Ammonium 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoate (CAS No. 62037-80-3, GenX), replaces perfluorooctanoic acid (PFOA) as a chemical precursor in the production of fluoropolymers. The compound persists in environmental media and human exposure occurs through drinking water and inhalation exposure. Based on a high-dose toxicokinetic study, GenX is rapidly absorbed and eliminated in its parent form via urine. There are no publications on GenX at environmentally relevant concentrations or the potential for GenX to cause CNS toxicity, so we decided to study the potential for low concentrations (0.1 – 1000 nM) of GenX to modulate the blood-brain barrier (BBB). The BBB plays a vital role in limiting exposures of toxicants to the brain, especially through the activity of ATP-Binding Cassette (ABC) efflux transporters. Using a steady-state luminal fluorescence-based assay, we investigated the effects of GenX on the transport activity of three well-characterized efflux transporters, P-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP), and Multidrug Resistance Protein 2 (MRP2). In our ex vivo studies in male and female SD rats, we observed slight changes in MRP2 at the highest concentration and latest time point. GenX may have a toxic effect on the capillaries, but at relevant concentrations (0.1-100 nM) and early timepoints (up to 3 h) capillary integrity is maintained. In males and females, GenX rapidly inhibited P-gp and BCRP at low concentrations. The effects on P-gp were reversible, but the effects on BCRP were irreversible up to four hours following removal of GenX. Western Blotting of male and female capillary membrane protein treated ex vivo (100 nM, 3 h) showed that GenX decreased expression of P-gp. In human ovarian cancer cells only expressing P-gp, 100 nM GenX significantly increased cell death due to Adriamycin, a toxic P-gp substrate and anti-cancer drug. In our in vivo studies, a three-hour exposure to a single oral gavage of GenX (0.01 mg/kg in males, 0.1 mg/kg in females) had no effect on P-gp activity in males, but induced P-gp activity in females. In addition, in vivo GenX exposure inhibited BCRP activity in males but had no effect in females. The lack of toxicokinetic data at the concentrations we used could explain the differences we observed in our ex vivo and in vivo assays. Inhibiting P-gp and BCRP activity reduces the neuroprotective function of the BBB, potentially exposing the CNS to toxic endogenous and exogenous substrates. P-gp and BCRP are also expressed in other tissues in the body, such as the liver, GI tract, and in other barriers such as the blood-placenta and blood-testis barrier. If GenX has a similar effect in these tissues, then exposure to GenX could alter pharmacokinetics of xenobiotics throughout the body.

Committee:

L.M. Ball, Ph.D (Academic Advisor)
Linda Birnbaum, Ph.D. (Research Advisor) (National Institute of Environmental Health Sciences)
Ron Cannon, Ph.D. (National Institute of Environmental Health Sciences)