TH2 (IL18/IL4) ratio, there was a concentration-dependent polarization to TH1 response. Overall, THP-1 cells produced a greater inflammatory response to particle exposure than RAW 264.7 cells and MWCNTs were more potent than CS. Data clustering showed MWCNTs and CS treated THP-1 and RAW cells had 24 and 7 common cytokines, respectively, and 11 cytokines were found to be common between both cell lines and particle types. Principle component Analysis showed that the response, at same doses can be easily distinguished between particle type and was more apparent in THP-1 than RAW cells.

In conclusion, both particle exposures resulted in significant cytotoxicity in a concentration-dependent manner. THP -1 cells were more responsive and the potency of MWCNTs observed was much higher compared to CS at equal mass possibly due to difference in particle size and also due to difference in ASC inflammasome/casp1 activation cascade between two cell types. Ongoing transcriptomic studies may further differentiate the mechanisms of particle toxicity in different types of macrophages.

MULTIMODAL MASS SPECTROMTRY ANALYSIS FOLLOWING REPEATED INTRATRACHEAL INSTILLATION OF DISPERSED SILVER NANOPARTICLES IN RATS.

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Silver nanoparticles are among the most widely manufactured nanomaterials and have been incorporated into a wide variety of consumer products such as textiles, detergents, medical devices, drug delivery products, anti-microbial sprays, personal care products, and paints/coatings. We have previously conducted an in vivo study to characterize pulmonary and systemic effects following repeated exposure where rats were intratracheally instilled once a week for eight weeks with 9.35 □g or 112 □g of dispersed silver nanoparticles (Nano-Ag) or dispersion medium (DM) as a vehicle control. Lung histopathology, and analyses of bronchoalveolar lavage fluid (BALF) and serum were performed at 7, 28, and 84 days after the last exposure. In the current study, a metabolomic approach was employed to characterized changes in the BALF and serum to further examine mechanisms of toxicity and establish biomarkers of exposure and effect. Metabolomics was conducted with matrix assisted laser desorption ionization (MALDI) and liquid chromatography mass spectrometry (LC-MS). The metabolomics analysis revealed a significant increase in 44 metabolites in BALF, including1,2-Dipalmitoyl-phosphoglycerol (DPPG) and cholesterol in the rats exposed to 112 □g at the 7- and 28-day time points. Rats exposed to the high dose had a significant increase in ~60 serum metabolites, with the greatest degree of change in the alanine biosynthesis pathway intermediates in the serum, which have been shown to be indicators of liver toxicity. There was a >2.0-fold increase in alanine, valine, and glutamate in the 112 □g exposed animals at the 7- and 28-day time points. The results of this study show that pulmonary exposure to nanosilver particles leads to changes in the BALF lipidome, which may be related to the pathway of lung injury and oxidative stress. In addition, increased levels of circulating metabolites indicative of liver toxicity in agreement with numerous studies by other investigators.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

MATERNAL EXPOSURE TO ENGINEERED NANOMATERIAL DURING GESTATION DIMINISHES FERTILITY IN F1 FEMALES.

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We have reported that maternal inhalation exposure to nano-titanium dioxide (nano-TiO_2) during gestation severely reduces circulating estrogen levels and compromises placental efficiency at gestational day (GD) 20 in Sprague Dawley (SD) rats. Alterations to the normal gestational milieu neonates are subjected to during development has been extensively shown to contribute to the developmental origins of health and disease. The objective of this study was to determine the impacts of gestational exposure on cyclicity, fertility, and pregnancy outcomes. Female, SD rats were housed in the West Virginia University Inhalation Facility under a regulated temperature and 12:12 hour light-dark cycle. Dams of F1 offspring were randomly assigned to either sham-control or nano-TiO_2 exposure groups and acclimated for 48-72-hours before mating. Inhalation exposures lasted for 6 days after GD 10 to decrease animal stress. The pregnant rats were exposed to an average target concentration of 12 mg/m^3. This exposure paradigm (12 mg/m^3, 6 hours/exposure, 6 days) produced a cumulative, calculated lung burden of 525±16 µg. 24 hours after the last exposure dams were sacrificed on GD 20. F1 females born to exposed dams experienced increased time to conception, requiring at least two matings prior to successful conception. Rats that became pregnant to second matings (n=4) had litter sizes (12.5±1.26 pups) comparable to sham-control dams. Dams exposed to nano-TiO_2 also had significantly reduced liter sizes (10.0±0.73) with decreased number of males (4.4±0.38), but not females (6.2±0.88) compared to sham-controls (12.7±0.71, 7.3±1.1, and 5.8±1.1, respectively). Maternal nano-TiO_2 exposure during gestation reduces liter size and male to female ratio. Furthermore, F1 females born to dams exposed during gestation experienced increased time to conception as well as decreased liter size ultimately leading to decreased fertility.

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CYTOTOXICITY OF PERACETIC ACID VAPOR EXPOSURES ON HUMAN BRONCHIAL EPITHELILAL CELLS.

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Peracetic acid (PAA) is a highly reactive peroxygen compound that is widely used as a disinfectant in healthcare settings and poultry processing plants. PAA is irritating and corrosive to the eyes, skin, and mucous membranes of the respiratory tract. Workers exposed to PAA vapors from the spraying and fogging of disinfectant solutions have reported symptoms such as headaches, lacrimation, coughing, wheezing, and blurred vision. Using a commercially available solution of PAA (32 weight % in dilute acetic acid), we identified the cytotoxicities associated with vapor exposures on normal human bronchial epithelial cells (NHBEs) using an *in vitro*, air-liquid interface exposure model. Using an in-house exposure chamber, NHBEs were exposed to filtered air (FA) for 1 hour (h), 2 h, and 4 h. This was to account for differences in temperature, relative humidity (RH) and carbon dioxide (CO_2) as compared to the cell culture incubator. Temperature in the chamber was 74.4 ℉, RH was 90.4%, and CO_2 in ambient air was 0.04%. Using the water soluble tetrazolium assay, no significant differences in viability were detected between FA-exposed cells and incubator controls. Next, NHBEs were exposed to either FA (controls), 12 or 22 ppm of PAA for 4 h and then returned to incubators for an additional 4 or 24 h recovery period. Cellular viability, lactate dehydrogenase (LDH) production, cytokine production (IL-1β, IL-6, IL-8, and TNFα) and microscopic changes in cells were assessed at 4 and 24 h post exposures. Compared to FA controls, PAA (22 ppm) reduced cellular viability and increased LDH release, denoting acute cytotoxicity upon exposure at both time points. Cytokine production in FA-treated cells was not significantly different than PAA-treated cells, except for IL-6 at both time points. Microscopic changes were assessed using H&E staining of cells. Compared to controls at 24 h, PAA caused cell necrosis and loss of cilia. Our studies show that exposure of NHBE cells to PAA causes significant changes in viability, LDH production, IL-6 production and microscopic abnormalities when compared to FA. Further studies are needed to delineate the exact mechanism(s) by which this occurs, with the goal of reducing workplace injuries and exposures.

Funding source: National Occupational Research Agenda/NIOSH

TELOMERES IN TOXICOLOGY: OCCUPATIONAL HEALTH.

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The ends of chromosomes shorten at each round of cell division, and this process is thought to be affected by occupational exposures. Occupational hazards may alter telomere length homeostasis resulting in DNA damage, chromosome aberration, mutations, epigenetic alterations and inflammation. Therefore, for the protection of genetic material, nature has provided a unique nucleoprotein structure known as a telomere. Telomeres provide protection by averting an inappropriate activation of the DNA damage response (DDR) at chromosomal ends and preventing recognition of single and double strand DNA (ssDNA and dsDNA) breaks or chromosomal end-to-end fusion. Telomeres and their interacting six shelterin complex proteins in coordination act as inhibitors of DNA damage machinery by blocking DDR activation at chromosomes, thereby preventing the occurrence of genome instability, perturbed cell cycle, cellular senescence and apoptosis. However, inappropriate DNA repair may result in the inadequate distribution of genetic material during cell division, resulting in the eventual development of tumorigenesis and other pathologies. Here we discuss the association of changes in telomere length and its interacting proteins with different occupational exposures and the potential application of telomere length or changes in the regulatory proteins as potential biomarkers for exposure and health response.

CHARACTERIZATION OF AEROSOLIZED PARTICLES GENERATED FROM MACHINING OF NANOCLAY-ENABLED COMPOSITES.

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Nanoclay-enabled polymer nanocomposites (NPCs) are poised to dramatically impact composite technologies across numerous applications. Release of airborne particulate containing nanoclays at key steps along the NPC cycle represents a little understood but emerging occupational inhalation exposure hazard. This study hypothesized that different types of surface organic coatings, percent nanoclay loading, and machining process would impact the physicochemical characteristics of generated airborne particulate during simulated industrial machining. Two different organomodified nanoclays (ONC), Cloisite 93A and Cloisite 25A, were embedded in polypropylene (PP) at three different percent loading (0%, 1%, and 4%). Each NPC was sanded in a controlled exposure chamber to generate airborne particulate, which was measured in real-time by direct reading instruments and filter collection of released particulates. ONC type and percent loading influenced bulk NPC strength and toughness, which significantly correlated with particle release. Both 1% ONC and 4% Clois93A NPCs exhibited significantly greater strength, toughness, total particle number, and respirable mass concentration than 4% Clois25A and virgin PP NPCs. A majority of mass from machined NPCs was within the inhalable fraction. A noticeable peak in the respirable fraction (<30 nm) was detected and varied in magnitude, with 1% NPCs producing more ultrafine particulate. ONC type and load influenced NPC dust particle size, mass, and elemental composition. ONC was primarily found protruding from NPC composite particles. In summary, NPC abrasion produced NPC particulate in the inhalable fraction with 1) protruding nanoclay platelets and 2) noticeably different concentrations of sanding particles depending on nanoclay type, loading, and NPC strength characteristics.

Funding Support: NIOSH NTRC, NSF CAREER 1454230

Keywords: Nanoclay, Nanocomposite, Exposure assessment methods, Tensile strength, Sanding, Mechanical processing

HUMAN HEALTH RISK ASSESSMENT OF HEAVY METALS INGESTION FROM BABY FOODS.

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In light of concerns regarding the presence of heavy metals in baby foods, we purchased and analyzed 36 organic and non-organic baby food samples representing four food categories (i.e., fruit, leguminous vegetable, root vegetable, or grain) for arsenic (As), cadmium (Cd), mercury (Hg), and lead (Pb). For the three detected metals (As, Cd, and Pb), we assessed the potential lifetime cancer and non-cancer health risks posed to infants and toddlers following daily consumption of each food type. Daily ingestion rates for each food category were selected from average food intake rates for children aged three years or younger from the U.S. Environmental Protection Agency's (USEPA) Exposure Factors Handbook (EFH); three age categories were evaluated: <1 year, 1 to <2 years, and 2 to <3 years. To calculate non-cancer hazard indices (HI), the median and maximum average daily doses (ADDs) were compared against the appropriate reference values. Cancer risk was evaluated for both the median and maximum lifetime average daily doses for Pb and As, which were compared against the OEHHA's oral slope factor and USEPA oral slope factor, respectively. For non-cancer risk, HIs indicated a potential for risk in limited exposure scenarios including: As exposure in grain (based on median and maximum As concentrations), Pb in grain (maximum Pb concentration only), and Pb in Root Vegetables (maximum Pb concentration only). Increases in lifetime cancer risks for all metals across the food categories evaluated were 4.7×10^{-5} and 5.1×10^{-5} based on median and maximum metal concentrations, respectively; cancer risks were driven by risk associated with arsenic exposure coming primarily from the detection of arsenic in grain products. Although this study is limited by small sample sizes, the results indicate that a child's typical intake of baby foods are unlikely to pose health risks above accepted tolerable risk levels under most scenarios, particularly as the exposure assumptions used in this analysis are conservative and are likely to overestimate non-cancer and cancer risks.

DISRUPTION OF BRONCHIAL CELL MONOLAYER INTEGRITY BY ORGANOMODIFIED NANOCLAYS AND THEIR INCINERATED BYPRODUCTS.

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Organomodified nanoclays (ONCs) represent one of the most used engineered nanomaterials (ENMs) as nanofiller in emerging advanced manufacturing strategies to produce a diverse number of polymer nanocomposites. Different organic quaternary ammonium coatings on these 2-dimensional montmorillonite nanoclays allow for their incorporation in novel or replacement technologies in thin-film, aerospace, automobile, consumer, and health care polymer nanocomposite applications. Compared with other ENMs, little information exists on risks to occupational pulmonary health along the ONC life cycle that encompass synthesis, handling, manipulation, and disposal. This study hypothesized that coating type, incineration status, and time-dependent effects of ONC exposure would impact bronchial epithelial cell monolayer integrity, a key target following inhalation exposure. High-throughput *in vitro* screening strategies including high content imaging, electric cell impedance sensing, and flow cytometry were employed to evaluate a set of pre- and post-incinerated ONCs for acute effects and fate of the monolayer post-exposure. Using each particle's IC_{50} cell viability in a BEAS-2B cell model, pristine nanoclay exposure caused acute loss of monolayer integrity, decreased metabolism, and increased apoptosis. Three different ONCs, however, displayed minimal loss to monolayer integrity despite coating type-dependent differences in apoptosis induction and decreased cell metabolism. Conversely, incinerated nanoclay byproducts caused decreased monolayer integrity, increased cell necrosis, and little evidence for reestablishment of the epithelial monolayer. These results suggest the type of quaternary ammonium coating and incineration status largely impacts mechanism of cytotoxicity, cell metabolism, and the recovery ability of the exposed bronchial epithelial cell monolayer. An integrated high-throughput *in vitro* screening strategy, using high content imaging and traditional in vitro methods, represents a rapid pulmonary epithelial toxicity assessment approach to prioritize ENMs for further evaluation and serves to inform 'prevention-by-design' material development strategies.

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Keywords: in vitro studies, lung epithelial, silicates, nanomaterial, incineration

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