Exposure to Nanomaterials during Gestation Affects Cardiovascular Health for at Least 12 Months

Author Block: S. B. Fournier, K. Wiersielis, V. Lam, M. Goedken, K. Reuhl, and P. A. Stapleton. *Rutgers, The State University of New Jersey, Piscataway, NJ.*

Nanosized - titanium dioxide ($nTiO_2$), is a naturally occurring oxide of titanium and is intentionally manufactured for use in a wide range of applications including industrial and personal care products. In laboratory studies, $nTiO_2$ has been used as a surrogate for ultrafine air pollution particulate. We have shown that exposure to $nTiO_2$ during pregnancy affects the cardiovascular health of the dam, fetus, and young adult offspring. It is unclear whether cardiovascular dysfunction in the progeny persists into middle age. Timed-pregnant Sprague-Dawley rats (Charles River) were exposed to $nTiO_2$aerosols [9.65 ± 0.07 mg/m^3, primary particle size 21 nm, agglomerate size 128.45 ± 1.83 nm (SMPS, TSI), calculated daily deposition 47.27 ± 1.88 µg] for 4 hours over 6.00 ± 1.31 days of the remaining gestation via inhalation (HPGA, IESTechno). A subset of animals was exposed to filtered air as controls. Animals delivered in-house, offspring were monitored weekly, and were sacrificed at 12 months. Pressure myography (LSI, Burlington, VT) was conducted to evaluate microvascular reactivity in coronary arterioles to assess endothelium-dependent (EDR) [acetylcholine (10^{-9} - 10^{-4} M)]. Gestational $nTiO_2$ exposure significantly impaired EDR relaxation (43.80 ± 5.49 %) compared with controls, a finding maintained from previous studies of young adult offspring. Following arteriolar isolation, hearts were collected, fixed in 10% formalin, sectioned, and reviewed for histopathological analysis. Samples from exposed offspring present histopathological alterations characterized by multifocal myocardial inflammation, degeneration, necrosis, loss and/or fibrosis compared with control tissue. These findings were consistent with repeated low-grade ischemia. Anecdotally, a neurological tick and seizure activity were observed in 5 female animals exposed *in utero* to $nTiO_2$. Brains from these animals were collected, fixed for 24 hours, sectioned, and reviewed. Early observations indicate histopathological changes within the pituitary. Overall, gestational exposure to $nTiO_2$ produced coronary microvascular dysfunction, accompanied by histological changes in the heart that persist to middle age. These results may provide experimental evidence for a better understanding of the developmental onset of cardiovascular disease after gestational exposure to aerosolized xenobiotic particulates. *Supported by NIH-R00-ES024783; P30-ES005022; T32-ES007148.*