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Tetrachloroethylene exposure and neurobehavioral performance among children living near multiple contamination sites

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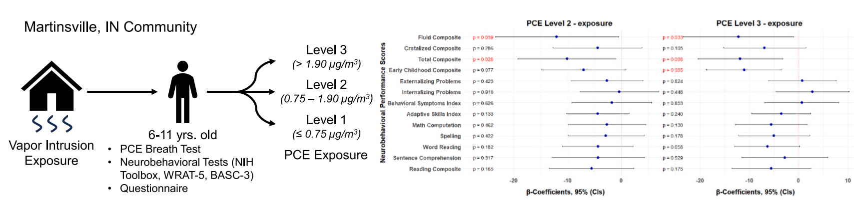
HIGHLIGHTS

- Low-level PCE exposure is associated with lower cognitive functions.
- Working and episodic memory, processing speed, executive function are impacted.
- No significant impact on behavioral or academic performance is detected.
- Observed PCE exposure level is relevant to populations beyond near waste sites.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Tetrachloroethylene (PCE) is a known neurotoxicant mainly observed in populations with high level occupational exposure. Health effects of low-level community exposure are poorly understood. This study evaluated PCE exposure and neurobehavioral performance in 6 to 11-year-old children living in a community with multiple PCE contamination sites.

Methods: This cross-sectional study recruited eighty-nine children who attended public schools in Martinsville, Indiana. PCE was measured in exhaled breath using proton transfer reaction mass spectrometry. Children were classified into three exposure groups: 'Level 1' ($\leq 0.75\ \mu g/m^3$), 'Level 2' (>0.75–$1.90\ \mu g/m^3$), and 'Level 3' ($>1.90\ \mu g/m^3$). A battery of tests assessed children's neurobehavioral performance related to their cognition, behavior, and academic achievement and a questionnaire collected demographic and exposure characteristics. Adjusted regression models estimated associations of PCE exposure with neurobehavioral outcomes.

Results: Seventy-three participants completed data collection. The average scores for all participants on the Fluid, Total, Early Childhood Composites, Behavioral Symptoms Index, and Math Computation were significantly lower than standard scores of normative sample, with 30 % of participants having one or more scores two standard deviations worse than the standard scores. Compared to children having the lowest PCE exposure, significant inverse associations were identified for PCE exposure with Fluid Composite for Level 2 ($\beta = -12.0$ (95 % CI = -23.4, -0.6)) and Level 3 (-12.2 (-23.4, -1.0)) exposure groups, Total Composite for Level 2 (-10.1 (-19.2, -1.1)) and Level 3 (-11.8 (-20.4, -3.2)) exposure groups, and Early Childhood Composite for Level 3 exposure group (-11.0 (-18.7, -3.4)).

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Conclusions: This study identified associations of PCE in exhaled breath with lower cognitive functioning, problem-solving abilities, and adaptive functioning in children. Mainly, working memory, episodic memory, processing speed, and executive function-cognitive flexibility were associated with PCE exposure. These results underscore the need for further investigations, considering the impact of low-level environmental exposure on children's neurobehavioral outcomes.

1. Introduction

Tetrachloroethylene (PCE), also known as PERC, is a volatile organic compound widely used in industrial processes such as dry cleaning, metal degreasing, and chemical synthesis. PCE is also an ingredient in many household products, such as paint removers, furniture strippers, wood cleaners, water repellents, silicone lubricants, spot removers, suede protectors, glues, and wood cleaners (Wisconsin DHS, 2022). Once released into the environment, PCE breaks down slowly, with a half-life of approximately 100 days in the air (Atkinson, 1989). In groundwater, its half-life is generally considered to be between 9 months and 6 years (Dilling et al., 1975; Pearson and McConnell, 1975). Workers in the dry-cleaning industry or metal degreasing operations may be exposed to PCE at levels much higher than those encountered in non-occupational settings, where exposure to PCE could occur as a result of off-gassing from dry-cleaned clothes and the use of household products in an indoor environment. Due to the wide use of PCE and poor waste management, PCE has been found at many contamination sites. According to the U.S. Environmental Protection Agency (EPA), PCE has been identified in at least 949 of 1854 Superfund sites designated by the National Priorities List (Agency for Toxic Substances and Disease Registry (ATSDR), 2019; Liu et al., 2022), representing locations that need significant federal cleanup efforts to remediate environmental contaminations. PCE is also found in many unlisted hazardous waste sites. The primary exposure pathways for people residing near the contaminated sites include drinking contaminated water, inhaling contaminated water vapor (e.g., during a shower or doing laundry), and inhaling indoor air that is contaminated due to vapor intrusion. Vapor intrusion is a phenomenon that occurs when chemical vapors migrate from the subsurface into buildings, a process similar to the transport of radon (a radioactive gas) into homes (Forand et al., 2012; Pennell et al., 2013).

Exposure to PCE has been associated with various health effects such as liver, kidney, respiratory, and neurological disorders. PCE is classified as "probably" carcinogenic to humans (Group 2A) by the International Agency for Research on Cancer (IARC, 2014), with the exposure being shown to increase the risk of bladder cancer, multiple myeloma, and non-Hodgkin's lymphoma (Blair et al., 2003; Colt et al., 2011; Gold et al., 2011; Pesch et al., 2000; Radican et al., 2008). Additionally, PCE targets the central nervous system, which leads to alterations in neural conduction velocity by interfering with neuronal receptors (Briving et al., 1986; Kyrklund et al., 1990), particularly in the frontal cerebral cortex where complex organizational behavior, attention, executive functioning, and reasoning are centered (Kyrklund et al., 1988; Wang et al., 1993). Signs and symptoms of acute high-dose exposure in occupational or accidental exposure settings include headache, dizziness, drowsiness, ataxia, mood changes, coma, and seizures (*Agency for Toxic Substances and Disease Registry (ATSDR),* 2019). A growing body of evidence from animal and human studies link chronic PCE exposure with neurotoxic outcomes such as schizophrenia, visual and neurological disturbances, cognitive impairments impacting memory and processing speed, and motor deficits compromising coordination and reaction time (*Agency for Toxic Substances and Disease Registry (ATSDR),* 2019; Bale et al., 2011; Cavalleri et al., 1994; Echeverria et al., 1995; Gobba et al., 1998; Guyton et al., 2014; Perrin et al., 2007; White et al., 1995). Specifically, neurobehavioral effects observed with prolonged occupational exposure to PCE include deficits in short-term memory for visual designs, reaction times, perceptual function, attention, and intellectual function in dry cleaning workers exposed to PCE (Altmann et al., 1995; Cavalleri et al., 1994; Echeverria et al., 1995). These detrimental outcomes are not restricted to occupational exposures. Individuals living in close vicinity to dry cleaning operations with low levels of PCE exposure were observed to have altered visual acuity, color discrimination, and contrast sensitivity (Schreiber et al., 2002; Storm et al., 2011). However, health effects, especially neurological effects, among people living in communities near PCE contaminated sites, which impact many people, remain poorly understood.

Children may be more susceptible to the negative health consequences of PCE exposure due to their unique physiology and developmental stage. For instance, their developing nervous system tissues are more susceptible to damage (Guzelian et al., 1992; National Research Council (U.S.), 1993). Immature metabolic pathways reduce the ability to metabolize PCE to less toxic metabolites during the early stages of life (Clewell et al., 2004; Sarangapani et al., 2003). Some investigations reported associations between maternal occupational exposure to PCE and behavioral disorders as well as adverse effects on intelligence, language, and motor skills among offspring (Laslo-Baker et al., 2004; Till et al., 2001). Prenatal and early childhood exposure to contaminated drinking water was linked to long-term subclinical visual dysfunction and increased frequency of risky behaviors such as drug use, as well as increased risk of mental illness in early adulthood (Aschengrau et al., 2011, 2012, 2016; Getz et al., 2012; Janulewicz et al., 2012; Perrin et al., 2007). In contrast, others reported no significant associations between PCE exposure during pregnancy and neurobehavioral outcomes among children of occupationally exposed mothers (Eskenazi et al., 1988). Similarly, Janulewicz et al. (2008) reported no behavioral impairments among children exposed to PCE through contaminated drinking water. Nevertheless, the literature is scarce regarding the neurobehavioral effects of low-level PCE exposure in children living at or near contamination sites.

This study aimed to assess the effect of PCE exposure on neurobehavioral performance among children living in or near PCE-contaminated areas in Martinsville, Indiana, with a hypothesis that low-level exposure to PCE was associated with adverse effects on children's neurobehavioral performance. Martinsville represents many similar communities facing the challenge of PCE contaminations in groundwater, soil, and indoor air. The city overlays four groundwater contamination sites, including an EPA-designated Superfund site and three other known contamination sites (Liu et al., 2022). The total size of the groundwater contamination is over 60 acres, all located in the same aquifer, with PCE being identified as a primary contaminant. This pilot study adds knowledge about the impact of low-level environmental exposure on children's neurobehavioral outcomes. The findings can be used to inform and guide future investigations. The project also provides an opportunity to build a sustainable academic-community partnership to address community concerns about the exposure and potential health impacts related to the PCE contamination in Martinsville, as well as in other communities in a similar situation.

2. Materials and methods

2.1. Study site and population

Martinsville is a community located in Central Indiana with a population of approximately 12,000 people. The city is situated upon four groundwater contamination areas (also called "plumes"), one of which is an EPA-designated Superfund site known as the Pike and Mulberry

Streets PCE Plume (Pike and Mulberry Streets PCE Plume Martinsville, IN, n.d.). Three other known groundwater contamination sites are O'Neil, Twig, and Harman-Becker plumes which are under investigation and remediation supervised by the Indiana Department of Environmental Management (Liu et al., 2022). The primary contaminants include PCE, trichloroethylene, and other volatile organic compounds (VOCs) (Liu et al., 2022). PCE was identified in one of the municipal water source wells in 2002. The potential sources of contamination included a commercial and institutional dry cleaning and laundry company that operated from 1986 to 1991. Since 2005, an activated carbon filtration system has been operating, which protects people from exposure to PCE and potentially other chlorinated volatile organic compounds through using or drinking municipal water. However, the EPA's investigations reveal that these contaminants may harm people's health via drinking or using water from private wells or breathing indoor air that is contaminated through vapor intrusion (Agency for Toxic Substances and Disease Registry (ATSDR), 2020).

Eighty-nine children aged 6 to 11 (male and female) who attended public schools in the Metropolitan School District of Martinsville and had lived in Martinsville for at least four years were recruited between July 2021 and April 2022. The requirement of at least four years of residence aimed to increase the likelihood of prolonged exposure, as the neurobehavioral effects studied are chronic, and the critical window of exposure is unknown. Since the neurobehavioral testing instruments used in this study were English-based and normalized on children with English as the primary language, only children with English as their primary language or bilingual and attending school without the need for ESL/ENL supports (English as Second / Next Language) were eligible. Exclusion criteria included children with diagnosed neuromotor disorders, such as cerebral palsy, muscular dystrophy, spina bifida; and/or metabolic/genetic disorders, such as phenylketonuria, homocystinuria, down syndrome, and/or fragile x syndrome. Recruitment efforts involved distributing informational flyers and door-knocking. The flyers were distributed at locations such as coffee shops, grocery stores, farmers markets, restaurants, a public library, churches, and local community events. In addition, social media platforms such as Facebook were utilized to facilitate communication between the research team and community members, and a dedicated website was created to provide project updates. The study took a community-engaged research approach, with community partners deeply involved in multiple aspects of the study including designing recruitment strategies, disseminating study information in the community, and hosting study information sessions throughout the study period. Several community partners received certification in human subject research and participated in recruitment and field data collection. Study procedures and methods were approved by the Institutional Review Board (IRB) at Purdue University (Purdue IRB-2020-353). Participants completed informed consent and assent documents prior to being enrolled. Among eighty-nine participants enrolled, fourteen participants were lost to follow-up and two had missing responses, resulting in complete data for seventy-three participants ($n = 73$).

2.2. Measurement of PCE exposure

PCE levels in participants' exhaled breath were measured using a proton transfer reaction time-of-flight mass spectrometry (PTR-TOF-MS), that quantifies volatile organic compounds at very low concentrations. PCE in exhaled breath was chosen as the exposure measure because it closely represented a person's recent exposure. Approximately 97–99 % of PCE total intake is eliminated unmetabolized into the expired air with an elimination half-life of several days (Chiu et al., 2007; Chiu and Ginsberg, 2011; Fernandez et al., 1976; Gordon et al., 1988; Liu et al., 2022) This non-invasive method offers advantages over measuring PCE in blood samples, which can be distressing for children. Exhaled breath samples were collected as described in detail previously (Liu et al., 2022). Details on the quantification of PCE in exhaled breath are reported separately (Lee et al., 2024). Briefly, exhaled breath samples were collected from participants in a clean environment at home on weekend mornings in May 2022. One-liter plastic sampling bags (SKC Tedlar 249-01-PP, Eighty-Four, PA) were used to collect exhaled breath, following the National Institute for Occupational Safety and Health Method 3704 (National Institute for Occupational Safety and Health, 1998) with slight modifications. Parents were instructed a week preceding the sample collection to avoid bringing home dry-cleaned clothes or using PCE-containing consumer products such as paint, glue, brake cleaner, wood cleaner, spot removers, or suede protectors that could interfere with the breath testing. Also, a brief survey was administered on the day of exhaled breath sample collection to gather information on various factors potentially influencing exhaled breath measurements, such as dairy consumption, medication usage, household pesticide or cleaning product utilization, and the recent introduction of dry-cleaned clothes into the home during the preceding week. Exhaled breath samples were transported in a cooler with ice blocks and analyzed within 2–4 h on the day of sample collection using the PTR-TOF-MS that was equipped in a mobile van located at the study site. The instrument was a PTR-TOF-MS 4000 model from Ionicon Analytik Ges.m.b.H (Austria).

Exhaled breath samples were analyzed with mass spectra recorded at 1 Hz. Key operational parameters included an inlet flow rate of 700 ml min^{-1}, an electric field strength to gas number density ratio (E/N) of 139 Td, a reaction chamber pressure of 2.2 mbar, and temperatures of 80 °C (inlet) and 70 °C (reaction chamber). Calibrations with standard gas mixtures were performed daily. Post-sampling data processing involved mass calibration, peak identification, and trace exportation using the PTR-MS Viewer software (Version 3.2.2, Ionicon Analytik Ges.m.b.H., Innsbruck, Austria). Calibration curves were generated to convert instrument signals (in count per second) into concentrations (Lee et al., 2024). The detection limit (DL) varied across days, ranging from 0.34 $\mu g/m^3$ to 1.08 $\mu g/m^3$. Participants with PCE concentrations in exhaled breath samples lower than DL ($n = 5$ participants) were assign a value of $DL/\sqrt{2}$.

2.3. Questionnaire data collection

Parents or guardians of the participants were asked to complete a questionnaire administered via Research Electronic Data Capture, a secure, web-based application for collecting and entering research data, to provide information on demographics, exposure covariates, potential confounders, and children's health conditions and medications. Data were collected on factors such as maternal education, government-subsidized program status (as a surrogate of income), premature birth, prior elevated blood lead levels, smoking during pregnancy, children's school history, special education status, house characteristics including basement features, and sources of drinking water.

2.4. Neurobehavioral performance

Neurobehavioral performance was assessed using three test batteries. The Wide Range Achievement Test – Fifth Edition (WRAT-5) was employed to assess reading, spelling, and math skills. The NIH Toolbox Cognition Battery, a computer-based instrument, was used to evaluate five cognitive sub-domains: language, executive function-cognitive flexibility, episodic memory, processing speed, and working memory. Both WRAT-5 and NIH Toolbox are performance-based and were administered by trained doctoral psychology students supervised by a licensed clinical psychologist. Lastly, the Behavior Assessment System for Children – Third Edition (BASC-3) was administered via iPad and completed by a caregiver to gain insights into the behaviors and emotions of the participants.

The WRAT-5 is a standardized test designed to evaluate fundamental academic skills (e.g., reading, spelling, and math) for individuals aged 5 to 85+. The test is commonly used to assess academic abilities, identify learning difficulties, and track academic progress in clinical and educational settings. The WRAT-5 has demonstrated validity and reliability in diverse populations, including individuals with learning difficulties and those from different linguistic and cultural backgrounds. The WRAT-5 consists of four scores and one composite: Math Computation, Spelling, Word Reading, Sentence Comprehension, and Reading Composite.

The NIH Toolbox Cognition Battery is a standardized test battery designed by the National Institutes of Health (NIH) to assess cognitive function across various domains and age groups. It measures different cognitive abilities, including attention, memory, language, executive function-cognitive flexibility, and processing speed. The NIH Toolbox is age and sex-adjusted, ensuring accurate assessment across diverse populations. It has been utilized in numerous research studies and clinical settings to evaluate cognitive function in diverse populations, including children with developmental delays, individuals with neurological disorders, and healthy adults across the lifespan. The NIH Toolbox Cognition Battery is designed for ages 7+ and consists of seven test scores that are aggregated into four composites: Fluid, Crystalized, and Total Cognition (for ages 7+) Composites. The NIH Toolbox Early Childhood Cognition Battery is appropriate for children aged 4 to 6 and generates individual test scores and an Early Childhood Composite Score. The Total and Early Childhood Cognition Composites are linked to overall cognitive functioning, the Fluid Composite to problem-solving abilities and adaptive functioning, and the Crystalized Composite to language-related abilities.

The BASC-3 is an informant-based comprehensive instrument used to assess the behavioral and emotional concerns of subjects aged 2 to 25. This battery is widely employed in clinical, educational, and research settings to assess emotional and behavioral problems as well as monitor treatment effectiveness. Additionally, it has demonstrated validity and reliability across diverse cultural and ethnic groups. The BASC-3 can be completed by a caregiver or teacher. It consists of fourteen test scores that are aggregated into four composites: Externalizing Problems, Internalizing Problems, Behavioral Symptoms Index, and Adaptive Skills Index.

The standard scores for the NIH Toolbox Cognition Battery and WRAT-5 have a mean of 100, with a standard deviation (SD) of 15. The standard scores for the BASC-3 have a mean of 50, with an SD of 10. For the BASC-3, any score of two SD above the mean is considered clinically significant, except for reverse scoring on the Adaptive Skills Index Composite, where a score of two SD below the mean is considered clinically significant.

2.5. Statistical analyses

Descriptive statistics were used to summarize the demographic information and exposure, exposure covariates, and outcome variables. Frequencies and percentages were calculated for categorical variables, while means and SDs were calculated for continuous variables. Analysis of variance identified variables significantly associated with outcome measurements. The significant covariates were adjusted for in the final regression models.

Linear and logistic regression models assessed the associations between PCE exposure and neurobehavioral outcome measures. Thirteen neurobehavioral measures were modeled separately as dependent variables, including four NIH Toolbox composite scores (Fluid, Crystalized, Total, and Early Childhood), four BASC-3 composite scores (Externalizing Problem, Internalizing Problem, Behavioral Symptoms Index, and Adaptive Skills Index), and five WRAT-5 scores (Math Computation, Spelling, Word Reading, Sentence Comprehension, and Reading Composite). The PCE concentration in exhaled breath was the independent variable in these models. As the PCE concentration was lognormally distributed, it was log-transformed when included as a continuous variable. Both the exposure and the outcomes were modeled as continuous and categorical variables. We compared the model performance and chose models with continuous outcome and categorial exposure variables for final models (Supplementary Material). We compared different cut points to form exposure categories and, based on the PCE concentration distribution, formed 'Level 1 exposure' (PCE concentration $\leq$ 0.75 $\mu g/m^3$), 'Level 2 exposure' (0.75 $\mu g/m^3$ < PCE concentration $\leq$ 1.90 $\mu g/m^3$), and 'Level 3 exposure' (PCE concentration > 1.90 $\mu g/m^3$) groups (Supplementary Material).

Potential confounding variables, such as the mother's educational level, premature birth, blood lead level and mother's cigarette smoking during pregnancy were identified *a priori* from the literature. Covariates were retained in the model if they showed significant associations with outcome measurements. Results were interpreted based on the strength of association, dose-response trends, and consistency across analysis methods. Statistical significance was determined with a threshold of $p <$ 0.05. The analysis was executed using R Statistics (Version 4.2.2) and IBM SPSS (ver. 28.0.0.0), and visual representations were created with Graph Prism (Version 9.3.1).

3. Results

3.1. Demographic characteristics

Table 1 presents the demographic information of the seventy-three participants who completed the study procedures by PCE exposure groups. A total of 13 (17.8 %) participants had an Individualized Education Plan (IEP). This percentage is consistent with the state-level average of 17.6 % for the 2021–2022 academic year (Digest of Education Statistics, 2022, n.d.). The racial and ethnic distributions of the participants were similar to the profiles of the Martinsville general population. However, our sample had 48 % of mothers with bachelor's degrees or above, which is much higher than the Martinsville adult population rate of 13 % (US Census Bureau, n.d.). In addition, 84.3 % of families reported owning a house, compared to 63.8 % of the Martinsville general population in the 2022 census (U.S. Census Bureau (USCB) quickfacts: United States, n.d.).

3.2. Descriptive analysis of neurobehavioral performance scores

Both the NIH Toolbox and WRAT-5 assessments have a standard score with a mean score of 100, with higher scores indicating better performance. The BASC-3 assessment has a standard score with a mean of 50. Higher BASC-3 scores indicate poorer performance, except for the Adaptive Skills Index for which lower scores indicate poorer performance. The average scores of the study participants were significantly lower than the standard scores of the normative sample for Fluid Composite ($p < 0.001$), Total Composite ($p < 0.001$), Early Childhood Composite ($p < 0.023$), Behavioral Symptoms Index ($p < 0.019$), and Math Computation ($p < 0.026$) as shown in Fig. 1. It is notable that 30.1 % ($n = 22$) of the participants exhibited at least one score, with a >2 SD difference from the standard scores of the normative sample. Additionally, 5.5 % ($n = 4$), 4.1 % ($n = 3$), and 2.7 % ($n = 2$) participants had two, three, and four clinically significant scores, respectively.

3.3. Associations of covariates with neurobehavioral performance scores

We evaluated bivariate associations of the mother's education, mother's cigarette smoking during pregnancy, drinking alcohol during pregnancy, preterm birth, child's sex, child's age, elevated blood lead level, child's receiving an individualized education plan (IEP), house age, building type, and level of the house the child spent the most time

Table 1
Characteristics of seventy-three children by exhaled breath PCE (μg/m^3).

Groups		PCE Level 1 exposure (≤ 0.75 μg/m^3) (n = 22)		PCE Level 2 exposure (>0.75 μg/ m^3–1.90 μg/m^3) (n = 27)		PCE Level 3 exposure (> 1.90 μg/m^3) (n = 24)		Total (n = 73)	
Category		N	%	N	%	N	%	N	%
Sex	Female	13	59.1	13	48.1	15	62.5	41	56.2
	Male	9	40.9	14	51.9	9	37.5	32	43.8
Race	White	21	95.5	27	100.0	24	100.0	72	98.6
	Other	1	4.5	0	0.0	0	0.0	1	1.4
Ethnicity	Hispanic / Latino	0	0.0	1	3.7	0	0.0	1	1.4
	Not Hispanic / Latino	22	100.0	26	96.3	24	100.0	72	98.6
Age (years)	Average / Standard Deviation	8.09	1.82	8.18	1.59	8.71	1.80	8.33	1.732
Mother Education	High School or less	4	18.2	7	25.9	5	20.8	19	26.0
	Some College or Associate's	9	40.9	4	14.8	6	25.0	19	26.0
	Bachelor's or Above	9	40.9	15	55.6	11	45.8	35	48.0
Individualized Education Plan (IEP)	Has an IEP	5	22.7	2	7.4	6	25.0	13	17.8
	No IEP	17	77.3	24	88.9	17	70.8	58	79.5
	No Response	0	0.0	1	3.7	1	4.2	2	2.7
Premature Birth	Born Premature	1	4.5	5	18.5	3	12.5	9	12.3
	Not Born Premature	21	95.5	22	81.5	21	87.5	64	87.7
Handedness	Right	21	95.5	23	85.2	23	95.8	67	93.1
	Left	1	4.5	4	14.8	1	4.2	6	8.3
Home Arrangement	Renters	0	0.0	8	29.6	3	12.5	11	15.7
	Owners	22	100.0	18	66.7	19	79.2	59	84.3
WIC* service	Yes	0	0.0	0	0.0	1	4.2	1	1.4
	No	22	100.0	27	100.0	23	95.8	72	98.6
SNAP* service	Yes	1	4.5	2	7.4	6	25.0	9	12.3
	No	21	95.5	25	92.6	18	75.0	64	87.7
Lives over a plume	Yes	2	9.0	10	37.0	2	8.3	14	19.2
	No	20	91.0	17	63.0	22	91.7	59	80.8

Frequencies and percentages for categorical variables. Means and standard deviations for continuous variables.
SNAP*: Supplemental Nutrition Assistance Program.
WIC*: Women, Infants & Children.

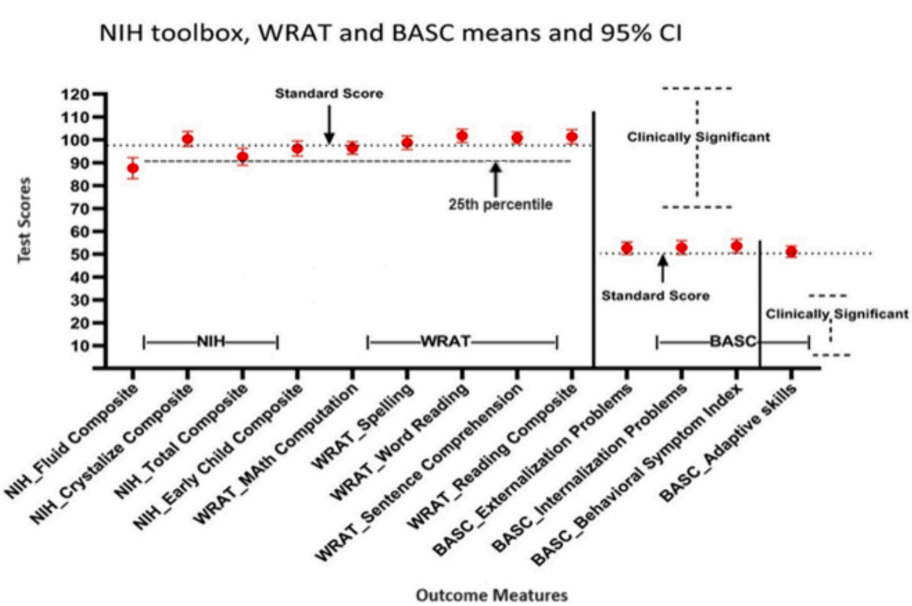

Fig. 1. Distributions of neurobehavioral performance test scores.

with neurobehavioral scores (Table 2). The NIH Toolbox's Crystallized Composite and BASC-3 Externalizing Problems Composite were not influenced by any covariate. Mother's education had a significant association with 6 out of 13 assessments, followed by IEP and premature birth, which were significantly associated with 4 and 3 assessments, respectively.

Fig. 2 visually illustrates our exploration of the relationship between PCE exposure and children's neurobehavioral outcomes. Maternal education, smoking during pregnancy, and premature birth were potential confounding factors to be controlled in the analysis. IEP was identified as a potential collider, not a confounder, and was therefore not controlled for in regression analyses.

Table 2
Covariates impacting neurobehavioral performance.

Assessment		Co-variate(s)(P-value)*
NIH	Fluid Composite	Mother Education (3 categories) ($p = 0.006$)
	Crystallized Composite	None
	Total Composite	Premature Birth ($p = 0.046$), Mother Education (p = 0.002)
	Early Childhood Composite	Premature Birth (p = 0.028), Mother Education ($p = 0.014$)
BASC-3	Externalizing Problems	None
	Internalizing Problems	Premature Birth ($p = 0.017$)
	Behavioral Symptoms Index	IEP ($p = 0.007$)
	Adaptive Skills Index	IEP ($p = 0.001$), Mother Cigarette Smoking ($p = 0.004$)
WRAT-5	Math Computation	Mother Education (p = 0.001)
	Spelling	IEP ($p = 0.015$)
	Word Reading	IEP ($p = 0.045$)
	Sentence Comprehension	Mother Education (p = 0.002)
	Reading Composite	Mother Education ($p = 0.002$)

* Analysis of Variance (ANOVA) with a P-value <0.05.

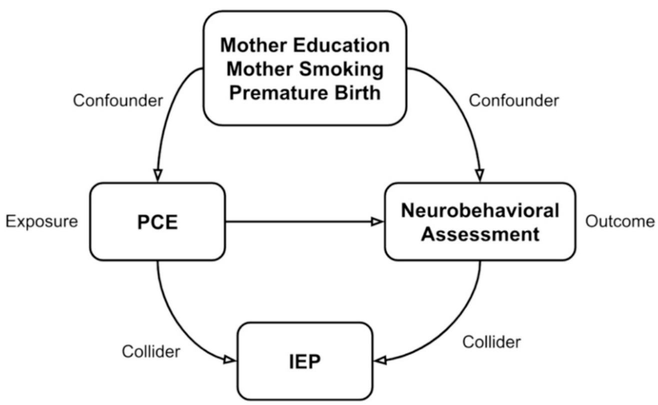

Fig. 2. Directed acyclic graph for multivariable analyses.

3.4. Association of PCE exposure with neurobehavioral performance scores

Table 3 presents the results of linear regression estimates adjusted for mothers' education, premature birth, and mothers' cigarette smoking during pregnancy. For the NIH Toolbox assessments, no statistically significant differences were observed between Level 1 exposure and Level 2 and 3 exposure groups in the Crystallized Composite. However, both Level 2 and Level 3 exposure groups showed a statistically significant negative effect in the Fluid Composite (Level 2: $\beta = -12.0$; 95 % CI (−23.4, −0.6); $p = 0.039$; Level 3: $\beta = -12.2$; 95 % CI (−23.4, −1.0); $p = 0.033$) and in the Total Composite (Level 2: $\beta = -10.1$; 95 % CI (−19.2, −1.1); $p = 0.028$; Level 3: $\beta = -11.8$; 95 % CI (−20.4, −3.2) $p = 0.008$) compared to the reference group. For the Early Childhood Composite, no statistically significant differences were observed between the Level 1 and Level 2 exposure groups. However, the Level 3 exposure group showed statistically significant negative effects ($\beta = -11.0$; 95 % CI (−18.7, −3.4); $p = 0.005$) compared to the reference group.

For both the BASC-3 and WRAT-5 assessments, no statistically significant differences were observed in the scores between the exposure groups, with Word Reading being borderline significant for the Level 3 exposure group.

4. Discussion

This study offers insights into the impact of PCE exposure on children's neurobehavioral performance. Notably, the two higher PCE exposure groups had lower cognitive performance involving tasks that assess working memory, episodic memory, processing speed, executive function-cognitive flexibility, and overall cognitive function than the lowest exposure group. However, statistical significance was observed only in the highest exposure group for tasks involved in the Early Childhood Composite assessment. In contrast, no significant associations were observed for the behavioral or academic performance tasks. These results suggest that PCE, a common environmental contaminant, might subtly affect how the central nervous system functions at the PCE exposure levels observed in this study.

Table 3
β-Coefficients, 95 % Confidence Intervals (CIs), and *p*-values for the associations of PCE exposure groups with neurobehavioral performance scores.

Assessment		PCE Level 1exposure (≤ 0.75 μg/m^3) ($n = 22$)	PCE Level 2 exposure β (95 % CI)* *P*-value (>0.75 μg/m^3–1.90 μg/m^3) ($n = 27$)	PCE Level 3 exposure β (95 % CI)* *P*-value (> 1.90 μg/m^3) ($n = 24$)
NIH	Fluid Composite[a]	*Ref*	−12.0 (−23.4, −0.6) 0.039	−12.2 (−23.4, −1.0) 0.033
	Crystallized Composite[b]	*Ref*	−4.4 (−12.7, 3.8) 0.286	−6.9 (−15.2, 1.5) 0.105
	Total Composite[a]	*Ref*	−10.1 (−19.2, −1.1) 0.028	−11.8 (−20.4, −3.2) 0.008
	Early Childhood Composite [c]	*Ref*	−7.0 (−14.8, 0.8) 0.077	−11.0 (−18.7, −3.4) 0.005
BASC - 3	Externalizing Problems	*Ref*	−2.7 (−9.3, 4.0) 0.423	0.8 (−6.1, 7.6) 0.824
	Internalizing Problems	*Ref*	−0.4 (−7.7, 6.9) 0.918	2.8 (−4.6, 10.2) 0.448
	Behavioral Symptoms Index [c]	*Ref*	−1.8 (−9.2, 5.6) 0.626	0.7 (−6.9, 8.3) 0.853
	Adaptive Skills Index	*Ref*	−4.4 (−10.2, 1.4) 0.133	−3.5 (−9.5, 2.4) 0.240
WRAT - 5	Math Computation	*Ref*	−2.7 (−9.8, 4.5) 0.462	−5.5 (−12.8, 1.7) 0.130
	Spelling	*Ref*	−2.9 (−9.9, 4.2) 0.422	−5.0 (−12.21, 2.3) 0.178
	Word Reading	*Ref*	−4.3 (−10.9, 2.1) 0.182	−6.3 (−12.9, 0.2) 0.058
	Sentence Comprehension [c]	*Ref*	−4.3 (−12.9, 4.3) 0.317	−2.8 (−11.5, 5.9) 0.524
	Reading Composite [c]	*Ref*	−5.5 (−13.4, 2.3) 0.165	−5.5 (−13.5, 2.5) 0.175

* β (95 % CI)*; β: Beta coefficient, (95 % CI): 95 % confidence interval.
a: Fluid, Total, $n = 57$, *b*: Crystallized, $n = 58$, *c*: Early Childhood, Behavioral Symptoms Index, Sentence Comprehension, Reading Composite, $n = 72$. Sample sizes were reduced from 73 to 72 and from 58 to 57 due to incomplete data from one participant.

The PCE concentrations in exhaled breath found in children in this study are lower than those reported in several previously published studies of dry cleaners, industrial workers, and those living near dry cleaning operations (Dias et al., 2017; McKernan et al., 2008; Scheepers et al., 2019; Schreiber et al., 2002; Solet et al., 1990; Storm et al., 2011). The average exposure level observed in our study was 2.17 μg/m^3, substantially lower than those reported for individuals living in the same building with dry cleaning operations and even lower than reported levels in the control groups of previous studies (Delfino et al., 2003; Storm et al., 2011). Only the average of the highest exposure group in this study (4.78 μg/m^3) was slightly higher than reported control group exposure of 4.4 μg/ m^3 (Delfino et al., 2003) and 4.6 μg/ m^3 for adults and 3.7 μg/ m^3 for children (Storm et al., 2011). The exposure levels observed in the current study were also lower than we observed in our feasibility study (Liu et al., 2022). Despite the relatively low exposure levels, we observed statistically significant associations between PCE exposure and lower neurobehavioral performance among children. This suggests that the impact on neurobehavioral performance of children may occur at PCE exposure levels lower than previously expected and thus public health impacts may be more widespread and applicable to children in the general population rather than just those living at or near contaminated areas. This warrants further investigation.

The analysis of the NIH Toolbox test scores provides insight into the distinctive cognitive domains affected in children by PCE exposure, indicating declines in attention and memory. In our exploration of cognitive performance assessments, we investigated the association between the NIH Toolbox tests and PCE exposure groups. The NIH Toolbox Cognition Battery is composed of seven tests that are aggregated into four composites, as shown in Fig. 3. The Total Composite incorporates all seven tests. The Early Childhood Composite uses short fluid (2 tests) and crystallized (one test) measures that are applicable to 4–6-year-old children. Two of the seven tests are related to vocabulary and reading measures that contribute to crystallized abilities, while the five other measures contribute to fluid abilities. These are mainly related to memory, attention, and processing speed (Akshoomoff et al., 2013). Three out of these five fluid measures are impacted by PCE exposure. One is related to attention, with a statistically significant difference for the highest versus lowest exposure group. The two others are related to memory; both episodic and working memory tests had lower performance with a statistically significant difference for the two higher versus the lowest exposure group. It is worth mentioning that a statistical significance was observed in the Total Composite and the Fluid Composite

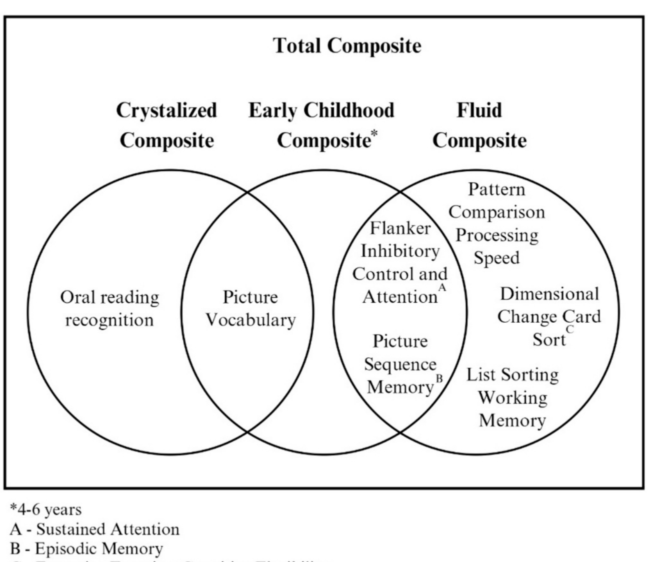

Fig. 3. NIH Toolbox Cognition Battery tests and composites.

even with a smaller sample size of fifty-seven participants, which represent 7–11 years old children in our participants.

Previous research has linked PCE exposure to neurobehavioral problems. Several occupational studies suggested that exposure to PCE leads to decreased cognitive function, disturbances in ocular function, reaction time, deficits in short-term memory for visual designs, perceptual function, attention, and intellectual function (Altmann et al., 1995; Cavalleri et al., 1994; Friedman et al., 2020; White et al., 1995). Three epidemiological investigations on neurobehavioral functions among dry cleaning workers (Seeber, 1989; White et al., 1995) or those living near dry cleaning facilities (Altmann et al., 1995) showed disturbances in memory, attention, and reaction time assessments. Residential investigations show similar effects among those living near dry cleaning enterprises with low levels of exposure (Schreiber et al., 2002; Storm et al., 2011). Our findings are consistent with these previously reported cognitive function impairments. Most of these studies were conducted on adults. Our study results complement these findings by showing cognitive function impairments in children exposed to PCE at low levels, which is consistent with a study conducted on children exposed to PCE in community settings (Janulewicz et al., 2008).

We did not observe a difference in PCE concentrations in exhaled breath samples among participants living in the contaminated areas and those not living in any known contaminated areas. However, we were able to find a significant association between exposure and cognitive functions, indicating that the current PCE exposure measure may potentially be correlated with long-term exposure to PCE. Notably, 67 % of our participants have either one or two addresses during their lifetime. We modeled the number of years living in the contaminated areas as a surrogate for cumulative PCE exposure but did not find any significant associations with neurobehavioral performance outcome measures. This was not fully unanticipated as the number of years living in the contaminated areas may not be a suitable surrogate of cumulative exposure. It is important to note that not all properties within the plumes exhibited vapor intrusion issues. This is likely due to variations in house characteristics, basement types and features, and soil characteristics beneath the properties. Another factor that might contribute to this is the presence of unmeasured indoor sources of PCE in homes.

This study has several limitations that should be considered. Due to the cross-sectional design, we cannot definitively establish a temporal relationship between PCE exposure and neurobehavioral outcomes. Longitudinal epidemiological studies would be valuable in exploring the long-term effects of PCE exposure. There could be potential exposure misclassification due to the single exposure measurement collected in the study. Efforts should be made in future studies to assess variations in the exposure and the association between PCE exposure and its concentrations indoors to better characterize the exposure and its sources and pathways. Relying on caregiver input to acquire some information on exposure and outcomes might have introduced recall bias and impacted the accuracy of data collected, contributing to the uncertainties in the assessment. The self-selected recruitment strategy could lead to selection bias. We did not have an unexposed control group in the study due to the limited time and resources of a pilot study. It would also be challenging to find a completely unexposed population since there are multiple common sources of PCE exposure that are not from environmental contaminations. Additionally, although we inquired about testing schools for PCE indoor air concentrations, this was not conducted in the study. Future studies should consider measuring PCE levels in schools, daycare centers, and other spaces where children spend time to better understand exposure sources and pathways. Finally, the small sample size limits our ability to generalize these results. However, our observation of significant associations in this small sample size warrants further investigation.

The strengths of this study go beyond its design and consistent results. By utilizing a range of assessment tools, such as the NIH Toolbox Cognition Battery, BASC-3, and WRAT-5, we were able to evaluate various aspects of neurobehavioral functioning. This approach provides an understanding of how PCE exposure may impact different domains within neurobehavioral performance in children. The observed pattern of exposure levels leading to more significant effects adds weight to the possibility of a causal association. These findings indicate that although the average scores did not uniformly indicate significant issues, a subset of participants displayed individual scores that warranted in-depth investigation. This study's findings contribute to the growing body of research demonstrating PCE's potential hazard to children's neurobehavioral development, especially for many communities near contaminated sites with PCE and other hazardous chemicals.

The United Nations' Sustainable Development Goals (SDGs) aim to promote health, well-being, and sustainable living environments globally. Our study aligns with SDG 3 (Good Health and Well-being) Target #9, which focuses on reducing illnesses and deaths caused by hazardous chemicals and pollution, as well as one of the outcome targets of SDG 11 (Sustainable Cities and Communities) that focuses on safe and affordable housing. Our findings highlight the importance of several practical recommendations to improve indoor air quality and reduce exposure to harmful chemicals, as outlined by the National Center for Healthy Housing, Indiana Healthy Homes Alliance, and Improving Kids' Environment (National Center for Healthy Housing (NCHH), n.d.). These recommendations include encouraging the use of safer cleaning products, limiting dry cleaning, maintaining heating, ventilation, and air conditioning systems with timely air filter replacements, increasing natural ventilation in homes when weather permits to reduce indoor air pollution, and mitigating exposure to PCE and other VOCs from dry-cleaned items by airing them out before bringing them indoors.

The findings of this study emphasize the need for continued monitoring and regulation of PCE exposure, especially in community and residential settings. By emphasizing the strengths and avoiding the limitations of the study, future research can better explore the underlying mechanisms and long-term effects of low-level PCE exposure. These recommendations will help improve public health strategies, ensuring safer living environments for children, particularly in communities near contaminated sites.

5. Conclusions

This study showed associations between PCE exposure in children and lower scores in various areas of cognitive functioning, including memory, attention, problem-solving abilities, and adaptive functioning. Specifically, it identified that PCE in exhaled breath was linked to impairments in working memory, episodic memory, processing speed, and executive function-cognitive flexibility. These associations were observed at relatively low levels of PCE exposure, compared to higher levels typically observed in occupational settings and residential areas near dry cleaning facilities, which suggests that even seemingly low levels of PCE exposure have a measurable impact on neurobehavioral performance among children. This is potentially generalizable to the greater population, as many similar communities face the challenge of widespread PCE exposure. Further research is needed to confirm these findings, explore the underlying mechanisms, and investigate the long-term effects of PCE exposure at low community exposure levels.

CRediT authorship contribution statement

Marwan Alajlouni: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Ian Kurz:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis. **Jung Hyun Lee:** Data curation. **Alaina K. Bryant:** Writing – review & editing, Writing – original draft, Data curation. **Jackson Pechin:** Writing – original draft, Formal analysis. **Brandon Tso:** Writing – original draft. **Abigail Valdez:** Writing – original draft. **Sujana Vemuru:** Data curation. **Monica Bozymski:** Writing – review & editing, Visualization, Resources, Project administration, Data curation. **Bethaney Latham:** Writing – review & editing, Resources, Investigation, Data curation. **Stephanie Littell:** Writing – review & editing, Resources, Investigation, Data curation. **Samantha Mills:** Writing – review & editing, Resources, Data curation. **Steven M. Koch:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Conceptualization. **Mary E. Turyk:** Writing – review & editing, Resources, Methodology, Investigation. **Sa Liu:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Sa Liu reports financial support was provided by Ralph W and Grace M Showalter Research Trust Fund. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2024.176172.

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