

PS 2102 Oral-Administered TiO₂ Nanoparticles Impact Basic Neurobehavioral and Cardiac Assessments and Biochemical Profiles in Rat Pups

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Titanium dioxide (TiO₂) is one of the most prevalent nanoparticles (NP) used as a food additive, and is found in baby formula, baked goods, candy, dairy products, etc., making ingestion unavoidable. Little is known about biological responses to NP exposure during infancy when both the intestinal tract and brain is still undergoing considerable development. In the study presented here male and female rat pups received four oral doses of 10 mg/kg TiO₂ P25 NP between postnatal day (PND) 2-5, 7-10, or 17-20, and were sacrificed at PND 21. Basic neurobehavioral (acoustic startle response, locomotor activity, and rotarod) assessments were performed at PND 20. Cardiac assessment (ECGenie) was conducted on PND 14 and 20. Six neurotransmitters/metabolites were quantified in brain by UPLC with electrochemical detection. Plasma metabolites (n = 181) were quantified using AbsoluteIDQ[®] p180Kits (Biocrates) analyzed by LC-MS. TiO₂ administered between PND 17-20 caused a decrease in locomotor activity (P<0.05). Dosing between PND 7-10 resulted in a decrease in heart rate in both male and female pups, however when dosed between PND 17-20 only female pups had a significantly decreased heart rate. Neurotransmitters/metabolites analyses show dopamine (DA), dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and norepinephrine (NE) were impacted in an age- and gender-specific manner: DA was increased for male and female pups dosed between PND 2-5 but decreased for males dosed PND 17-20. DOPAC was increased for male and female when dosed PND 7-10. HVA were decreased following administration at PND 7-10 and 17-20. NE were decreased for females dosed PND 17-20. Metabolomic analysis of plasma shows between 6-17 individual metabolites and metabolite ratios/sums were significantly different between exposure groups and vehicle controls. Our results show that the biological responses to orally dosed TiO₂ NP in early life happen in an age- and gender-specific manner. Our data suggest that TiO₂ NP may impact neurobehavioral and cardiac performance, neurotransmitter/metabolite concentrations in brain, as well as metabolite concentrations in plasma.

PS 2103 Understanding the Variable Drivers of Toxicity for the Broad Class of Carbon Nanotubes and Nanofibers from US Facilities

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Pulmonary exposure to carbon nanotubes or nanofibers (CNT/F) is known to induce inflammation, toxicity, or tumorigenesis, and is a concern in the occupational setting. Previously, we established toxicity profiles from male C57BL6/J mice aged 8-10 weeks exposed to either 4 or 40 µg of one of nine different CNT/F via oropharyngeal aspiration as well as human epithelial BEAS-2B cells (0-24 µg/ml), differentiated THP-1 cells (0-120 µg/ml), and human fibroblasts (0-2 µg/ml) for four primary outcomes of genotoxicity, inflammation, pathology, and translocation. An overarching goal of our expansive study was to use machine learning to determine the relationship between particle physicochemical characteristics with respective toxicity outcomes and the relationship between those four primary outcomes. The nine materials had a wide range of characteristics including diameter (6-397 nm), length (0.1-50 µm), surface area (18-238 m²/g), aspect ratio (2-1396), residual metal catalyst (0.3-6.2 %), density (0.007-0.220 g/cm³), etc., to consider. Unsupervised approaches were used to identify and define subsets of materials with similar outcomes. Subsequently, supervised learning approaches were used to identify physicochemical characteristics that define these outcomes. While some physicochemical characteristics were determined to be key drivers of specific toxicity outcomes, different characteristics were essential when considering other toxicity endpoints. More specifically, drivers of inflammation and/or pathology were not the factors driving translocation and/or genotoxicity. No single characteristic could be used as a toxicity predictor, therefore, multifactorial processes, or combination of characteristics, were necessary for an accurate and effective prediction model for responses. The

study identified physicochemical drivers of CNT/F toxicity using an integrated approach, combining experimental evidence with computational modeling, with potential for broad application.

PS 2104 A Long-Term Whole-Body Inhalation Study of Multiwalled Carbon Nanotubes in Mice with an Improved Dispersion and Inhalation System

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Inhalation study is essential for assessment of general respiratory toxicity including non-cancerous endpoint of the nanomaterials (NMs). In designing inhalation studies for NMs, it is important to control the status of aggregate and agglomerates (AA) to be consistent with the human exposure. For example, a multi-wall carbon nanotube (MWCNT) such as Mitsui MWNT-7 is a mixture of single fibers (SF) and their AA. Human ambient air, in general, is less agitated; the AA may sediment away faster, SF may suspend longer in the air and to be inhaled by humans. On the other hand, the air for animal experiments is rigorously agitated in order to ensure the homogeneity of the aerosol; when the aerosol is a mixture of SF and AA, the AA could be trapped by the upper respiratory tract and impede the SF to reach the alveolar region consequently induce AA-specific lesions (e.g. granulomas) which are considered to block and/or mask the nature of toxicity induced by the SF. Taking all into account, we considered that it is essential to make a well-dispersed aerosol without AA for the human-relevant exposure scenario. To generate well-dispersed aerosol, we developed the "Taquann" dispersion method and a "direct injection" whole body inhalation system for the dispersed sample (designated as "Taquann System" J Toxicol Sci. 2013). In this study, we have conducted a long-term inhalation exposure study of MWCNT (MWNT-7, Mitsui) by using Taquann system. Male C57BL/6 mice, 12-week-old were exposed to MWCNT aerosol, 2.7 and 5.1 mg/m³ in the low concentration group (LC) and in the high concentration group (HC), respectively. Duration of exposure was 6 hrs a day for 6 months every 4 weeks. MMAD on aerosol in the chamber was approx. 500 nm measured by MOUDI (Model125, Kanomax). Lung burden of the first time exposure were approx. 4 and 6 microgram per animal in the LC and in the HC, respectively. The fiber length recovered from the lungs was approx. 6.5 micrometer. Histologically, SF were found around terminal bronchioles to alveolar region. Macrophages surrounded and/or phagocytized cluster of SF. However, clear formations of granuloma were not observed. It is concluded that aerosol dispersibility should be considerations for risk assessment of NMs. This work was supported by the Health and Labour Sciences Research Grant, Japan.

PS 2105 The Effect of Disease State and Age on the Biodistribution Profile of Injected Gold Nanoparticles

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Many nanoparticle (NP) biodistribution studies focus on characteristics such as size, shape or dissolution that affect tissue accumulation and retention in healthy animals. However, little has been done to determine how factors such as disease state or age can alter barrier permeability and ultimately change NP biodistribution. Neuroinflammatory diseases, such as Alzheimer's disease (AD), often feature a compromised blood-brain barrier (BBB). Thus, we hypothesized that AD state and age would alter the biodistribution of blood-borne NPs, particularly to the brain. To study the effects of AD- and age-related changes in tissue NP accumulation, we used the 3xTgAD mouse model and varied age as a function of disease state. Young (3 mo) and aged (19 mo, 23 mo) 3xTgAD and non-transgenic (NTg) mice were injected intravenously with colloidal gold NPs (AuNPs, primary particle size 20 nm, 45-49 µg per mouse). Tissues were collected 24 hrs post-injection and processed by acid-assisted microwave digestion. Au tissue content was determined by atomic absorption spectrometry (liver, spleen) or inductively-coupled plasma mass spectrometry (kidneys, blood, microdissected brain). The total recovered Au dose in all tissues measured was higher in the aged mice as compared to young mice irrespective of genotype (p=0.0012). The biodistribution profile for both genotypes demonstrated that the livers accumulated the highest relative dose (65-85% of the recovered dose), followed by the spleen (14-33%), kidneys (2-3%), blood (<1%), then whole brain (<0.5%). Analysis of Au tissue concentrations in microdissected brain regions (olfactory bulb, hippocampus, striatum, frontal cortex, cerebellum) demonstrate regional differences in brain accumulation by age and genotype. When considering the brain as a whole, there was a significant interaction effect of age and genotype on Au accumulation (p=0.006), where elevated levels of Au were found with in-

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Preface

This issue is devoted to the abstracts of the presentations for the Continuing Education courses and Scientific Sessions of the 59th Annual Meeting of the Society of Toxicology, held at the Anaheim Convention Center, Anaheim, California, March 15–19, 2020.

An alphabetical Author Index, cross-referencing the corresponding abstract number(s), begins on page 542.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 580.

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