Nanoplastics and Human Health Initiatives

Significance, Innovation, and Impact: Nanoplastics are *an exponentially emerging concern* due to their ubiquitous presence in the environment and potentially detrimental effects on the human body, which have only recently come to light.[2,3-7] With global concentrations of nanoplastics rising with a doubling time of every ~10-15 years[4], and the reality that nanoplastics may take decades to form from the degradation of discarded plastic material, yet appear to be a dominant and understudied mode of accumulation[6,8], there is an urgent need to assess potential health effects before critical exposure thresholds are achieved.

Below we propose research projects that we deem of highest priority across 2 major areas of health: neurological conditions and cardiovascular disease.

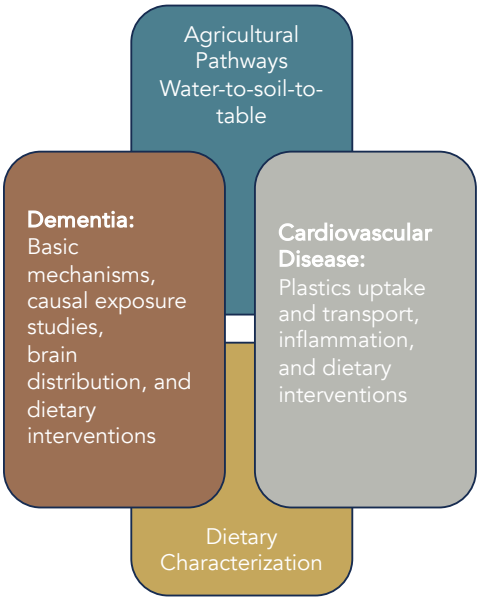

Figure 1. Overlapping components of an overall Nanoplastics and Human Health Center

1. Alzheimer's disease and related dementias (ADRD)

Our recent publication highlights the ability of microplastics to accumulate in the human brain, an effect that was more alarming in dementia cases. The chemical and physical nature of nanometer-scale plastic particles may promote aggregation of proteins involved in diseases like Alzheimer's and Parkinson's. There is also reason to consider the role of plastics – which are increasing rapidly in our world – as a cause of other increasing conditions like autism spectrum disorder and multiple sclerosis. The unique characteristics of plastics in the brain may make both syndromes more frequent and severe.

1.1 Clinical Studies: Can a low plastics diet reduce plastics in the brain and slow neurocognitive decline?

We will work with our UNM Alzheimer's Disease Research Center (ADRC) to recruit patients with early-stage cognitive decline. They will be divided into two groups: a low plastics diet (limiting meats, processed foods, and plastic packaging) and a no intervention group. Cerebrospinal fluid will be obtained prior to and after 6 months of this intervention; serum and urine will be collected on a monthly basis. Nanoplastics will be measured in liquid samples by pyrolysis-gas chromatography/mass spectrometry (Py-GC/MS). In addition, we will examine markers of disease (cytokines, neurodegeneration markers). Clinical metrics of cognition and disease progression will be assessed before and after treatment. Study can be expanded to partner institutes in the USA and Poland, which would 1) provide more confidence in outcomes and 2) inform regarding geographical differences in exposures. We would also conduct plastics assessments in diets to compile a quantitative comparison of exposures between groups and link to serum and urine levels to better understand uptake and elimination of nanoplastics.

1.2 Clinical Studies: Survey of the Nanoplastic Landscape in Normal, Dementia, and Parkinson's Disease Brains.

Conducting 3-D sampling using donor brains from the ADRC and Office of the Medical Investigator, we can conduct a thorough exploration fo the regional differences throughout major functional regions of the brain (e.g., frontal cortex, hippocampus, thalamus, cerebellum, etc) and construct 3D models to compare between different individuals and across these major diseases. Understanding the presence of plastics in the substantia nigra in Parkinson's disease, for example, might help us understand whether plastics can specifically impact dopaminergic centers.

1.3 Preclinical Mechanistic Studies: Does microplastics exposure drive neurodegeneration in mouse and cell culture models?

As human studies will provide mainly associative data, controlled exposure studies are needed to confirm whether plastics ingestion causes dementia or neurodegeneration. We will leverage our ocean-derived microplastics model, which is an environmentally relevant sample of aged plastics that are all <20 μm in diameter. Using mouse models that are prone to developing neurodegeneration (5xTgAD, LOAD3, etc), we will conduct dose-escalation studies to examine the changes in the brain biochemistry, histopathology, and behavior in response to the microplastics model.

We will conduct further studies in cell culture models to better understand how the ocean-derived microplastics models may affect the blood-brain barrier, trigger inflammation, and cause aggregation of key proteins (Tau, Abeta, etc).

2. Cardiovascular disease

2.1 Clinical Studies: How are nanoplastics trafficked to vascular lesions?

Building on the landmark New England Journal of Medicine study performed by Dr. Rafaele Marfella's group in Italy showing Links between plastics in arterial lesions and the risk of having a later heart attack. Our work in collaboration with UNM vascular Surgeon Dr. Ross Clark not only confirms these findings in carotid and coronary lesions, but also reveals significant differences in nanoplastic concentrations between non-diseased carotid arteries, asymptomatic carotid plaques, and plaques form patients with acute ischemic symptoms. This is a profound and clinically significant discovery, suggesting that nanoplastic accumulation may directly contribute to plaque formation and the transition from a silent disease to life-threatening cardiovascular events.

We are positioned to dive deeper to understand the links between nanoplastic distribution in carotid and coronary lesions, determine the specific cell types in which nanoplastics are localizing, and define how they alter transcriptomic and proteomic profiles of those cells. These studies will provide mechanistic insight into how nanoplastics influence vascular health, identify potential biomarker and therapeutic targets for nanoplastics associated atherosclerosis.

2.2 Clinical Studies: Can a low plastics diet improve cardiovascular risk factors?

Using a similar approach from the dementia studies, we will select a cohort of low- and high-risk subjects for randomization onto a low plastics diet or a non-intervention diet. Over six months, we will assess plastics (and plasticizing chemicals) levels in blood and urine, as well as collect clinical imaging for atherosclerosis markers (ultrasound, spiral-CT).

2.3 Preclinical studies: Models of atherosclerosis and vascular inflammation

Again, causality will need to be shown with the controlled exposures to microplastics in rodent chow studies and in cell culture models. Atherosclerosis models and assays to examine the impact of nanoplastics on inflammation pathways and plaque progression will be studied.

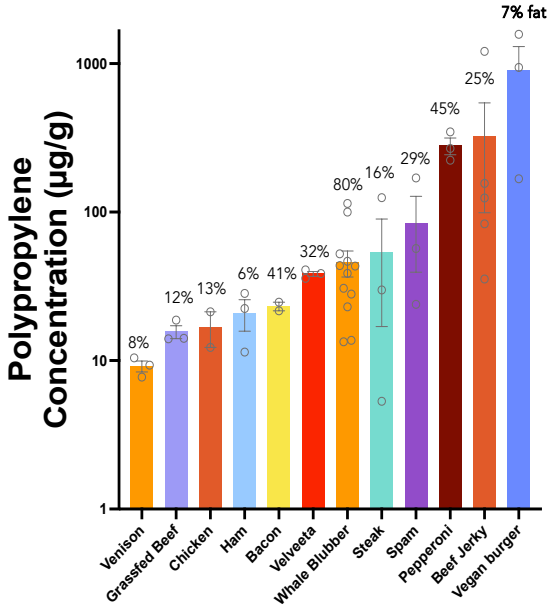

Figure 2. Assessments of polymers (specifically polypropylene, on a log10 scale) in samples of meats by py-GC/MS suggests that processed foods contain substantially higher concentrations. The fat percentage of each meat is listed atop each bar, to highlight that the plastics measured is better correlated with processing than with lipid content.

3. Understanding the exposure

A major question relates to how we are exposed. What requires in-depth research is the distribution of plastics in our *agricultural pathways* and in communities without conventional modern waste disposal resources. A comprehensive assessment of

plastics in major foods would be the best information for the public to help avoid exposures. In recent studies, we have shown that highly processed foods like spam, pepperoni, and vegan burgers have far greater plastics than naturally raised meats like venison and grass-fed beef. This program will launch a more complete assessment of fruits, vegetables, starches, and meats that addresses differences in geography and agricultural practices. We will also study the inputs to the agricultural system and where risks of contamination exist, such that strategies to avoid nanoplastics uptake in food can be implemented.