# Exhibit 129

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THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

**Biological Mechanisms of Dopaminergic Neurotoxicity from Trichloroethylene Exposure**

**Qualifications**

I am a Neurotoxicologist and Assistant Professor within the Center for Neurodegeneration and Experimental Therapeutics, Department of Neurology, University of Alabama at Birmingham (UAB). I have a secondary appointment within the Department of Pharmacology and Toxicology at UAB. I hold Associate Scientist positions within the UAB School of Medicine, the Comprehensive Neuroscience Center, the Center for Clinical and Translational Science, and the McKnight Brain Institute. I have held these current positions since 2020.

I received my PhD in Toxicology from the Department of Environmental and Radiological Health Sciences at Colorado State University, in Fort Collins, CO. I trained with Dr. J. Timothy Greenamyre as a Postdoctoral Fellow in the Pittsburgh Institute for Neurodegenerative Diseases within the Neurology Department at the University of Pittsburgh in Pittsburgh, PA. My research has focused on understanding the molecular and cellular mechanisms that cause Parkinson's related neurodegeneration from exposure to exogenous toxicants, and I have used cellular and animal experimental models to measure neurotoxicity.

At UAB, I direct a research lab focused on the mechanisms of neurotoxicity that cause neurodegeneration in Parkinson's disease (PD) and other parkinsonisms, such as Dementia with Lewy Bodies (DLB), from exposure to environmental toxicants, particularly the organic solvent trichloroethylene (TCE). I am an Associate Editor for the peer reviewed Elsevier journal *NeuroToxicology,* and I am a member of the scientific advisory committee for environmental risks for PD for the Michael. J. Fox Foundation. My research is funded through awards from the National Institutes of Health, the US Department of Defense, the Parkinson's Foundation, the American Parkinson's Disease Association, and the Parkinson's Association of Alabama. My curriculum vitae with a link to my published citations is attached to this report.

As part of my research and professional activities, I keep up to date on scientific literature relating to environmental risk factors for PD. Prior to my involvement in this case, I had previously reviewed and was familiar with the toxicological and epidemiological literature relating to the association between solvent exposures and PD, including peer reviewed, published literature related to exposures at Camp Lejeune, North Carolina. The terminology used in my peer reviewed publications follows the field standard of identifying exogenous factors that cause elevated risk for PD, and their mechanisms, based on statistically significant results determined *a priori* by statistical power. For the purposes of this report and where relevant, I have applied the standards and terminology used under legal review, which I have been instructed in this case to be, "equally as likely as not," regarding risk for PD from sustained exposures to TCE and other solvents.

**In Brief:**

***Questions Presented*: I was asked to evaluate evidence whether TCE exposure could cause the neuropathology that underlies Parkinson's disease, and Parkinson's risk.**

***Summary of Opinions*: To a reasonable degree of scientific probability, my opinions are that TCE can cause neurotoxicity that recapitulates the pathological hallmarks of Parkinson's disease; dopaminergic neurodegeneration, alpha-synuclein accumulation, and neuroinflammation. My assessment is that published epidemiological data shows that TCE exposure causes increased risk for Parkinson's disease, and experimental evidence supports a biological basis for the**

**underlying neuropathology that drives Parkinson's neurodegeneration. Thus, based upon my analysis of the scientific evidence, including the consistency between the three pillars of research science, epidemiological studies, *in vivo* experimental studies, and mechanistic data, it is my professional opinion that supports a conclusion that TCE exposure is more likely than not, known to cause Parkinson's disease. My opinions are based upon my education, training, experience, and research in the field of Neurotoxicology and Parkinson's disease.**

***Methodology:*** **The methods I used to assess these conclusions applied the same standards as I would use in preclinical research and peer review. These included, reviewing robust and rigorous peer-reviewed literature on epidemiological and experimental studies related to TCE exposure and Parkinson's disease risk, assessing the statistical significance of reported outcome measures in relation to the statistical power and effect size, and weighing the limitations of published data.**

**Executive Summary**

Parkinson's disease (PD) is the most common neurodegenerative movement disorder and is a progressive disease that manifests with motor and non-motor symptoms. The key neuropathological hallmarks of PD are (1) the loss of dopaminergic neurons within the substantia nigra (SN) and their terminal projections to the caudate putamen (also called the striatum), and (2) the accumulation of Lewy bodies, which are protein inclusions within neurons comprised of aggregated alpha-synuclein (αSyn)[4,5]. A third hallmark, neuroinflammation, is considered to be both a consequence of neuron death and dysfunction, as well as a contributor to the pathogenesis and progression of PD[6,7].

Genetic risk for PD has been extensively characterized[8], and while there are several inherited mutations in genes associated with increased disease risk, only about 10-30% of PD cases can be attributed in some manner to genetic mutations[9]. Thus, most PD is considered *idiopathic* – a term suggesting that the underlying cause is spontaneous, and does not originate from inherited mutations alone[10]. In line with this, published epidemiological and experimental data strongly support the conclusion that PD risk is influenced by certain types of environmental exposures, including industrial byproducts like organic solvents and pesticides[11].

In relation to this case, both epidemiological and experimental evidence support a link to PD risk from exposure to chlorinated organic solvents, such as trichloroethylene (TCE)[1,3,12-17].

- **Epidemiological:** Published data from a retrospective cohort study comparing PD risk in veterans from the Camp Lejeune Marine Base in North Carolina, where TCE and other solvents contaminated the water (e.g., perchloroethylene [PCE]), and veterans from Camp Pendleton, California, that did not report the same contamination, shows 70% increased PD risk in veterans who resided at Camp Lejeune (Odds Ratio 1.70; 95%CI: 1.39-2.07)[14]. Furthermore, individuals who were exposed to TCE (and PCE) contaminated water appear to also display faster progression of the disease, with increase hazard ratios (HRs) for fall (HR 2.64, 95% confidence interval [CI]: 0.97-7.21), fracture (HR 2.44, 95% CI: 0.91-6.55), and psychosis (HR 2.19, 95% CI: 0.99-4.83)[13], which are symptoms of PD phenotype and progression. The Goldman et al., 2023, and 2024 studies provide strong evidence that TCE exposure, modeled at a median level of 0.366 mg/L[18], causes a significantly increased risk for Parkinson's disease over an average of three months of exposure[13,14].
- **Experimental:** Published data from laboratory studies in rats and mice show that exposure to TCE causes the selective degeneration of dopaminergic neurons from the SN and their terminal projections to the striatum in brain tissue[1,3,15-17], the key pathological hallmark of PD in humans. In addition to dopaminergic neuron loss, animals exposed to TCE display the accumulation of αSyn within neurons of the SN[3,15,16], the main component of Lewy bodies, as well as neuroinflammation marked by activated microglia, the resident immune cells of the brain[1,3,16]. Thus, experimental data supports biological plausibility for the development of PD from TCE exposure, where animals exposed to TCE under controlled conditions recapitulate hallmark PD pathology.

Taken together, and discussed in detail below, there are several lines of evidence that establish a link to PD development from TCE exposure, as well as a tendency towards increased morbidity or progression. In the following report, I will further detail the mechanisms that underlie PD risk from TCE exposure from a toxicological perspective, the methodology applied to reach these conclusions, and sum of the evidence supporting a relationship between TCE exposure and PD pathology.

**Introduction to Parkinson's disease**

Parkinson's disease (PD) is a progressive, neurodegenerative disorder that causes both motor (e.g. resting tremor, slowed movements, postural instability) and non-motor disease symptoms (e.g. loss of smell, dementia, psychosis, gastrointestinal issues, pain)[19]. Most PD – approximately 70-90% – is considered idiopathic[8], with no known genetic mutations that increase inherited risk for the disease, and conversely, a large body of evidence suggests that environmental exposures heavily influence idiopathic PD risk[20]. In addition, the most commonly inherited genetic risk factors for PD, such as mutations in LRRK2 and GBA*, display incomplete penetrance[8], which indicates that not all individuals who inherit these mutation are diagnosed with PD. Thus, only a subset of those with the inherited risk genes actually develop PD, indicating that other exogenous risk factors, such as environmental exposures, play a role in the pathogenesis of most PD cases[20].

**Parkinson's Neuropathology**

The major hallmark brain pathologies of PD are: (1) the loss of dopamine producing neurons from the substantia nigra (SN) and their axon projections to the caudate putamen (striatum), and (2) intracellular protein accumulation of α-synuclein (αSyn) into inclusions called Lewy bodies and Lewy neurites, which aggregate in presynaptic neurons and spread throughout the brain as the disease progresses (**Figure 1**)[19]. Neuroinflammation is also a key pathological outcome in PD, driven by the activation of microglia, the resident immune cells of the brain, infiltrating immune cells from the periphery (e.g., monocytes, T cells, B cells), and the soluble cytokines and chemokines produced by these cells to perpetuate inflammation.

Many of the mechanisms driving PD etiology are predicated on evidence that dopaminergic neurons in the SN are a ***selectively vulnerable*** population of cells in the brain, causing these neurons to be at increased risk for degeneration in relation to other neuron subtypes[21,22]. Selective vulnerability of nigral dopaminergic neurons stems from several key factors including (1) long, extensively branched axons, (2) high energetic demands, (3) the reactivity of dopamine and its ability to be oxidized and cause oxidation[21]. Because of this, dopaminergic neurons are highly vulnerable to ***mitochondrial dysfunction***, which when disrupted, causes oxidative stress, reduced energy production, and ultimately, may cause the death of neurons[22].

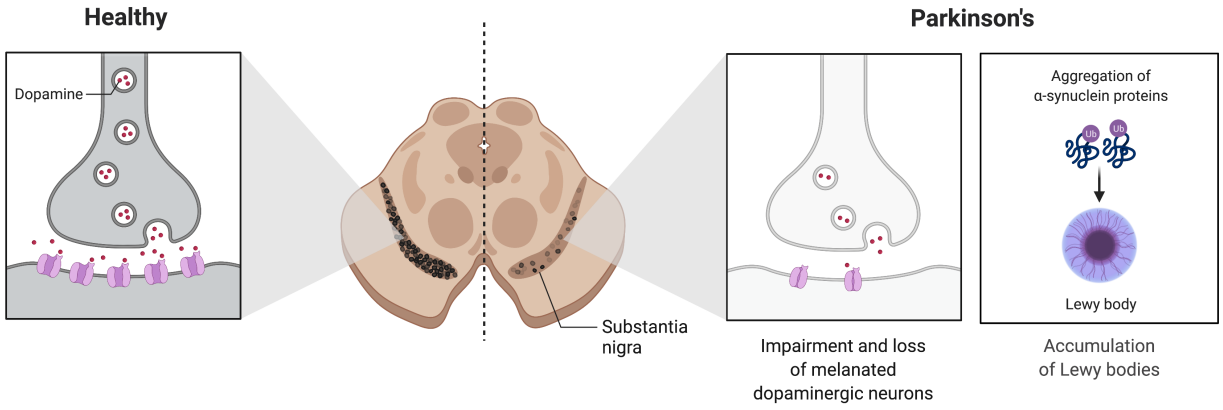



**Figure 1. Neuropathology of Parkinson's disease.** Dopaminergic neurons are melanated cells (pigmented with neuromelanin, giving rise to the nucleus name *substantia nigra*). Lewy bodies are protein aggregated within dopaminergic neurons, and are comprised mainly of the protein α-synuclein.

As PD is classified as a **synucleinopathy**, the accumulation and aggregation of αSyn also plays a key role in the pathogenesis of the neurologic disorder[23,24]. αSyn is a protein with a putative role in presynaptic neurotransmitter release[24], and typically exists as a monomeric protein that is considered intrinsically disordered[25], forming an alpha helical structure when bound to biological membranes[24]. Under pathologic conditions, αSyn misfolding into oligomers and fibrils causes its aggregation, resulting in toxicity to neurons both from the loss of its normal function and the direct damage caused by protein aggregation within the cell[26] (also reviewed extensively in Stefanis et al., 2012[25]). The multifactorial damage caused by aSyn in dopaminergic neurons can ultimately cause cell death and the chronic accumulation into Lewy bodies[27].

* Leucine rich repeat kinase 2 (LRRK2), Glucocerebrosidase (GBA)

In PD, αSyn aggregation into Lewy pathology spreads throughout the brain in a predicted pattern defined by Heiko Braak (known as the Braak hypothesis), from the brainstem throughout the cortex, resulting in the possibility to stage PD based on the severity of αSyn or Lewy pathology[28]. Not all PD cases follow this exact pattern of αSyn aggregation[29], and though rare, some PD cases may have little to no Lewy pathology[30]. However, there is strong evidence that αSyn misfolding and aggregation is one of the most important pathological events in PD pathogenesis, as a new type of biomarker for PD, the αSyn Seeding Amplification Assays (SAA) that detects misfolded αSyn in cerebrospinal fluid and skin biopsies[31], shows remarkable accuracy in diagnosis PD cases and even individuals considered to be in the prodromal† phase of the disease[32]. In addition to αSyn accumulation in the brain, elevated levels of misfolded αSyn are present in peripheral tissues of individuals with PD, particularly in the gut, further showing that PD is a systemic disorder, affecting multiple organ systems[33-36].

**Environmental Exposure and PD Risk**

A number of environmental contaminants increase risk for PD, such as pesticides, metals, and industrial solvents[37], including TCE[38]. While structurally different, each of these environmental contaminants share common pathways of toxicity for dopaminergic neurons, such as oxidative stress, mitochondrial dysfunction, neuroinflammation, and impairment of lysosomal function, which can cause the accumulation of protein including αSyn[23]. Published data also suggests that **chlorinated solvents, in particular TCE, represent a risk factor for dopaminergic neurotoxicity, which can ultimately result in PD development** if an individual or population sustains exposure to these industrial chemicals[12,38].

**Trichloroethylene (TCE)**

One of the most common organic solvents, TCE has been used as an effective degreasing agent for over a century. Biological exposure to TCE occurs in three ways: (1) inhalation, (2) ingestion, and (3) dermal exposure. TCE may contaminate soil or water, however, as a volatile organic compound (VOC), TCE can evaporate from its liquid form to a vapor, which is then inhaled[39,40]. Thus, the predominant method of TCE exposure is inhalation, even when drinking water or soil is the major contamination site, which results in both ingestion and inhalation exposure simultaneously. An example of this could be in a home that has contaminated drinking water, TCE exposure may occur through ingestion (drinking water) and through inhalation, as TCE off-gasses in the home as water is heated for cooking or bathing. Dermal exposure to TCE might occur with contact with contaminated water[41].

Exposure to TCE results in its distribution to every tissue and compartment of the body, as TCE is a lipophilic, small molecule that readily passes through biological membranes[42]. A primary site of exposure for TCE following inhalation is the brain and central nervous system (CNS), which causes the immediate neurological effects reported from acute TCE exposure – dizziness, sleepiness, and reduced reaction time[42]. Following absorption, TCE is extensively metabolized to putative reactive metabolites that further elicit biological toxicity, such as trichloroethanol (TCOH), trichloroacetic acid (TCA), S-(1,2-dichlorovinyl)glutathione (DCVG), and 1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline (TaClo) (**Figure 2**)[43-49].

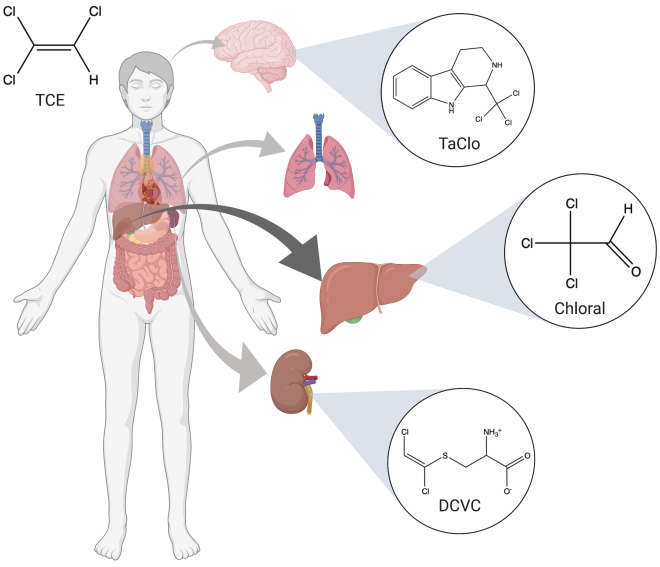



**Figure 2. Exposure to TCE.** Exposure to TCE predominantly occurs via inhalation, but TCE may be ingested in drinking water, or through dermal contact. TCE is extensively metabolized by the liver and kidney, which produces metabolites that cause toxicity to certain organs, such as chloral, DCVC, and TaClo.

**Epidemiological Evidence of PD Risk from TCE**

In addition to the reported acute neurological effects of TCE, chronic exposure to TCE is linked to elevated risk for PD development[12,14], with the largest (N=155,122) retrospective cohort showing a 70% increase in risk for PD for veterans exposed to TCE and other solvents at Camp Lejeune, NC at an estimated median water

† Prodromal: the course of PD pathogenesis prior to clinical diagnosis from motor symptoms

concentration of 366 µg/L[18], compared to veterans from Camp Pendleton, CA without the same reported TCE contamination (Odds Ratio 1.70; 95%CI: 1.39-2.07)[14]. Given the large sample size of this study, the robust data collected by Veterans Affairs, and the narrow confidence interval[50], this study represents highly rigorous epidemiological evidence linking exposure to TCE and other solvents to PD risk. These data were expounded upon in a follow up study, where individuals exposed to TCE and other solvents at Camp Lejeune also appear to have a faster rate of PD progression, resulting in higher hazard ratios for fall (HR 2.64, 95% confidence interval [CI]: 0.97-7.21), fracture (HR 2.44, 95% CI: 0.91-6.55), and psychosis (HR 2.19, 95% CI: 0.99-4.83), indicative of worsened motor symptoms[13]. These data expand on one of the first studies to systematically identify PD risk from TCE exposure, Gash et al., 2008, which characterized a cluster of PD cases in relation to their proximity to an open vat of TCE[51]. As idiopathic PD is a disease of aging[52], many PD cases from TCE exposure are predicted to continue to rise[53]. Thus, as epidemiological data continues to develop, experimental data to support a biological basis for PD risk from TCE exposure provide key information on how this environmental risk factor could cause the specific type of neurotoxicity that results in clinical, idiopathic PD diagnosis.

**Experimental Evidence of Parkinsonian Neurotoxicity from TCE**

In support of the epidemiological link to PD, published experimental studies show that systemic exposure to TCE in laboratory animals results in toxicity to vulnerable populations of neurons, namely, the dopaminergic neurons of the SN[3,15,17,54]. In addition to dopaminergic neurodegeneration, αSyn accumulation, neuroinflammation, and other pathological pathways that lead to parkinsonism are also replicated in experimental TCE studies[3,15,16]. For example, inhalation exposure to 50 ppm of TCE for 7 hours a day, 5 days per week for 8 weeks caused significant and selective dopaminergic neurodegeneration in adult rats ($p < 0.0001$), consistent with a parkinsonian lesion (**Figure 3**)[3]. TCE-induced loss of dopaminergic neurons also caused a reduction in locomotor activity and gait disturbances in adult rats, similar to the motor impairments characterized in human PD[3]. In addition to the death of dopaminergic neurons in the SN, published data shows animals exposed to TCE also exhibit other hallmark PD pathology, such as the accumulation of αSyn, neuroinflammation, and oxidative stress[1,3,15].

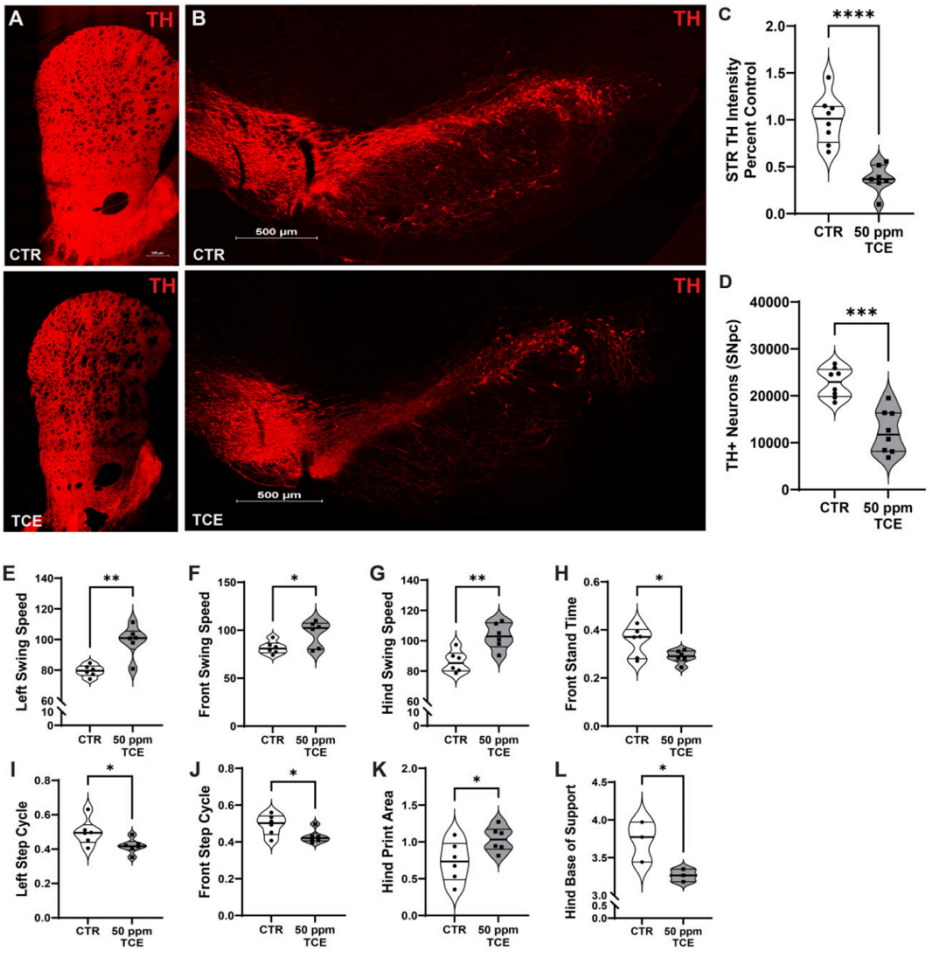



**Figure 3. Inhalation exposure to TCE induces nigrostriatal dopaminergic neurodegeneration and motor deficits in adult Lewis rats.** Representative images (20x) of 35 *µ*m brain tissue sections of the striatum (A) and substantia nigra (B) immunostained for tyrosine hydroxylase (TH) from male and female Lewis rats exposed to 50 ppm TCE inhalation or filtered room air (control). Quantification of dopaminergic terminal loss from the striatum (C) and dopaminergic neuron loss from the SNpc (D). Quantitative parameters measured from the Noldus CatWalk XT gait analysis system showed significant differences in left swing speed ($p = 0.0012$; E), front swing speed ($p = 0.0350$; F), hind swing speed ($p = 0.0040$; G), front stand time ($p = 0.0437$; H), left step cycle ($p = 0.0479$; I), front step cycle ($p = 0.0400$; J), hind print area ($p = 0.0041$; K), and hind base of support ($p = 0.0453$; L). Statistical analysis unpaired t-test, error bars represent SEM, (N = 8). Data published in Adamson et al., 2023, *Toxicological Sciences.*

There is a high degree of concordance across published experimental studies that TCE treatment can cause dopaminergic neurodegeneration in rodents[1,3,15,16,54-56]. Prior to the development of the inhalation exposure system characterized in Adamson et al., 2023[3], many studies relied on oral delivery of TCE in systems of adult rats or mice, which necessitated higher doses (e.g., 200 – 1000 mg/kg) due to the first pass hepatic metabolism of TCE in the liver[45,46,57,58], and elevated metabolism rates of TCE in rodents comparatively to humans[44]. Thus, while the dose used in some experimental model systems is considered high, the assumed resulting brain concentrations can still inform proof-of-principle mechanisms involved in parkinsonian neurodegeneration (further discussed below). Importantly, these studies all concluded that ***systemic TCE exposure in rodents caused the selective loss of dopaminergic neurons***, as well as other key PD pathology that can drive neurodegeneration such as αSyn aggregation and neuroinflammation and the molecular mechanisms responsible for inducing this observed cellular dysfunction.

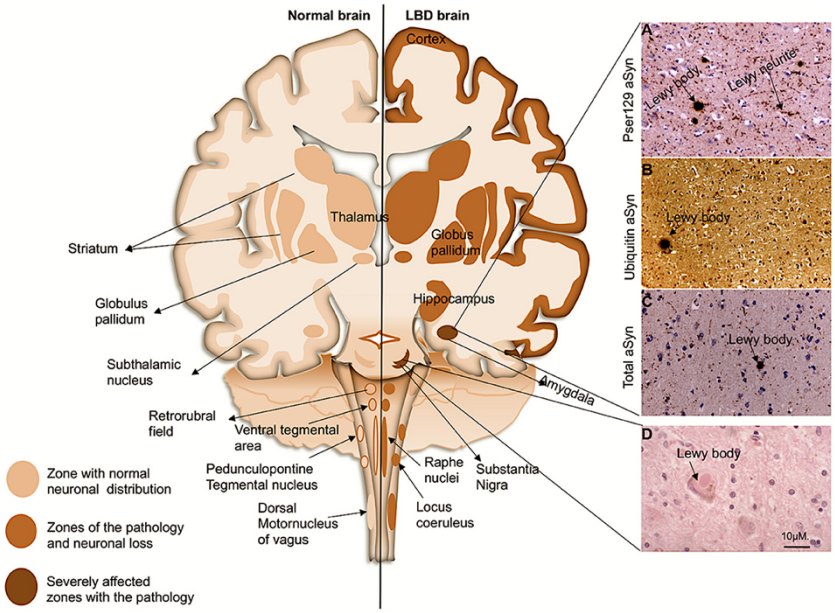



**Figure 4. αSyn accumulation in Lewy pathologies.** αSyn is the primary accumulating protein in Lewy pathologies/synucleinopathies such as PD and can affect disease severity. As shown in this review figure, αSyn aggregation and spread occurs in regions of the brain affected in PD such as the SN, globus palladus, and into the cortex. αSyn severity can affect disease presentation and cognitive impairment in PD. *Figure from de Oliveira Manzana et al., 2021[2].*

## Experimental TCE Exposure Induces αSyn Accumulation

As previously stated, PD is classified as a synucleinopathy, a disease in which the primary aggregated protein in the brain is αSyn[59]. One functional measure of αSyn aggregation is the accumulation of phosphorylated αSyn, in particular, phospho-129-αSyn (pSer129-αSyn), a residue associated with toxic forms of αSyn that are more likely to aggregate or have aggregated[60], as shown in the review **Figure 4**. The type and severity of protein accumulation in the brain can also determine disease ***phenotype***, the clinical manifestation of pathological disease sequelae[61].

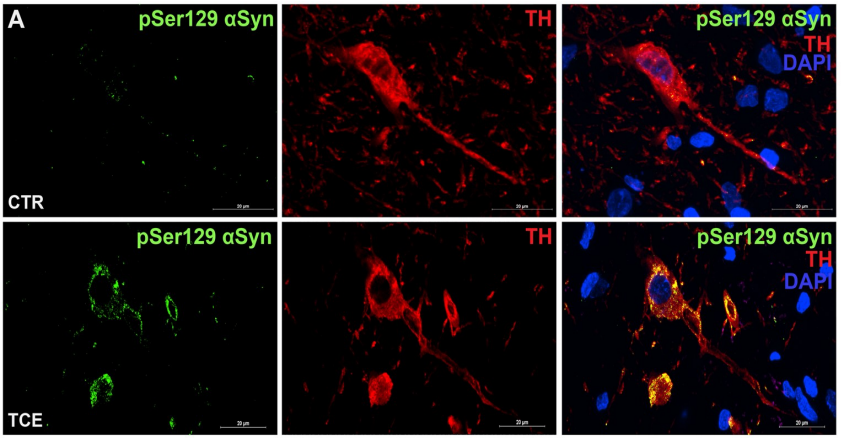



**Figure 5. TCE exposure caused αSyn accumulation in dopaminergic neurons.** pSer129-αSyn (green) is accumulated in dopaminergic (TH, red) neurons in the SN from animals exposed to 50 ppm TCE for 8 weeks. P=0.0049 N=9). *Figure from Adamson et al., 2023[3].*

While parkinsonism is an umbrella term, individuals may be diagnosed with PD, Parkinson's disease dementia (PDD), and Dementia with Lewy Bodies (DLB), which are defined clinically by the timing of cognitive and motor symptoms[62]. Individuals with worsened protein aggregation typically present with cognitive symptoms earlier in the disease course[61], and therefore may be considered PDD or DLB[62]. Given that PD is predominantly idiopathic, it has been posited that environmental exposures could influence the type of PD an individual presents with[11,63]. For example, TCE inhalation exposure in rats (50 ppm of TCE for 8 weeks) caused a significant aggregation of

pSer129-αSyn within dopaminergic neurons of the SN (**Figure 5**)[3], which is consistent with published data from other systems of TCE exposure[15,16,64].

**TCE Exposure Elevates Neuroinflammation**

Along with dopaminergic neurodegeneration and αSyn aggregation, another hallmark pathology of PD is neuroinflammation[65]. In the brain, inflammation is regulated by resident immune cells microglia, which are of myeloid lineage (arise from bone marrow)[66]. Under normal conditions, microglia survey their microenvironment for pathogens and cell damage with their long, branched processes, resulting in a cellular morphology termed ramified or "resting"[67]. When microglia sense pathogenic or damaged cell material, they become activated, typically resulting in a morphological shift to an ***amoeboid shape*** indicative of the cell phagocytosing debris from damaged neurons or other glial cells[67]. An example of microglial morphology is shown in **Figure 6**, a graphic representation of microglia published in Lecours et al., 2018[68], a review paper on microglia in PD.

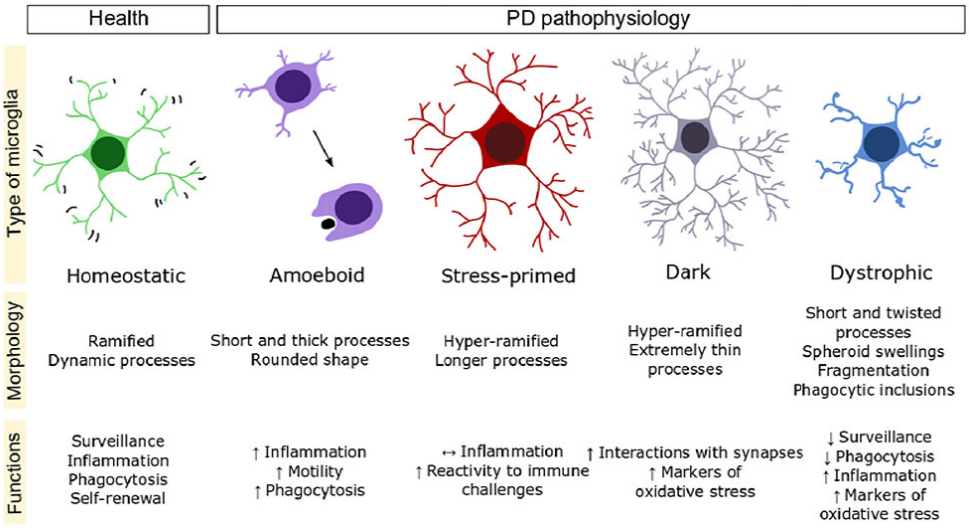



**Figure 6. Types of microglia observed in PD.** *Figure from Lecours et al., 2018.*

Microglial morphology can be used to measure whether microglia are activated in rodent brain tissue from TCE exposure. In addition to morphology, one of the most reliable ways to quantify the activated status of microglia is by measuring the protein CD68, a lysosomal protein that becomes enlarged in activated, amoeboid microglia[69]. As noted in **Figure 7**, rats exposed to 50 ppm of TCE for 8 weeks displayed activated microglia within the substantia nigra brain region, around dopaminergic neurons that are dead or degenerating, which can also be visualized in **Figure 7A** (dopaminergic neurons; red)[3]. As visualized in **Figure 7B**, microglia displayed activated morphology (IBA1, magenta), with reduced branching and more amoeboid shape. These immune cells also

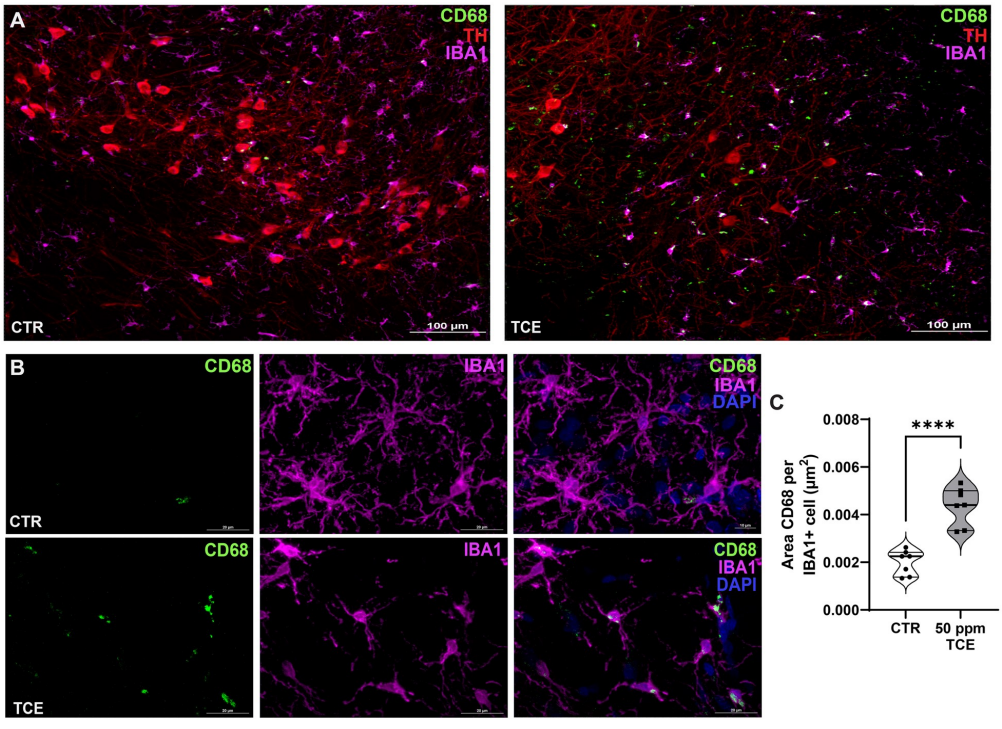



**Figure 7. Microglial activation was observed in the substantia nigra of adult rats exposed to TCE via inhalation.** Markers of microglial activation were measured using IHC in male and female Lewis rats. (A and B) Representative confocal images (20× and 60×) of phagocytic activation marker CD68 (green) within microglia immunoreactive for IBA1 in the SN (magenta). (C) Quantification of CD68 area within microglia following TCE exposure ($p = .0117$). Statistical analysis unpaired *t* test, density curves visually reflect the distribution of the data, ($N = 8$ vehicle, 8 TCE). *Figure and legend from Adamson et al., 2023[3].*

expressed significantly expanded CD68 protein (green; p<0.0001), a marker of activated glia. Activated microglia have similarly been reported in brain tissue of other TCE exposure systems[15,16], and has been linked to neuroinflammation[70,71].

While microglial activation may be induced in part from signaling sent from degenerating neurons, chronic neuroinflammation is a damaging pathological feature of PD, and contributes to the progression of the disease[7,72]. Both the innate and adaptive immune response play a role in PD-related neuroinflammation[73-75], and both may be involved in the inflammatory damage caused by TCE exposure. As described, microglia, which are part of the ***innate immune system,*** become activated in the brain of TCE exposed rodents. However, TCE is also linked to dysfunction in the ***adaptive immune system***, as it has been implicated in activation of CD4+T cells[70,71,76-81]. There is evidence that CD4+T cells are specifically involved in αSyn-mediated neurodegeneration, with both human and experimental evidence showing a relationship between CD4+ T cell activation and αSyn accumulation[74,75,82,83]. Thus, TCE may influence neuroinflammation and neurodegeneration by the activation of the adaptive immune system, which could have implications in the accumulation and toxicity of αSyn.

**Experimental TCE Exposure Recapitulates PD Pathology *In Vivo***

PD is a complex neurological disorder, but several pathological hallmarks define the disease including (1) the loss of dopaminergic neurons from the nigrostriatal tract, (2) the accumulation of αSyn, and (3) sustained and damaging neuroinflammation[4]. While no model system is a perfect replication of human disease, TCE exposure in experimental models can recapitulate several hallmarks of PD pathology. Furthermore, the loss of dopaminergic neurons in the brain of rats and mice caused functional deficits in motor behavior that mirrors some of the motor dysfunction observed in humans, such as slowed and asymmetric gait (as published in Adamson et al., 2023). Taken together, there is strong experimental evidence that systemic TCE exposure results in specific brain pathology that aligns with idiopathic PD. In the sections below, the mechanisms of how this may occur are discussed in further detail.

***Mechanisms of TCE induced neurodegeneration***

**The role of mitochondrial dysfunction in TCE-induced neurodegeneration**

One of the earliest predictions for the mechanism by which TCE induced dopaminergic neurodegeneration was mitochondrial dysfunction[51]. As previously noted, dopaminergic neurons are highly vulnerable to mitochondrial dysfunction, particularly from exogenous chemicals that impair mitochondrial electron transport[84-87]. In Gash et al., 2008, an experimental exposure to TCE in adult male Fisher 344 rats showed a reduction in mitochondrial function in brain tissue compared to vehicle exposed animals[51]. This appeared to be largely and specifically due to a reduction in activity levels of mitochondrial **electron transport complex I**, which is a common pathological feature of PD-associated environmental toxicants[85,88], and is a molecular mechanism implicated in PD pathogenesis[89]. For example, the organic pesticide rotenone is a prototypical inhibitor of mitochondrial complex I, and also causes the selective degeneration of dopaminergic neurons in animal models of PD[90,91]. Similarly, the synthetic chemical 1-methyl-4-pheny-1,2,3,6, tetrahydropyridine (MPTP) which is used extensively in experimental settings to induce parkinsonian pathology from dopaminergic neurodegeneration, works predominantly by inhibiting complex I[85,92,93]. Thus, there is a biological basis that mitochondrial dysfunction driven by TCE exposure is a mechanism by which TCE selectively damages dopaminergic neurons.

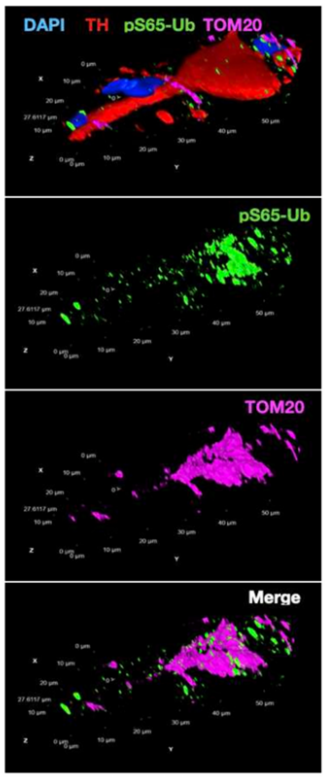



**Figure 8. TCE caused damage to mitochondria in dopaminergic neurons of exposed rats.** Adult female Lewis rats exposed to 200 mg/kg TCE for 6 weeks displayed elevated pS65-Ubiquitin (pS65-Ub, green) that colocalized with TOM20 (magenta) a marker for mitochondria in dopaminergic neurons (TH, red) of the SN. Image is a volumetric (3-dimensional) projection of a single dopaminergic neuron from the rat brain. Figure adapted from Ilieva et al., 2024[1].

In addition to direct complex I inhibition, other evidence suggests that mitochondrial dysfunction is a driving pathology of TCE neurotoxicity. For example, oxidative damage is significantly elevated in dopaminergic neurons

within the SN of animals exposed to TCE[1,15,16,94], which is evidence that reactive oxygen species (ROS) released by impaired or damaged mitochondria caused oxidative damage to cellular macromolecules[95]. In addition, direct evidence of mitochondrial damage was visible in dopaminergic neurons of rats exposed to TCE using a marker that is specific for mitochondrial damage (pS65-Ubiquitin; **Figure 8**)[1]. In postmortem PD brain tissue, markers of both mitochondrial dysfunction and oxidative stress‡ are consistently measured[96], including pS65-Ubiquitin, which is being investigated as a potential PD biomarker[97]. Functionally, oxidative stress is implicated as a mechanism driving nearly all PD pathology, including the selective vulnerability of dopaminergic neurons to cell death as well as αSyn aggregation and neuroinflammation[22,23,98,99]. Thus, there is evidence that TCE can induce mitochondrial damage that results in the selective degeneration of dopaminergic neurons, which contributes to neurodegeneration and other hallmark PD pathology.

**The role of endolysosomal impairment in TCE-induced neurodegeneration**

As noted, PD is a synucleinopathy, which involves the pathogenic accumulation of αSyn protein within cells, causing neuronal dysfunction, neuroinflammation, and neurodegeneration[23,61,100]. Underlying the accumulation of cellular protein is dysfunction within the systems that breakdown protein for removal, which the autophagy-lysosomal pathway (ALP), made up by vesicles (e.g., endosomes, lysosomes) that traffic along microtubules within the cell[101], and the proteasome[102]. In PD, dysfunction within systems that regulate proteostasis (ALP and proteasomal) is correlated with disease pathogenesis, with evidence that impairment of the endolysosomal system is an early and important pathogenic feature[103]. Additionally, ALP dysfunction is linked to PD through genetic mutations that are associated with risk for the disease, such as the lysosomal hydrolase glucocerebrosidase, which causes increased PD risk in individuals who carry mutations in its gene, *GBA1*[104]. Published evidence suggests that αSyn is predominantly broken down via the ALP[105], in a process involving chaperone-mediated autophagy (CMA) at the lysosome[106]. Thus, dysfunction in ALP and other protein degradation pathways is thought to cause, at least in part, the accumulation of Lewy pathology in PD and other neurodegenerative diseases[107].

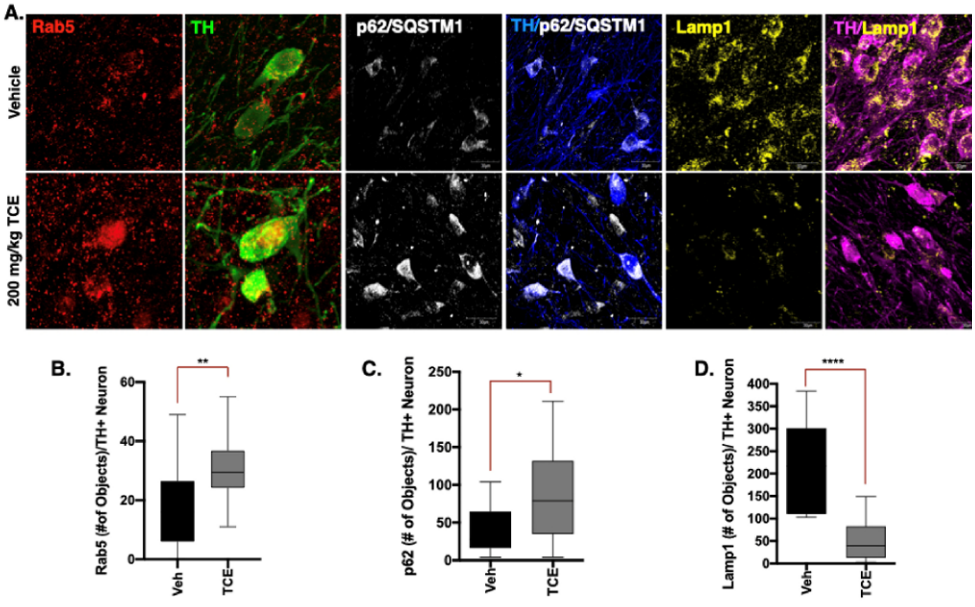



**Figure 9. Endolysosomal dysfunction and protein accumulation occurs in dopaminergic neurons of TCE-treated rats. A.** Representative confocal images of Rab5 (200x, red), p62/SQSTM1 (100x, white), and Lamp1 (100x, yellow) in the SNpc of vehicle or TCE treated rats at 200 mg/kg for 6 weeks (counterstained for TH, green, blue, magenta, respectively). **B.** The early endosome marker Rab5 is significantly elevated in dopaminergic neurons in the SNpc of rats exposed to TCE ($p$ = 0.0087). **C.** The ubiquitin like protein p62/SQSTM1 is also significantly elevated in TCE treated rats ($p$ = 0.035). **D.** The lysosomal membrane protein Lamp1 is significantly reduced in dopaminergic neurons of rats treated with TCE ($p$ < 0.0001). Figure from *De Miranda et al., 2021.*

In line with this, there is evidence that protein degradation systems can be targets of environmental exposures[108], including TCE. For example, TCE exposure significantly reduced the expression of the late endosome-lysosome protein Lamp1, while protein destined for lysosomal degradation (p62/SQSTM1) accumulated within dopaminergic neurons of exposed rats (**Figure 9**)[15]. In addition, a marker for early endosomes (Rab5), which mature into late endosomes then lysosomes[109], was also accumulated in dopaminergic neurons of TCE exposed rats, suggesting that proper vesicular maturation along the ALP was impaired. Taken together, these data provide a biological basis for a molecular mechanism by which TCE could impair ALP function and influence αSyn accumulation and Lewy pathology.

‡ Oxidative stress: the cellular imbalance between reactive oxygen species and antioxidants to detoxify them

**Dose and the Complexities of Experimental TCE Exposures**

Most published experimental studies that specifically focus on neurodegeneration as the primary outcome measure used oral gavage to expose animals to TCE. The route of exposure to a volatile organic compound like TCE is important for brain concentrations; thus, a larger dose is likely necessary to produce equivalent brain concentrations as what might occur under conditions in human populations. Published data in Adamson et al., 2023 on TCE inhalation show that even with much lower doses of inhaled TCE, rats and mice had more severe dopaminergic neurodegeneration than animals that received TCE via oral gavage[3,15]. This can also be considered in the opposite direction, where the ingested dose of 200 mg/kg TCE in rats (corrected by the density of TCE 1.46 g/cm$^3$) is equivalent to 25,063.10 ppm. Therefore, in either direction the conversion shows that inhalation of TCE was 500x more potent than ingestion for dopaminergic toxicity in rats (**Appendix 1**). As referenced in Goldman et al., 2023, the estimated median TCE water concentration of the population assessed for PD risk was 0.366 mg/L[18].

The route of toxicant exposure is implicated in overall PD risk as well as disease phenotype, as reviewed in Chen et al., 2022 and Dorsey at al., 2024[11,63]. The topic is complex, however, a general hypothesis for PD risk stemming from inhalation toxicity is the lack of first-pass hepatic metabolism that occurs upon a nasal route of exposure[11,63,110]. As shown in **Figure 10**, TCE is extensively metabolized by cytochrome P450 (CYP) enzymes that have the highest concentration in the liver[111]. Thus, TCE may be less readily detoxified (or more slowly detoxified) when inhaled versus ingested[110]. In addition, inhalation is a more direct route to the brain, whether through the olfactory bulb or through circulatory perfusion from the lungs[112]. Under conditions of environmental contamination, such as drinking water contamination with TCE and other volatile organic chemicals, exposure to TCE could presumably occur through all routes – inhalation, ingestion, and dermal. For example, bathing and cooking with TCE contaminated water provides multiple routes of exposure simultaneously[42].

As previously mentioned, both inhalation and ingestion of TCE have been shown to cause dopaminergic neurotoxicity in experimental studies[1,3,15,16,56,94,113], however, published studies also show ingested TCE can influence gut microbiome changes[77,114,115], similar to gut microbiome dysbiosis observed in idiopathic PD[116-118]. Thus, as with any disease condition, experimental systems cannot replicate the complex conditions that occur in human populations, and instead, experimental modeling of neurodegeneration with TCE must be considered through the lens of the pathological conditions associated with disease phenotype observed in humans. Experimental models of TCE exposure can replicate hallmark cellular PD pathology with evidence for the same molecular mechanisms in the brain that are widely recognized as contributors to PD pathogenesis (e.g., mitochondrial and lysosomal dysfunction).

**Structurally Similar Chlorinated Solvent Neurotoxicity**

TCE represents one of many organic solvents that have been implicated in PD risk, as structurally similar compounds, such as tetrachloroethylene (PCE), are also associated with elevated PD risk from epidemiological studies[12]. Human exposure to chlorinated solvents rarely occurs in isolation, and exposure to a mixture of chlorinated solvents, for example simultaneous TCE and PCE exposure could cause additive[§] or synergistic[**] neurotoxicity[119]. As both TCE and PCE are metabolized through oxidation and conjugation metabolic pathways to produce the same or similar metabolites[43,120,121] (**Figure 10**) a combined exposure to two or more chlorinated solvents could result in even greater risk for parkinsonian neurotoxicity[38], which is

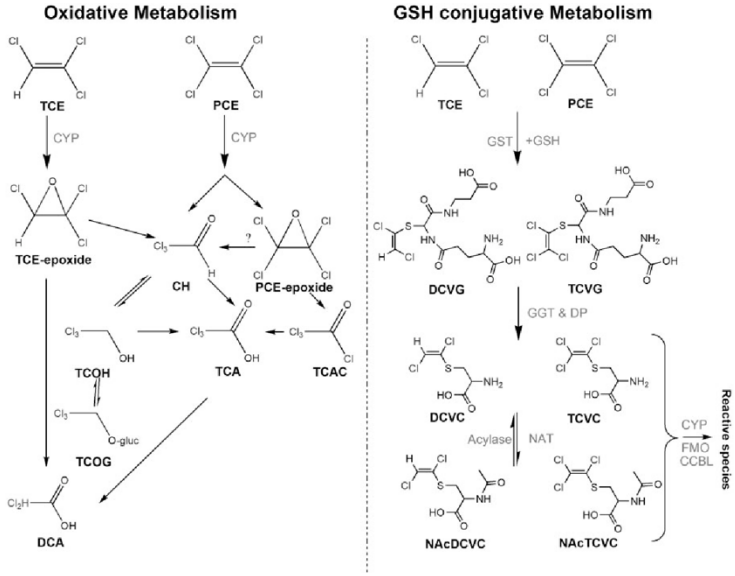



**Figure 10. TCE and PCE Metabolism.** *Figure from Lu et al., ToxSci, 2018.*

§ Additive toxicity: the combined effect of two or more chemicals is the sum of each chemical independently (e.g., added together).

** Synergistic toxicity: the combined effect of two or more chemicals is *greater* than the sum of each chemical independently.

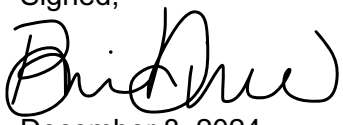
supported by data published in human epidemiological studies showing PD risk is associated with different types of solvent exposures[12]. As data are still emerging on PD and the risk for neurotoxicity from combined exposure to solvents, there are few, if any, studies to show the magnitude of neurodegeneration from combined versus single solvent exposures. However, published literature on solvent toxicity suggests that additive effects would be predicted from combined exposures, as different solvents induce damage in specific pathological pathways that could render cells and tissue more vulnerable. For example, benzene, a widely studied chemical for cancer risk, reduces levels of antioxidant enzymes in the blood of exposed individuals, such as superoxide dismutase (SOD) and glutathione (GSH)[122]. Experimentally, PCE demonstrates similar ability to induce oxidative stress in cells as compared to TCE[1], thus, it could be predicted that in a system where TCE, PCE, and benzene are present, a greater degree of toxicity could arise from (1) elevated oxidative stress and (2) reduced antioxidant enzymes to minimize oxidative damage to cellular macromolecules. Thus, these data support a premise that exposure to multiple solvents simultaneously would induce worsened neurotoxicity than exposure to any one solvent in isolation.

**Weight of Experimental Evidence and Relationship to Epidemiological Data**

As summarized, exposure to TCE under experimental laboratory conditions replicates PD pathology at the cellular and molecular level, proving a biological basis for the development of PD from TCE exposure. The dose and route of exposure to TCE has implications on its neurotoxicity, with evidence supporting inhaled TCE as more potent to dopaminergic neurodegeneration, requiring smaller doses to produce the same effects as oral ingestion. There are limitations to experimental and animal models of disease, however, in totality, there is a high degree of concordance among published data that TCE exposure can cause dopaminergic neurodegeneration, neuroinflammation, and αSyn accumulation within the brain. Furthermore, TCE can induce the molecular pathology that underlies hallmark PD pathology, such as oxidative damage and endolysosomal dysfunction. Together with the epidemiological evidence showing increased risk for PD from TCE exposure[14] as well as potentially worsened morbidity[13], these data support a conclusion that TCE exposure under the conditions described at Camp Lejeune, NC is more likely than not to cause PD. Under the Camp Lejeune Justice Act, the standard of causation is defined as “at least as likely as not,” which is lower than the “more likely than not” standard which my opinions reach.

These opinions, to a reasonable degree of scientific certainty, were based on my education, training, and experience in the field of Parkinson’s disease and Neurotoxicology research and represent the assessment of the published literature from a toxicological standpoint, evaluating the neuropathological effects of TCE exposure and the relationship to PD pathology. I conducted this review using an unbiased, scientific approach and relied on published literature indexed in PubMed from the NIH National Library of Medicine, using keyword search terms such as: trichloroethylene, tetrachloroethylene, Parkinson’s disease, dopaminergic, alpha-synuclein, neuroinflammation, lysosomal, mitochondrial, complex I, oxidative stress, microglia, inhalation, and cytochrome P450. I was compensated at a rate of 250 USD per hour for my time to produce this review outside of my normal research activities, and provided this information as a service to the Parkinson’s disease community.

Signed,



December 8, 2024
Briana R. De Miranda, PhD

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THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

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## EDUCATION

**Ph.D. Toxicology** 2008-2014
*Colorado State University, Fort Collins, CO*
Dissertation: Molecular regulation of glial inflammation in Parkinson's disease

**Bachelor of Science,** Biological Science 2004-2008
*Colorado State University, Fort Collins, CO*
Biomedical science minor

## RESEARCH TRAINING & EXPERIENCE

**Postdoctoral Fellow** 2014-2020
*Pittsburgh Institute of Neurodegenerative Diseases, University of Pittsburgh, Pittsburgh, PA*

**Graduate Research Assistant** 2009-2014
*Toxicological Sciences, Colorado State University, Fort Collins, CO*

## POSITIONS & SCIENTIFIC APPOINTMENTS

**Assistant Professor** 2020-Present
Center for Neurodegeneration and Experimental Therapeutics, Department of Neurology, University of Alabama at Birmingham, Birmingham, AL

**Assistant Professor, Secondary** 2020-2024
Department of Pharmacology and Toxicology, University of Alabama at Birmingham, Birmingham, AL

**Associate Scientist** 2020-Present
Center for Neurodegeneration and Experimental Therapeutics

**Associate Scientist** 2020-Present
McKnight Brain Institute, University of Alabama at Birmingham, Birmingham, AL

**Associate Scientist** 2022-Present
Comprehensive Neuroscience Center

## PUBLICATIONS

***Denotes senior author**

Keeney MT, Rocha EM, Hoffman EK, Farmer K, Di Maio R, Weir J, Wagner WG, Hu X, Clark CL, Castro SL, Scheirer A, Fazzari M, **De Miranda BR,** Pintchovski SA, Shrader WD, Pagano PJ, Hastings TG, Greenamyre JT. LRRK2 regulates production of reactive oxygen species in cell and animal models of Parkinson's disease. *Sci Transl Med*. (2024).

Ilieva, N.M., Hoffman, E.K., Ghalib, M.A., Greenamyre, J.T., **De Miranda B.R**.* LRRK2 kinase inhibition protects against Parkinson's disease-associated environmental toxicants. *Neurobiology of Disease* (2024).

Dorsey ER, **De Miranda BR**, Horsager J, Borghammer P. The Body, the Brain, the Environment, and Parkinson's Disease. *J Parkinsons Dis.* (2024)

Dorsey, R., Kinel, D., Pawlik, M., Zafar, M., Lettenberger, S., Coffey, M., Auinger, P., Hylton, K., Lustig, C., Adams, J., Barbano, R., Braun, M., Schwarz, H., Lawrence, P., Kieburtz, K., Tanner, C., **De Miranda, B.,** Goldman, S. Dry Cleaning Chemicals and a Cluster of Parkinson's Disease and Cancer. *Movement Disorders* (2024).

Adamson, A., Ilieva, N., Stone, W., **De Miranda, B.R.*** Low-dose inhalation exposure to trichloroethylene induces dopaminergic neurodegeneration in rodents. *Toxicological Science* (2023). **Selected as the Featured Article and cover of the journal.

Dorsey ER, Zafar M, Lettenberger SE, Pawlik ME, Kinel D, Frissen M, Schneider RB, Kieburtz K, Tanner CM, **De Miranda BR**, Goldman SM, Bloem BR. Trichloroethylene: An Invisible Cause of Parkinson's Disease? *Journal of Parkinson's Disease* (2023).

Adamson, A.B., Buck, S.A., Freyberg, Z., **De Miranda, B.R.*** Sex differences in dopaminergic vulnerability to environmental toxicants - implications for Parkinson's disease. *Current Env Health Reports* (2022).

Ilieva, N.M., Wallen, Z.D., **De Miranda, B.R.*** Oral ingestion of the environmental toxicant trichlorethylene in rats induces alterations in the gut microbiome: relevance to idiopathic Parkinson's disease. *Toxicology and Applied Pharmacology* (2022).

Ilieva N.M., **De Miranda B.R.*** Rest and Digest-The Basal Role of Autophagy in Neurons and Its Relevance to Parkinson's Disease. *Movement Disorders* (2022).

Rocha, E.M., Keeney, M.T., Di Maio, R., **De Miranda, B.R.**, Greenamyre, J.T., LRRK2 and idiopathic Parkinson's disease. *Trends in Neuroscience* (2022).

***De Miranda, B.R.,** Goldman, S.M., Miller, G.W., Greenamyre, J.T., Dorsey, E.R. Preventing Parkinson's Disease: An Environmental Agenda. *Journal of Parkinson's Disease* (2021).

***De Miranda, B.R.,** Castro, S.L., Rocha, E.M., Bodle, C.R., Johnson, K.E., Greenamyre, J.T. The industrial solvent trichloroethylene induces LRRK2 kinase activity and dopaminergic neurodegeneration in a rat model of Parkinson's disease. *Neurobiology of Disease* (2021).

Buck, S.A., **De Miranda, B.R.**, Logan, R.W., Fish, K.N., Greenamyre, J.T., Freyberg, Z. VGLUT2 is a determinant of dopamine neuron resilience in a rotenone model of dopamine neurodegeneration. *J. Neurosci* (2021).

**De Miranda, B.R**, Blossom, S. J. "The environmental pollutant trichloroethylene disrupts key neural pathways during brain development.**"** *Neuroscience of Development* (2021).

**De Miranda, B.R.,** Rocha, E.M., Castro, S.L., Greenamyre, J.T. Protection from α-synuclein-induced dopaminergic neurodegeneration by overexpression of the mitochondrial import receptor TOM20 in the rat midbrain. *NPJ Parkinson's disease* (2020).

Buck, S.A., Steinkeller, T. et al., Despoina, A., Villenueve, S., Bhatte, S.H., Childers, V.C., Rubin, S.A., **De Miranda, B.R.**, et al., Freyberg, Z. VGLUT modulates sex differences in dopamine neuron vulnerability to age-related neurodegeneration. *Aging Cell* (2021).

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Rocha, E.M., **De Miranda, B.R.**, Castro, S., Drolet, R., Hatcher, N.G., Yao, L., Smith, S.M., Keeney, M.T., Di Maio, R., Kofler, J., Hastings, T.G., Greenamyre, J.T. LRRK2 inhibition prevents endolysosomal deficits seen in human Parkinson's disease. *Neurobiology of Disease* (2019).

**De Miranda, B.R.**, Greenamyre, J.T. Response to rotenone and Parkinson's disease; reduced sensitivity in females. *Toxicological Sciences* (2019).

**De Miranda, B. R.**, Fazzari, M., Rocha, E. M., Castro, S., Greenamyre, J. T. Sex differences in rotenone sensitivity reflect the male-to-female ratio in human Parkinson's disease incidence. *Toxicological Sciences* (2019).

Zharikov, A., Bai, Q., **De Miranda, B. R.**, Van Laar, A. D., Greenamyre, J. T., Burton, E.A. Long-term RNAi knockdown of α-synuclein in the adult rat substantia nigra without neurodegeneration. *Neurobiology of Disease* **125,** 146–153 (2019).

Di Maio R., Hoffman E. K., Rocha E. M., Keeney M. T., Sanders, L. H., **De Miranda, B. R.**, Zharikov, A., Van Laar, A., Stepan, A. F., Lanz, T. A., Kofler, J. K., Burton, E. A., Alessi, D. R., Hastings, T. G., Greenamyre, J. T. LRRK2 activation in idiopathic Parkinson's disease. *Science Translational Medicine* (2018).

**De Miranda, B. R.,** Rocha, E. M., Bai, Q., El Ayadi, A., Hinkle, D., Burton, E. A., Greenamyre, J. T. Astrocyte-specific DJ-1 overexpression protects against rotenone-induced neurotoxicity in a rat model of Parkinson's disease. *Neurobiology of Disease* (2018).

Greenamyre, J. T., **De Miranda, B. R**., Bucher, M. L., Singleton, A. B., Tansey, M. G. The Gordon Research Seminar & Conference on Parkinson's disease: state of the science 200 years after James Parkinson's essay on the Shaking Palsy. *NPJ Parkinson's Disease* (2017).

**De Miranda, B. R.,** Greenamyre, J. T. "Etiology and Pathogenesis of Parkinson's disease." *Oxidative Stress and Redox Signaling in Parkinson's Disease*. Royal Society of Chemistry (2017), pp. 1-16.

Rocha, E. M., **De Miranda, B. R.,** Sanders, L. H. Alpha-synuclein: Pathology, mitochondrial dysfunction and neuroinflammation in Parkinson's disease. *Neurobiology of Disease* (2017).

**De Miranda, B. R.,** Van Houten, B., Sanders, L. H. "Toxin-Mediated Complex I Inhibition and Parkinson's Disease." *Mitochondrial Mechanisms of Degeneration and Repair in Parkinson's Disease.* Springer (2016), pp. 115-137.

**De Miranda, B. R.,** Popichak, K. A., Hammond, S.L., Jorgensen, B.A., Phillips, A. T., Safe, S., Tjalkens, R.B. The Nurr1 Activator 1,1-Bis(3'-Indolyl)-1-(p-Chlorophenyl)Methane Blocks Inflammatory Gene Expression in BV-2 Microglial Cells by Inhibiting Nuclear Factor κB. *Molecular Pharmacology*, 87(6), 1021-1034 (2015).

**De Miranda, B. R**., Popichak, K. A., Hammond, S. L., Miller, J. A., Safe, S., & Tjalkens, R.B. Novel Para-Phenyl Substituted Diindolylmethanes Protect Against MPTP Neurotoxicity and Suppress Glial Activation in a Mouse Model of Parkinson's Disease. *Toxicological Sciences*, 143(2), 360-373 (2014).

Streifel, K. M., Gonzales, A. L., **De Miranda, B**., Mouneimne, R., Earley, S., & Tjalkens, R. Dopaminergic neurotoxicants cause biphasic inhibition of purinergic calcium signaling in astrocytes. *PLoS ONE* (2014).

**De Miranda, B. R**., Miller, J. A., Hansen, R. J., Lunghofer, P. J., Safe, S., Gustafson, D. L., Colagiovani, D., Tjalkens, R.B. Neuroprotective Efficacy and Pharmacokinetic Behavior of Novel Anti-Inflammatory Para-Phenyl Substituted Diindolylmethanes in a Mouse Model of Parkinson's Disease. *Journal of Pharmacology and Experimental Therapeutics*, 345(1), 125–138 (2013).

Miller, J. A., **Trout, B. R.**, Sullivan, K. A., Bialecki, R**.** A., Roberts, R. A., & Tjalkens, R. B. Low-dose 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine causes inflammatory activation of astrocytes in nuclear factor-κB reporter mice prior to loss of dopaminergic neurons. *Journal of Neuroscience Research*, 89(3), 406–417 (2011).

**FUNDING**

***Current***

**1R01ES034846** (PI: De Miranda) 2/01/2024 -1/31/2029
The role of lysosomal dysfunction in trichloroethylene induced Parkinsonian neurodegeneration
NIEHS ONES/R01

**1R01ES034037** (PI: Freyberg/ Co-I De Miranda) 9/01/2022 - 8/31/2027
Novel Roles of VGLUT in Sex Differences in Dopamine Neuron Vulnerability to Toxicant-induced Neurodegeneration
NIEHS

**TX220241** (PI: De Miranda) 9/01/2023 - 8/31/2026
The role of adaptive immune activation in solvent-induced Parkinson's neurodegeneration
CDMRP Toxin Exposure Research Program, US Department of Defense

**1058111** (PI: De Miranda) 9/01/2023 - 8/31/2024
Cdk5 inhibition as a protective mechanism against environmental toxicant indued Parkinson's disease
American Parkinson's disease Association

**1064207**(PI: De Miranda) 7/01/2023 - 6/31/2026
Environmental exposures accelerate senescence and influence Parkinson's neurodegeneration
Parkinson's Foundation Stanley Fahn Award

**F31 ES036890-01** (PI: Adamson, Mentor: De Miranda)
The role of cell cycle regulators in trichloroethylene induced Parkinson's dementia 8/01/2024 - 7/31/2026
NIEHS

**F31 ES037227-01** (PI: Ilieva, Mentor: De Miranda) 6/01/2025 – 5/31/2027
The role of lysosomal dysfunction in STING-mediated neurodegeneration from trichloroethylene exposure
NIEHS

**1R01ES034846 Diversity Supplement** (PI: De Miranda, Co-I: Smith) Funded, Awaiting NOA
Diversity Supplement to the role of lysosomal dysfunction in trichloroethylene induced Parkinsonian neurodegeneration
NIEHS

***Completed***

**R00ES029986** (PI: De Miranda) 8/01/2020 - 7/31/2024
Environmental mitochondrial toxicants cause LRRK2 activation in Parkinson's disease
NIEHS

**Parkinson's Association of Alabama** (BRD, PI) 09/01/2021 – 09/01/2022

**PF-FBS-1892** (BRD, PI) 5/01/2018 - 12/1/2020
Fellowship Transition Award
Parkinson's Foundation

**MJFF PATH to PD Consortium Grant** 2/01/2018 - 1/31/2020
Michael J. Fox Foundation
PI: J. T. Greenamyre
Role: Project Lead for Aim 1- *Common Genetic & Environmental Mechanisms in PD*

**T32 NS086749** 9/01/2014 - 9/01/2016
NIH
Training in the Neurobiology of Neurological Disease

## HONORS AND AWARDS

**Parkinson's Research Program Early Investigator Research Award** 2023
US Department of Defense
**Collat Endowed Scholar in Neuroscience** 2020
University of Alabama at Birmingham
**Toshio Narahashi Endowment Award** 2019
Neurotoxicology Specialty Section, 2019 Annual Society of Toxicology meeting, Baltimore, MD
**Allegheny-Erie Society of Toxicology**, Postdoctoral Presentation Award 2018
**Toshio Narahashi Endowment Award** 2016
Neurotoxicology Specialty Section, 2016 Annual Society of Toxicology meeting, New Orleans, LA
**Toshio Narahashi Endowment Award** 2015
Neurotoxicology Specialty Section, 2015 Annual Society of Toxicology meeting, San Diego, CA
**Cell and Molecular Biology Research Symposium**, Poster Presentation Honors 2013
**Molecular, Cellular and Integrative Neuroscience**, Travel Fellowship 2013
**Environmental Health Sciences,** Outstanding Graduate Student Researcher Award 2012
**Front Range Neuroscience Group Meeting Poster Presentation**, Highest Honors 2011
**Society of Toxicology**, Graduate Student Travel Fellowship 2011
**AstraZeneca Gordon Research Conference**, Travel Fellowship 2011
**Research Colloquium Health Aging**, Scientific Poster Contest Award 2009

## SELECTED PRESENTATIONS

### *Invited Talks*

**University of Iowa** University of Iowa, 2024
"Mechanisms underlying solvent-induced neurotoxicity and risk for Parkinson's disease"

**Virginia APDA Regional Meeting – Keynote Speaker** Williamsburg, VA, 2024
"Relationships between Parkinson's and the Environment"

**World Parkinson Congress** Barcelona, Spain, 2023
"Chemical toxicant contribution to human Parkinson's disease"

**UK Dementia Research Institute** Imperial College London, 2022
"Mechanisms of Parkinson's disease neurodegeneration from environmental exposures"

**Interdisciplinary Toxicology Program Seminar – Keynote Speaker** University of Georgia, 2022
"Mechanisms of trichloroethylene toxicity in Parkinson's disease"

**University of New Mexico Department of Pharmaceutical Sciences** University of New Mexico, 2021
"Gene environment interaction with industrial contaminants as a risk factor for Parkinson's disease"

**NINDS Udall Centers National Meeting** University of Alabama at Birmingham, 2020

"Gene-environment interaction with widespread industrial contaminants and LRRK2 as a risk factor for Parkinson's disease"

**Center for Urban Responses to Environmental Stressors Seminar** Wayne State University, 2019
"Identifying Novel Gene-Environment Interaction in Parkinson's disease"

**2019 Parkinson's disease Gordon Research Conference** Sunday River, ME, 2019
"The environmental toxicant, trichloroethylene, activates LRRK2 and causes nigrostriatal degeneration"

**Michael J. Fox Foundation PD Pathogenesis Meeting** University of Pittsburgh, 2019
"Common Genetic and Environmental Mechanisms in PD"

## TEACHING

**Co-Director** 2024-Present
GBS 700, Molecular Neurodegeneration

**Co-Director** 2023-Present
GBSC 720, Innovative Techniques Journal Club

**Lecturer, University of Alabama at Birmingham**
Course: GBS 700, Molecular Neurodegeneration 2020-Present
Course: GBS 729, Translational Approaches in Neurodegeneration 2021-Present
Course: NBL 239, Brain Science 2024
Course: GBS Neuroscience Small Groups 2023-Present

**Guest Lecturer, University of Pittsburgh** 2018-2020
Course: Neuroscience Proseminar Undergraduate Course

**Graduate Teaching Assistant, Colorado State University** 2010-2014
Course: ERHS 502, Fundamentals of Toxicology

**Graduate Teaching Assistant, Colorado State University** 2011-2012
Course: BZ 214, Animal Biology - Vertebrates

## MENTORING

**Postdoctoral Fellows**
- Dr. Allie Smith, Brain PRIME Postdoctoral Fellow, Department of Neurology, UAB 2024-present

**Predoctoral Students**
- Ms. Neda Ilieva, PhD Student, Neuroscience Track, Graduate Biomedical Science Program, UAB 2021-present
- Ms. Ashley Adamson, PhD Student, Neuroscience Track, Graduate Biomedical Science Program, UAB 2021-present
- Ms. Gwendolyn Cohen, PhD Student, Immunology Track, Graduate Biomedical Science Program, UAB 2024-present
- Ms. Teel Walters, Behavioral Neuroscience Behavioral Science Graduate Program, UAB 2024-present

**Masters, Undergraduate Students**
- Ms. Sarah Wilson, undergraduate researcher, MPH student UAB 2022-present
- Ms. Suneeti Chambers, undergraduate researcher, UAB 2021-2024
- Ms. Anantha Korrapati, undergraduate researcher, MPH student, UAB 2021-2023
- Mr. Ikjoon Shin, Sci Tech undergraduate researcher, UAB 2020-2022
- Ms. Alyson Skloff, undergraduate researcher, University of Pittsburgh 2018-2020
- Ms. Taylor Gatesman, undergraduate research internship, University of Pittsburgh 2018
- Ms. Funto Babalola, undergraduate researcher, University of Pittsburgh 2014-2016
- Dr. Bryce Jorgensen, Toxicology Masters Student, Colorado State University 2011-2014

- Dr. Rachel Padmanabhan, Toxicology Masters Student, Colorado State University 2011-2013

**UAB Blazer BRAIN Summer Research Mentor**

- Mr. Tariq Asim, Morehouse College 2023
- Ms. Julia Langman, Nova Southeastern University 2022

**Movement Disorders Fellows**

- Dr. Jason Massa, Neurology Movement Disorders Fellow, University of Pittsburgh 2018-2020

## LEADERSHIP

**Women in Neurology, UAB** 2022-present
Leadership team, co-director

**Neurotoxicology Specialty Section, Society of Toxicology** 2021-2023
Councilor
Secretary Treasurer 2024-2026

**Allegheny-Erie Society of Toxicology Regional Chapter** 2018-2020
Postdoctoral Representative
Councilor for postdoctoral members of the A-ESOT chapter, assist with regional and national SOT meeting organization.

**Gordon Research Seminar, Parkinson's disease** 2015-2017
Chair
Established and chaired the first Parkinson's disease Gordon Research Seminar, a meeting for graduate students and early career scientists in the PD field.

**Neurobiology of Disease Journal Club** 2020-2023
Co-director
Established a national journal club for trainees and early career scientists that meets virtually once a month to discuss current literature focused on molecular mechanisms of neurodegenerative disease.

## PROFESSIONAL ASSOCIATIONS

- Society for Neuroscience 2015-Present
- Society of Toxicology 2011-Present
- Southeastern Society of Toxicology Regional Chapter 2020-Present
- Allegheny-Erie Society of Toxicology Regional Chapter 2018-2020
- Mountain West Society of Toxicology Regional Chapter 2011-2014
- Front Range Neuroscience Group 2009-2014
- Rocky Mountain Regional Neuroscience Group 2009-2014

## PEER REVIEW & SERVICE

**Associate Editor** *NeuroToxicology* 2024-Present
**Editorial Board Member** *NeuroToxicology* 2021-2024
**Editorial Board Member** *Frontiers in Neuroscience* 2023-Present
Manuscript peer review:

- Cell Death and Differentiation
- Clinical and Translational Medicine
- Environmental Neuroscience
- Environmental Science, Process and Impacts
- Environmental Toxicology
- European Journal of Neuroscience
- Food and Chemical Toxicology
- Journal of Clinical Investigation
- Journal of Parkinson's Disease
- Molecular Neurobiology
- Molecular Neurodegeneration

- Movement Disorders
- Nature
- Nature Publishing Journals, Parkinson's disease
- Neurology International
- Neurobiology of Disease
- Neurotoxicology
- Pesticide Biochemistry
- PLOS One
- Science
- Science Advances
- Science Translational Medicine
- Scientific Reports
- Toxicology
- Toxicological Sciences
- Toxicology and Environmental Health

**Grant review panelist:**

- **National Institutes for Environmental Health Sciences (NIH/NIEHS)**, ZES1 LWJ-S(K9)
- **National Institutes for Environmental Health Sciences (NIH/NIEHS)**, NAL, June 2023
- **National Institutes for Environmental Health Sciences (NIH/NIEHS)**, 2025/01 ZRG1 ICN-W (02) M
- **National Institutes for Neurologic Disease and Stroke (NIH/NINDS)**, 2024/10 ZRG1 CN-K (57) R
- **National Institutes for Neurologic Disease and Stroke (NIH/NINDS)**, NST-2 2024/05
- **Congressionally Directed Medical Research Programs (Department of Defense)** Neurotoxin Exposure Treatment Program (NETP), Parkinson's Research Program (PRP). *Note, DoD review panel names are not allowed to be shared publicly.
- **UAB Adair Award**, August 2024
- **Parkinson's Foundation**, standing member for Postdoctoral Fellowship, Launch Awards, 2023-present
- **Veterans Affairs Airborne Hazards and Burn Pits**, September 2023
- **Van Andel MiND Program,** September 2023
- **Cure Parkinson's Trust**, September 2022
- **CNET T32 Applications** June 2022
- **UAB CNC Grants in Preparation**, 2021
- **Michael J. Fox Foundation**, Investigating Environmental Risk Factors in Parkinson's disease, October 2020

**Service to Legal Cases Involving Parkinson's Disease Risk:**

- Expert Witness, Biological Plausibility Reports Provided To:
    - Hartley Law Group, PLLC
    - Metzger Law Group
    - Bell Legal Group
    - The Miller Firm, LLC

# APPENDIX 1

1g/cm3 = 1 kg/l

| | | | | |
|---|---|---|---|---|
| Ingestion | | | | |
| | **200 mg/kg** | mg/kg | 200 | |
| | | mg/l | 136.986301 | <- divided by the density of TCE (1.46 g/cm3) |
| Inhalation | | | | |
| | **50ppm** | mg/l | 0.27328285 | |
| | | | | |
| | | | | |
| | **Dose Comparison** | | 501.261976 | <- ingestion is 500x higher |

200 mg/kg = 25,000 ppm 25,063.10

501.26196