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Trichloroethylene and Parkinson's disease: dissolving the puzzle

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"The ubiquitous nature of trichloroethylene in the environment mandates a prompt and thorough evaluation of its potential role in the etiology of Parkinson's disease."

Identified genetic causes are responsible for only a small percentage of Parkinson's disease (PD) cases, and the lifetime penetrance of the most common causal mutation, *LRRK2* G2019S, is estimated at approximately 30% [1–4]. Twin studies have found similar PD concordance rates in monozygotic and dizygotic twin pairs, suggesting a primary role for environmental etiologic determinants [5,6]. Despite these observations, geographic [7,8] or temporal clusters of PD [9,10] – which should occur if large environmental exposures are sufficient to cause disease – have rarely been reported, and only a handful of environmental risk factors have been implicated [11].

Solvents have long been suspected as potentially causative agents in typical PD because of their ability to induce symptoms of parkinsonism. Over the past 100 years, there have been a number of reports of acute parkinsonism occurring in individuals exposed to large amounts of solvents, including methanol [12], n-hexane [13] and hydrocarbon solvent mixtures [14–16]. However, the syndromes caused by these intoxications were almost always distinct from PD in both their clinical phenomenology and neuropathology.

Numerous epidemiologic studies have attempted to investigate associations of solvents with PD, and the results have not been convincing. Although several studies found associations with self-reported solvent exposures [17–19], several large methodologically rigorous studies have found no association. Indeed, the performance of tasks likely to involve solvent exposure was not associated with PD in a study using custom task-based interviews [20], or in another that included a job-exposure matrix and industrial-hygienist review to impute lifetime solvent exposures [21]. A German study found a significantly increased risk of PD associated with self-reported solvent exposure and similarly increased risk for 'glues, paints, lacquers', but these associations were not confirmed when exposures were estimated using an unbiased job-exposure matrix [22]. Similarly, a recent population-based study failed to find an association with either self-reported or industrial hygienist-estimated solvent exposure [23].

There are several likely explanations for this. First, the term 'solvent' is exceedingly broad, encompassing a huge range of compounds, whose only common characteristic is their ability to dissolve other substances. These include aliphatic and aromatic hydrocarbon compounds of various lengths and substitutions, and hydrocarbon mixtures, such as gasoline or kerosene. Solvents are present in fuels, paints, glues, lubricants, degreasers, cleaning solutions and many household products. Although most solvents can be readily absorbed through respiratory and dermal contact and are oxidative stressors [24,25], there is little reason to assume that disparate molecular compounds share a common toxicity toward the dopaminergic neurons of the substantia nigra pars compacta. Given that most epidemiologic studies assess solvent exposure as a single variable, the relationship with any particular etiologic agent is likely to be obscured. Add to this the inability to accurately estimate exposure dose – and the likelihood that disease-relevant exposures may have occurred years or even decades before symptom onset – and it is easy to see why so little is known regarding the potential etiologic associations.

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Recently, Gash *et al.* reported a cluster of three PD patients who had been extensively exposed to the solvent trichloroethylene (TCE) in a small manufacturing plant [26]. The patients had all worked near each other, and had copious dermal and respiratory exposure to TCE for more than 25 years. The authors successfully traced 27 of their coworkers, 14 of whom self-reported parkinsonian symptoms. Although none of the 27 met diagnostic criteria for PD, tests of fine motor hand tasks were significantly slower than those of age-matched healthy controls.

Additionally, two prior publications reported anecdotal association of TCE exposure with PD. Guehl *et al.* described a female patient diagnosed with PD in her late thirties, who had used TCE extensively as a house cleaner [27]. Kochen *et al.* reported three patients with PD who each had prior substantial TCE exposure over many years [28].

> "Approximately 50 million pounds of trichloroethylene is released annually into the environment in the USA."

Trichloroethylene is a common solvent used in a wide variety of industrial processes and products. It has been used worldwide since the 1920s as a dry-cleaning and degreasing agent, and as an additive in many common household products, including typewriter correction fluid, adhesives, paints and carpet and spot removers [29]. In 1977, the US FDA banned its use as a general anesthetic, skin disinfectant, grain fumigant and coffee decaffeinating agent [30]. Today, it is primarily used as a degreasing agent in metal parts fabrication and in some textiles manufacturing.

Trichloroethylene is ubiquitous in the environment. A nonflammable liquid at room temperature, TCE evaporates easily into air, but once in groundwater, or particularly in soil, it may remain for long periods of time. Approximately 50 million pounds of TCE is released annually into the environment in the USA. It is detected in air, soil, food and human breast milk, and is the most frequently reported organic contaminant in groundwater, detected in up to 30% of US drinking water supplies [30,31,101]. TCE enters the body via inhalation, ingestion or through the skin. Owing to its lipid solubility, it readily distributes in all body tissues, especially the brain. Its half-life in adipose tissue is approximately 5 h, and it can be detected in urine for several weeks after significant exposures [30], and perhaps much longer in highly exposed individuals [28]. The highest exposures occur in individuals working directly with TCE, and in persons living near sites of industrial usage.

Despite mounting anecdotal evidence, and the ubiquitous nature of TCE in the environment and in some occupational settings, the association of TCE with PD risk had never been specifically assessed in a population-based epidemiologic study. Therefore, we studied TCE exposure in a well-characterized population of twins. The cohort has been described previously [5]. Twin pairs discordant for PD were identified from the National Academy of Sciences – National Research Council World War II-Veteran Twins Cohort using multistage screening and expert examinations. We developed job-task-based occupational questionnaires in order to systematically collect detailed information on job processes and materials in a broad range of occupational settings. Lifelong histories were collected from the age of 10 years until PD diagnosis in the affected twin. An industrial hygienist blinded to disease status reviewed histories and inferred solvent exposures. Exposure to TCE was compared in 99 twin pairs discordant for PD. In analyses adjusting for smoking, PD risk was significantly increased more than fivefold in twins who had been occupationally exposed to TCE [32]. Consistent with prior case reports, exposures occurred several decades before disease onset. Thus, these results are the first evidence of increased PD risk in a population-based study of occupational TCE exposure, and confirm previous case reports. The use of an industrial hygienist to rate exposures while blinded to disease status reduces the likelihood that the association was due to selective over-reporting of exposure by case subjects (i.e., recall bias), and the twin design is resistant to many types of confounding, especially those due to differences in genetic factors. However, the risk estimate was imprecise and epidemiologic confirmation is clearly needed before a causal link between TCE and PD can be inferred.

Of note, Liu *et al.* recently reported a rodent model of TCE exposure that further supports a potential etiologic role in PD [33]. Oral administration of TCE in rats for 6 weeks caused selective dose-dependent loss of dopaminergic neurons in the substantia nigra, sparing cholinergic and GABAergic neurons, as well as dopaminergic neurons of the ventral tegmental area. In addition, they noted marked and selective accumulation of α-synuclein protein in the dorsal motor nucleus of the vagus nerve and the substantia nigra pars compacta, paralleling Braak pathological staging of PD [34]. Finally, they observed specific inhibition of mitochondrial complex 1 activity, the toxic site of action of the selective parkinsonism-inducing neurotoxin 1-methyl-4-phenyl pyridinium [35].

> "...Parkinson's disease risk was significantly increased more than fivefold in twins who had been occupationally exposed to trichloroethylene."

Considerable epidemiologic evidence is required before we can conclude that TCE increases the risk of PD. Causal inference requires replication in multiple studies using a range of study designs, ideally in populations with well-characterized exposure histories. However, anecdotal case reports and small PD clusters associated with TCE exposure have now been augmented by a population-based study and an animal model exhibiting many of the key features of PD. This model also awaits replication in other laboratories and other species. The ubiquitous nature of TCE in the environment mandates a prompt and thorough evaluation of its potential role in the etiology of PD.

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