Apartment Residents' and Day Care Workers' Exposures to Tetrachloroethylene and Deficits in Visual Contrast Sensitivity

Judith S. Schreiber,[1] H. Kenneth Hudnell,[2] Andrew M. Geller,[2] Dennis E. House,[2] Kenneth M. Aldous,[3] Michael S. Force,[3] Karyn Langguth,[4] Elizabeth J. Prohonic,[4] and Jean C. Parker[5]

[1]State of New York, Office of Attorney General, Albany, New York, USA; [2]Office of Research and Development, National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA; [3]New York State Department of Health, Wadsworth Center, Albany, New York, USA; [4]New York State Department of Health, Center for Environmental Health, Troy, New York, USA; [5]Office of Research and Development, National Center for Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC, USA

Tetrachloroethylene (also called perchloroethylene, or perc), a volatile organic compound, has been the predominant solvent used by the dry-cleaning industry for many years. The U.S. Environmental Protection Agency (EPA) classified perc as a hazardous air pollutant because of its potential adverse impact on human health. Several occupational studies have indicated that chronic, airborne perc exposure adversely affects neurobehavioral functions in workers, particularly visual color discrimination and tasks dependent on rapid visual-information processing. A 1995 study by Altmann and colleagues extended these findings, indicating that environmental perc exposure at a mean level of 4,980 μg/m^3 (median=1,360 μg/m^3) alters neurobehavioral functions in residents living near dry-cleaning facilities. Although the U.S. EPA has not yet set a reference concentration guideline level for environmental exposure to airborne perc, the New York State Department of Health set an air quality guideline of 100 μg/m^3. In the current residential study, we investigated the potential for perc exposure and neurologic effects, using a battery of visual-system function tests, among healthy members of six families living in two apartment buildings in New York City that contained dry-cleaning facilities on the ground floors. In addition, a day care investigation assessed the potential for perc exposure and effects among workers at a day care center located in the same one-story building as a dry-cleaning facility. Results from the residential study showed a mean exposure level of 778 μg/m^3 perc in indoor air for a mean of 5.8 years, and that perc levels in breath, blood, and urine were 1–2 orders of magnitude in excess of background values. Group-mean visual contrast sensitivity (VCS), a measure of the ability to detect visual patterns, was significantly reduced in the 17 exposed study participants relative to unexposed matched-control participants. The groups did not differ in visual acuity, suggesting that the VCS deficit was of neurologic origin. Healthy workers in the day care investigation were chronically exposed to airborne perc at a mean of 2,150 μg/m^3 for a mean of 4.0 years. Again, group-mean VCS, measured 6 weeks after exposure cessation, was significantly reduced in the nine exposed workers relative to matched controls, and the groups did not differ significantly in visual acuity. These results suggested that chronic, environmental exposure to airborne perc adversely affects neurobehavioral function in healthy individuals. Further research is needed to assess the susceptibility of the young and elderly to perc-induced effects, to determine whether persistent solvent-induced VCS deficits are a risk factor for the development of neurologic disease, and to identify the no observable adverse effect level for chronic, environmental, perc exposure in humans. *Key words:* **color discrimination, human exposure, perchloroethylene, tetrachlorethylene, vision, visual contrast sensitivity.** *Environ Health Perspect* **110:655–664 (2002). [Online 24 May 2002]**

http://ehpnet1.niehs.nih.gov/docs/2002/110p655-664schreiber/abstract.html

Perchloroethylene (perc; also called tetrachloroethylene or tetrachloroethene) is a polychlorinated organic compound ($Cl_2C=CCl_2$) used by most dry-cleaning facilities and in other applications that require a nonpolar solvent (*1*). The U.S. Environmental Protection Agency (EPA) designated perc as one of 33 hazardous air pollutants in the Urban Air Toxics Strategy because of concerns for human health (*2*), and the International Agency for Research on Cancer classified perc as a probable human carcinogen (*3*). Occupational studies indicated that chronic perc exposure adversely affects the central nervous system, kidneys, liver, and the reproductive system (*4*), even at airborne exposure levels well below the 8-hr, time-weighted average, threshold limit value of 170,000 μg/m^3 (25 ppm; 6,800 μg/m^3 = 1ppm) proposed by the American Conference of Governmental Industrial Hygienists (*5*). Inhalation was usually the major route of exposure to perc because it is highly volatile. In addition to occupational exposure to perc, screening for environmental exposure indicated that 76% of the general population had detectable perc in urine (*6*). A survey identified 600 operating dry-cleaning facilities in residential buildings in New York State (*7*) that were estimated to expose 170,000 residents and workers. Residential indoor air perc levels ranged from several hundred to thousands of micrograms per cubic meter (*8*), far in excess of background indoor air perc levels of 5–6 μg/m^3 (0.75–0.89 ppb) (*9,10*). The U.S. EPA has not yet issued a reference concentration (RfC) guideline level for environmental exposure to airborne perc, but the New York State Department of Health (NYSDOH) developed an air quality guideline of 100 μg/m^3 (15 ppb) (*11*). The observations of perc-induced health effects in occupationally exposed populations (*4*) and of environmental perc exposure in the general population (*6–8*) indicate that research is needed on which to base human-health risk assessments of environmental perc exposure.

Address correspondence to H.K. Hudnell, MD-74B, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711 USA. Telephone: (919) 541-7866. Fax: (919) 541-4849. E-mail: hudnell.ken@epa.gov

We thank S. House and D. Sharron of the New York State Department of Health for their assistance in sample collection and data analysis; R. Narang of the Wadsworth Laboratory of NYSDOH, D. Ashley of the Centers for Disease Control and Prevention, and W. Dekant of the University of Wurzburg, Germany, for sample analysis; and D. Monahan of Mt. Sinai Medical Center for blood sample collections. We also thank reviewers of the paper for the U.S. EPA clearance process—P. Bushnell, C. Scott, R. Hetes, within EPA's Office of Research and Development, and F. Gobba, Universita di Modena e Reggio Emilia, Italy—for their insightful comments and suggestions. We express our appreciation to the families who participated in the study for their generous cooperation.

This work was supported by U.S. EPA Cooperative Agreement CR824400-01. This manuscript was reviewed by the National Health and Environmental Effects Research Laboratory, U.S. EPA, and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the agency, nor does mention of trade names or commercial products constitute endorsement or recommendation. This manuscript was reviewed by the Office of the New York State Attorney General and approved for publication. Approval does not signify that the contents necessarily reflect the views and policies of the Attorney General's Office. J.S. Schreiber collected the data discussed in this article while employed at the New York State Department of Health prior to employment with the Attorney General's Office.

Received 15 August 2001; accepted 2 January 2002.

Acute, high-level perc exposures have been associated with blindness (*12*) and child death (*13*), whereas neurobehavioral tests have associated chronic, lower-level exposures with subclinical neurologic effects in studies of dry-cleaning workers (Table 1). Relative to matched control subjects, perc-exposed workers had worse performance on neurobehavioral tests of color vision (*14*) that developed within 2 years (*15*), perceptual speed (*16*), sensory-motor and cognitive functions (*17,18*), as well as an increased prevalence of central nervous system symptoms (*19*). Table 1 shows that similar effects were reported in residents living near dry-cleaning facilities where the median indoor air perc level was 1,360 μg/m^3 (*20*). The neurobehavioral tests used to detect perc-related effects at increasingly lower exposure levels tended to more selectively activate visual system processes (*14,15)* or processes dependent on rapid visual detections and information processing (*20*).

Although not applied in previous studies of perc-exposed populations, visual contrast sensitivity (VCS), a measurement of visual pattern detection ability, has been a sensitive indicator of neurotoxicity induced by other organic solvents. Persistent or permanent VCS deficits in the presence of normal visual acuity have been observed in workers exposed to styrene (*21,22*) and mixed solvents (*23–26*), as have color discrimination deficits (*27–38*) in the absence of detectable optical, retinal, or optic nerve head pathology (*39*). VCS, a nonspecific indicator of subclinical visual impairment (*40*), also revealed neurologic effects associated with exposure to toxic *Pfiesteria sp.*-inhabited estuaries (*40–42*), with lead and mercury exposure (*43–47*), and was useful in differentiating vision effects from other exposure-induced deficits in neurobehavioral functions (*48*).

The current residential study and day care investigation sought to characterize perc exposure and screen for subclinical neurologic effects using a battery of visual function tests in two populations with potential environmental perc exposure due to close proximity with dry-cleaning facilities. The first population resided in apartment buildings with a dry-cleaning facility located on the ground floor, a population previously considered at risk for perc exposure (*6*). The second population worked at a day care facility located adjacent to and within the same building as a dry-cleaning facility. In addition, the NYSDOH and the Centers for Disease Control and Prevention (CDC) conducted a pediatric neurologic assessment of current and former day care students, the results of which are reported elsewhere (*49*).

Methods

The residential study and day care investigation were approved by the U.S. EPA's Office of Research and Development and the NYSDOH.

Participant recruitment and selection. **Residential study.** Preliminary measurements of perc in air were made in 16 apartments in eight New York City buildings containing operating dry-cleaning facilities to determine the range of perc concentrations across apartments. Two buildings, in which apartment mean perc concentrations ranged from 650 to 6,100 μg/m^3 between mid-October and late January were selected for the study. Both dry-cleaning facilities operated third-generation, dry-to-dry (washing and drying are done in the same machine) machines with refrigerated condensers but without carbon absorbers. Families contacted about potential study participation were enrolled in the study if the family resided for ≥ 1 year in one of the buildings, and each family member or guardian voluntarily agreed to *a*) the collection of environmental samples in their apartment; *b*) provide biologic samples and undergo vision testing; and *c*) complete a questionnaire. Six families with 17 members living in the two buildings were recruited for study participation. All participants or their guardians signed voluntary consent forms approved by the NYSDOH Institutional Review Board before their participation in the study began. Of the 17 exposed participants (mean age = 34.35 years ± 4.41 SEM; median = 37 years; 9 male; 8 female), 4 were children aged 6–13 years (3 male; 11 female), 11 were adults of 22–50 years (4 male; 7 female), and 2 were > 60 years (both male). Age- (within 2 years) and sex-controls were recruited for visual function assessment from NYSDOH workers in Albany and their children. In some cases, more than one matched control was selected

Table 1. Human perc exposure and effect studies.

Study (reference)	Study participants	Indoor air perc and duration	Effect
Echeverria et al., 1995 (*17*)	Dry cleaners	Mean = 41.8 ppm (284,240 μg/m^3) Mean at main job = 14.6 years Mean at same shop = 20.2 years	Visual reproduction, pattern memory and recognition
Cai et al., 1992 (*19*)	Dry cleaners	10 > geometric mean < 20 ppm[a] (68,000–136,000 μg/m^3) Mean work = 3.0 years	Neurologic symptoms
Ferroni et al., 1992 (*18*)	Dry cleaners	Median = 15.0 ppm (102,060 μg/m^3) Mean work = 10.1 years	Visual reaction time Serum prolactin
Seeber et al., 1989 (*16*)	Dry cleaners	Mean = 12.3 ppm (83,400 μg/m^3) Mean work = 11.8 years	Perceptual speed, digit symbol, and reproduction, attention
Cavalleri et al., 1994 (*14*)	Dry cleaners	Mean = 6.23 ppm (42,364 μg/m^3) Mean work = 8.8 years	Lanthony D15-d color discrimination
Gobba et al., 1998 (*15*)	Dry cleaners	Geometric mean increase 1.67 to 4.35 ppm (11,356 to 29,580 μg/m^3) over 2 years	Lanthony D15-d color discrimination
Altmann et al., 1995 (*20*)	Neighbors of dry cleaner	Mean = 0.73 ppm (4,980 μg/m^3) Median = 0.20 ppm (1,360 μg/m^3) Mean residence = 10.6 years	Visual memory, visual reaction time, vigilance
Current residential study[b]	Apartment residents above dry cleaner	Mean = 0.11 ppm[c] (778 μg/m^3) Median = 0.05 ppm (350 μg/m^3) Mean residence = 5.8 years Lifetime dose = 3,400 μg/m^3 years[d]	Visual contrast sensitivity trend in Lanthony D15-d
Current day care investigation	Day care workers sharing building with dry cleaner	Mean = 0.32 ppm (2,150 μg/m^3) Median = 0.32 ppm (2,150 μg/m^3) Mean work = 4.0 years Lifetime dose = 1,978 μg/m^3 years[d]	Visual contrast sensitivity

[a]Subgroup in 10–20 ppm range from population with geometric mean = 20 ppm. [b]Data are based on the study measurements, not the preliminary measurements (see Table 2). [c]Mean of daytime and overnight samples. [d]Lifetime dose = mean airborne concentration × (mean years × mean % time at exposure site), not an internal dose estimate.

for an exposed participant, resulting in the testing of 25 control participants. When more than one control participant was matched with an exposed participant, data from the controls were averaged for comparison to data from the exposed participant, yielding 17 matched-control (mean age = 33.24 years ± 4.41 SEM; median = 36 years; 9 male, 8 female) comparisons. Control participants were considered representative of the general population not living near dry-cleaning facilities, for whom nationwide surveys indicated that mean perc exposures were much lower than for populations exposed through proximity to a dry-cleaning facility (Table 2).

Day care investigation. A day care center in Albany County, New York, was located in a one-story building separated by an interior wall from an operating dry-cleaning facility that used a third-generation machine. A parent of a day care student contacted the NYSDOH and expressed concern about perc exposure. Air samples showed elevated perc levels in the absence of a detectable perc odor. Upon notification, the owner of the dry-cleaning facility ceased active dry cleaning. All nine adult staff (mean age = 27.20 years ± 3.03 SEM; median = 24.5 years; all female) of the day care center were invited and agreed to participate in the study. The nine control participants (mean age = 27.67 years ± 2.81 SEM; median = 25.3 years; all female) were age- and sex-matched acquaintances of the exposed participants, local retail shop employees, NYSDOH employees, or staff from other local day care centers with no known perc exposure. Both the exposed and control participants volunteered and signed informed consent forms approved by the NYSDOH Institutional Review Board, indicating their willingness to undergo visual function testing and complete a questionnaire.

Test administration. **Residential study.** A questionnaire on sociodemographics, lifestyle factors, medical history, and neurotoxicant exposures was administered to the exposed and control study participants. Sociodemographic questions assessed age, sex, ethnicity, residence location, presence of odors in residence, and hours spent in the residence during each day of the week. Lifestyle factors assessed included personal or family member smoking, alcohol consumption, and exercise. The medical assessment included a 74-item symptom checklist, questions on suspected or diagnosed ocular/visual, auditory, respiratory, liver, kidney, diabetic, neurologic, or psychiatric conditions, current and past medication usage, general physical condition, and body size. Potential neurotoxicant exposure was assessed using job title, 22 specific occupations and work environments, hobbies that might involve solvent exposure, in-home use of solvent-containing products, in-home dry cleaning, and pumping gas. The Profile of Mood States (POMS) questionnaire was administered to exposed participants to assess affective status on six scales: tension, depression, anxiety, vigor, fatigue, and confusion. The vision tests were administered to all participants by investigators who were aware of the participants' group assignments.

Day care investigation. The vision tests and questionnaire were administered to all exposed and control study participants about 6 weeks after the dry-cleaning facility ceased cleaning on site. The questionnaire was altered as needed to obtain data relevant to work in the day care center as opposed to residence in an apartment. All data were collected by investigators who were aware of the participants' group assignments.

Sample collection. **Residential study.** The dry-cleaning facilities were located on the first floors of the apartment buildings. Both buildings were of high-rise steel and concrete construction. The ventilation and physical layout of hallways, windows, doors, and stairwells varied between buildings. In building A, two families lived on the second floor, one directly above the dry-cleaning facility and the other on the opposite side of the building. Four families lived in building B; one on the third floor vertically in line with the dry-cleaning facility, another on the opposite side of third floor, and one each on the fourth and sixth floors vertically in line with the dry-cleaning facility. Other apartments in the buildings were not sampled.

All exposed subjects were asked to provide urine and exhaled breath samples. Exposed subjects over age 17 were also asked to provide blood samples. Breast milk samples were requested from two participating nursing mothers. All samples were analyzed for perc, and urine samples were also analyzed for metabolites of perc. Multiple indoor air samples were collected at each study residence. Neither building had central air conditioning. Some rooms contained window air conditioners, and the windows were open in some other rooms. All exposed participants wore passive organic vapor sampling devices (carbon type adsorbent badges) for measuring personal exposure to perc.

Continuous indoor air and personal air samples were collected using 3M brand (Minnesota Mining and Manufacturing Co., Minneapolis, MN) passive organic vapor sampling devices (PSDs). Perc concentrations in indoor air were measured in rooms where residents spent significant amounts of time, such as the living room, bedroom, and kitchen. Participants wore PSDs on their outer clothing, clipped to the front on a shirt, coat, jacket, or nightclothes to sample

Table 2. Residential study: summary of air concentrations and biomarkers of dose.

Samples	No.	Range	Mean ± SEM	Median	Background mean (reference)
Indoor air (µg/m^3)[a]					5 (*9*), 6 (*10*)
Preliminary day	12	650–6,100	2,408 ± 848	1,450	Median = 2 (*10*)
Indoor air (µg/m^3)[b,c]					
Study, daytime	54	65–5,300	1,198 ± 622	620	
Study, overnight	50	50–1,300	358 ± 133	205	
Personal air (µg/m^3)[b,c]					10 (*50*)
Daytime	17	5–4,100	948 ± 640	403	32 (*10*)
Overnight	17	75–1,025	420 ± 174	206	
Breath (µg/m^3)[b,d]					12 (*50*)
Afternoon	17	110–1,000	413 ± 164	186	
Morning	17	107–1,125	439 ± 166	231	
Blood (µg/L)[b,d,e]					0.19 (*51*)
Afternoon	13	1.1–18	6.43 ± 2.47	4.95	0.21 (*10*)
Morning	13	1.1–7	4.87 ± 0.91	5.75	0.15 (*6*)
Urine (µg/g creatinine)[b,d,f]					
Perc					< 0.5 (*49*)
Afternoon	10	< 0.33–4.7	4.07 ± 2.18	2.85	0.11 (*6*)
Morning	10	< 0.28–3.2	1.29 ± 0.65	0.77	
TCA					1.8 (*49*)
Afternoon	10	< 0.83–21.0	6.62 ± 4.83	2.53	
Morning	10	< 0.44–6.8	3.59 ± 1.35	3.68	
TCEtOH					1.2 (*49*)
Afternoon	10	< 0.33–4.5	1.39 ± 1.04	0.40	
Morning	10	< 0.28–4.0	1.83 ± 0.86	1.51	

[a]Preliminary measurements made during active dry cleaning period in both apartment buildings (one family in October 1996; three families in January 1996; two families in January 1997). [b]Study measurements made in February, March, and November 1996 in buildings A and B (four families) during active dry-cleaning period; study measurements made in February 1997 in building B (two families) when active dry cleaning had ceased for 1 month. [c]Continuous daytime air samples collected 0700–1900 hr; continuous overnight samples collected 1900–0700 hr. [d]Discrete afternoon biologic samples collected in late afternoon and correspond to daytime air samples; discrete morning samples collected in early morning and correspond to overnight air samples. [e]Perc levels in blood samples from one participant were 42 ug/L immediately after extensive use of an exercise bicycle and 43 µg/L 7 hr later; data from this special assessment are not included in the table values. [f]One-half of the detection limit was used for nondetected concentrations.

perc near their breathing space. PSDs were removed from participants' clothing at bedtime and placed near their pillows. PSDs were kept on a counter in the bathroom away from direct water (humidity does not interfere with PSDs) when participants bathed or showered. Duplicate samples (two samples collected simultaneously in the same location) were collected overnight (approximately 12 hr), and again on the following day (approximately 12 hr). An activity diary was completed by each participant for 48 hr before and during PSD use to track the amount of time spent in the apartment and elsewhere. At the end of sampling periods, investigators sealed the PSD by affixing the impermeable, hard plastic lid provided by the manufacturer.

Participants forced air through tapered glass tubes equipped at both ends with stainless-steel shut-off valves for alveolar breath collection (*52*). Participants held their breath for 10 sec before forceful exhalation, and the last 40 mL of breath was captured for analysis. Blood samples were collected by a board-qualified phlebotomist according to a standard NYSDOH protocol (*53*), using glass vials certified to be free of volatile organic compounds. The vials had airtight caps. Samples were collected in early morning and late afternoon from participants ≥ 18 years of age. Breast milk samples were collected in glass containers certified to be free of volatile organic compounds using standard procedures (*54*).

Urine samples were collected upon waking (first void urine) by each exposed participant in containers certified to be free of volatile organic compounds, provided by the investigators. Time of sample collection was noted by the participant on the container label and on a log sheet. All urine samples were analyzed for perc, for the perc metabolites, trichloroacetic acid (TCA), and trichloroethanol (TCEtOH), and for creatinine, a normal component of urine. In addition, the toxic end-urinary acetyl metabolite from the newly discovered mercapturic acid pathway (*55–57*) was assayed in urine samples from four exposed participants.

Day care investigation. PSDs were used to measure indoor air perc concentrations at the day care center on one day in August while the dry cleaning facility was in operation. Consultation between the facility operator and NYSDOH personnel led to the cessation of active dry cleaning the day after sample results were available, and the cleaning equipment was subsequently removed. The questionnaire and vision data were collected 6 weeks after on-premises dry cleaning ended. Personal air, breath, blood, and urine samples were not collected in the day care investigation due to the 6-week time lag between the closing of the dry cleaning facility and issuance of approvals for the study from appropriate boards. Perc elimination half-lives range from about 12 to 40 hr in various biologic tissues (*58*).

Sample analysis methods. The Wadsworth Center Laboratory for Organic Analytical Chemistry performed the chemical analyses. The PSD analysis methods of Amin and colleagues (*59*) were used for measurement of perc in personal air, ambient air, and indoor air with a detection sensitivity of about 5 $\mu g/m^3$. Standards of perc in nitrogen were used to calibrate the gas chromatograph/electron capture (GC/EC) system response to perc. Breath samples were anlayzed by direct injection to a gas chromatograph equipped with an election capture detector (*60*). Carbon dioxide levels in the breath samples were also measured using GC with a thermal conductivity detector.

The method of Ashley and colleagues (*61*) was adapted for the analysis of perc in blood using purge-and-trap gas chromatography/mass spectrometry (GC/MS). Results from split sample analyses performed by the CDC indicated good correspondence between laboratories. The detection limit was 0.5 µg/L, with an average spike recovery of 105%. Similar procedures were used to measure perc in breast milk.

Urine sample analyses used a purge-and-trap method with a Tekmar LSC-1 (Tekmar-Dohrman, Mason, OH) unit fitted with a #1 (tenax) trap configured to a Hewlett-Packard 5890/5970 GC/MS. A Restek 105 meter Rtx 502.2 column (Restek Corp., Bellefonte, PA) was used to separate the perc from other volatile components. Analyses of TCA and TCEtOH were performed using a modification of the U.S. EPA method 552 for haloacetic acids (*62*). These metabolites were measured by GC/EC after methylation with diazomethane and micro-extraction of the esters from the reaction mixture using methyl tertiary butyl ether (MTBE). The extract was then analyzed using an HP 7673 liquid autosampler (Agilent Technologies, Wilmington, DE) configured to the same GC/EC system described above. Creatinine concentrations in urine samples were determined by reaction with alkaline picrate to produce a red color [Jaffe reaction (*63*)]. The spectrophotometric test was performed using a Sigma Diagnostics Kit (Sigma, St. Louis, MO) and UV/visible spectrophotometer (LKB Novaspec 4049; LKB Biochrome, Cambridge, England). The detection limit for perc, TCA, and TCEtOH was 0.5 µg/L, with average spike recoveries of 90, 95, and 115%, respectively.

Split urine samples from four exposed participants were analyzed for the mercapturic acid (glutathione conjugation) pathway perc metabolite, *N*-acetyl-*S*-(1,2,2-trichlorovinyl)-L-cysteine (N-ac-TCVC), in the University of Wurzburg Institute of Toxicology, Wurzburg, Germany, using procedures published previously (*64,65*). A GC/MS capture mass spectometer with splitless injection (valve time = 1.0 min) was used to measure N-ac-TCVC and the internal standard, d_3-N-ac-TCVC. Characteristic fragments (m/z 178, m/z 180, m/z 181, and m/z 183) were monitored to quantitate the metabolite and standard using methane chemical ionization and negative ion detection procedures in the single ion monitoring mode.

Visual function test methods. Three tests of visual function—near visual acuity, near visual contrast sensitivity, and color discrimination—were administered in the study concurrent with air sampling for perc. The vision tests were administered separately to each eye of each subject under standard conditions as described below. Test stimuli were illuminated by a daylight flourescent lamp (correlated color temperature of approximately 6,500°K; color rendering index > 90; intensity = 1,150 lux) which provided a luminance of approximately 70 foot-lambert. All subjects who normally used corrective lenses for near-point viewing wore them during vision testing. A card holder placed just under the cheek bones was used to position test cards at a constant distance from the eyes.

Visual acuity. To test visual acuity, we used the Rosenbaum Pocket Vision Screener (Grass Instrument Co., Quincy, MA). The card contained rows of numbers and figures that progressed from a larger angular subtense (size) at the top to a smaller angular subtense at the bottom. The investigator asked the subjects to read the numbers in each row, progressing from top to bottom. The Snellen distance equivalent of the row with the smallest numbers that were all correctly identified was recorded as the visual acuity score. An ideal score for near visual acuity was 20:20 vision, indicating that the subject correctly identified numbers on the chart that were of an angular subtense that would yield a score of 20:20 on a far visual acuity test administered at a distance of 20 feet. Higher scores (e.g., 20:40) indicated worse performance (the angular subtense of the correctly identified stimuli corresponded in size to that which could be correctly identified by a viewer with 20:20 far visual acuity at a distance of 40 feet).

Vision contrast sensitivity. To test vision contrast sensitivity, we used the Functional Acuity Contrast Test, F.A.C.T. 101 (Stereo Optical Co., Chicago, IL). The contrast sensitivity test measured the ability to distinguish subtle differences in shades of gray. The test card contained a matrix (5 × 9) of

circles filled with sinusoidal gratings (dark and light bars). Spatial frequency [1.5, 3, 6, 12 and 18 cycles per degree (cpd) of visual arc] increased from top to bottom, and contrast decreased from left to right in steps of approximately 0.15 log units. The grating bars were oriented either vertically or tilted 15 degrees to the left or right. As the investigator called out each circle from left to right, row by row, subjects responded by saying either vertical, left, right, or blank. Participants were encouraged to name an orientation if they had any indication that the bars could be seen. Participants were asked to point in the direction to which the top of the grating was tilted if they had any difficulty in verbalizing the orientation. If orientation was misidentified, the subject was instructed to view each preceding patch to the left until a correct response was again obtained. Testing then proceeded to the right, and the last patch correctly identified was taken as the contrast sensitivity score for that spatial frequency. The procedure was repeated for each row in descending order. Scores were recorded on a graph showing the normative range (90% confidence interval).

Color discrimination test. To test color discrimination, we used Lanthony's Desaturated 15 Hue Test according to Farnsworth-Munsell (D-15d) (Luneau Ophthalmology, Paris, France). The color vision test measures the ability to distinguish differences in color tones (hues) and can detect both congenital and acquired discrimination deficits (*66*). Subjects were shown a rectangular box containing 16 color chips arranged in chromatic order. The investigator removed 15 chips, leaving the first as a standard, and randomized them in front of the subjects. Subjects were instructed to identify the chip which most closely matches the standard in hue, to place it in the box next to the standard, and to continue the process until all chips were in the box. Subjects were allowed to rearrange chips in the box at any time and to take as long as needed to complete the test. The order of chip placement was recorded for use in analyses.

Data analysis. SYSTAT for Windows, Version 5 computer software (SPSS, Inc., Chicago, IL) was used to calculate means, medians, and ranges for all the environmental and biologic data. Data from duplicate PSD samples were treated as separate results in the calculations. The results for both PSDs in a duplicate sample were excluded from further analysis if their values differed ≥ 20%. Eight of the 113 duplicate pairs (7%) of PSDs collected during the residential study were excluded on this basis. The eight pairs of PSDs that were excluded were nonsystematically distributed throughout the range of perc concentrations. The indoor air study mean and medium perc concentrations in Table 2 were derived from mean values for each apartment. This approach prevented weighting the means with more samples from one apartment than another.

For personal air and biologic media concentrations, we calculated mean values for each family to prevent weighting the overall study means with more samples from one family than another. First, the results for each participant for a given medium were averaged. Then the individual means from all family members were averaged to produce a family mean for that medium. The family means were used to calculate an overall study mean for each medium. Therefore, the study means in Table 2 represent the means of six families, whereas the range and median values were derived directly from individuals' data.

The *a priori* criterion for the inclusion of vision data in analyses was that the eye have a corrected visual acuity Snellen Distance Equivalent score of 20:70 or better. This approach avoided possible confounding of the color discrimination and VCS results by excessive optical refraction error. In the residential study, the data from one eye in each of two exposed participants were excluded from analyses due to failure to meet this acuity criterion. No eyes failed to meet the criterion in the day care investigation. The unit of analysis for vision scores was the mean score of the two eyes for each participant, except the two excluded eyes. In these cases, vision scores from the qualifying eyes of the participants were used in the analyses. Visual acuity was analyzed using two-tailed Student's *t*-tests with an $\alpha = 0.05$ and matched-pair techniques to determine if differences between exposed- and control-group scores were statistically significant.

The VCS data were analyzed with SAS software (version 6.0; SAS Institute, Cary, NC) using multivariate analyses of variance (MANOVA, with the Wilks' lambda statistic) procedures suitable for repeated measures and matched-pairs with an $\alpha = 0.05$. The factors in the model were group, spatial frequency, and their interaction term. Mean VCS scores for each eye of each exposed participant were compared to the percentile ranking of control scores when significant group differences were observed.

Quantitative analyses of dyschromatopsia used Bowman's (*66*) method to describe color-confusion space. A total color distance score (TCDS) was calculated based on the order of chip placement. We calculated a color-confusion index (CCI), the ratio of the TCDS and the ideal score, for each participant. Group differences in the CCI were assessed using two-tailed Student's *t*-tests ($\alpha = 0.05$) for matched-pair analyses.

SYSTAT software was used to calculate Pearson correlation coefficients to evaluate possible associations between the environmental data and biologic and vision data from each exposed study participant. Multiple regression analyses, using the VCS scores at mid-spatial frequency (6 cpd) as the dependent variable and the independent variables of years exposed in an apartment or the day care center, percentage of time spent at the exposure site, and perc levels in indoor air, also assessed potential associations.

Results

Residential study. **Questionnaires.** Analyses of the questionnaire data indicated that the exposed and control groups did not differ significantly in age or sex, and that none of the participants had occupational or avocational exposure to perc. Low to moderate alcohol consumption, defined as consumption of standard serving sizes of beer, wine and/or liquor < 10/week, was reported by 61% of the exposed and 52% of the control, adult study participants. Alcohol consumption was reported to be ≥ 10 per week by one participant in each group. The other participants did not drink alcoholic beverages. The exposed participants had no known exposures to other neurotoxicants, ongoing illness, current use of neuroactive drugs, or a medical history indicative of neurologic dysfunction. The POMS test scores of all exposed participants were within normal limits; no cases of clinical depression or other neuropsychiatric conditions were observed.

Exposure. The 17 exposed participants resided in their apartments for an average of 5.75 years ± 0.82 SEM, with a median duration of 6 years while the dry-cleaning facilities were in operation. The group spent a mean of approximately 76% of their time in the apartments. Preliminary apartment indoor air measurements were made during periods of active dry cleaning in both buildings (Table 2). Subsequent air and biologic samples were collected before or about 1 month after the facility operators were ordered to cease operation because of public health concern (Table 2). In the two apartments in building B (7 of 17 participants) where study samples were collected postoperation, indoor air perc levels decreased by a mean of 81% between the preliminary and postoperation measurement periods.

Airborne perc levels in apartment rooms were elevated far above background levels in both buildings during preliminary and study (daytime median = 620 μg/m^3) measurement periods (Table 2). Nearly all of the air samples exceeded the NYSDOH air guideline of 100 μg perc/m^3 (*11*). Only night samples from one apartment, collected after the dry-cleaning facility ceased operation for

the day, showed a mean perc level below 100 μg/m^3. Measurements made 1 month after the both facilities permanently ceased operating dry cleaning machines showed that perc levels in indoor air in both buildings had declined substantially but were still elevated up to eight times above guideline levels (10–800 μg/m^3).

Perc in personal air followed the same trend toward elevation as perc in room air (Table 2). Only one of 34 mean perc levels in personal air was below the U.S. mean personal air level of 10 μg/m^3 (*50*). The personal air samples correlated highly with the room air samples. The overnight samples (r = 0.99) were more highly correlated than daytime samples (r = 0.91), possibly because subjects spent more time in their apartments during the overnight sampling periods.

Levels of perc in breath samples (Table 2) were much higher than the mean perc level in breath (12 μg/m^3) reported by the U.S. EPA (*50*). Perc levels in breath were highly correlated with perc levels in room air (overnight r = 0.91; daytime r = 0.78) and personal air (overnight r = 0.93; daytime r = 0.86), indicating breath is a good biomarker for recent exposure to perc.

Blood samples collected from the 13 adult participants contained perc at levels much higher (Table 2) than the mean (0.19 μg/L) and 95th percentile values (0.62 μg/L) from a U.S. survey (*51*). Follow-up samples collected 1 month after dry cleaning operations ceased showed perc levels in blood in building B residents (mean <0.5 μg/L) decreased to background levels, but remained elevated in building A residents (mean = 6.9 μg/L), as did air levels. Perc levels in blood correlated well with perc levels in room air (overnight r = 0.85; daytime r = 0.93), personal air (overnight r = 0.91; daytime r = 0.99), and breath (overnight r = 0.88; daytime r = 0.99), indicating that blood is a good biomarker for recent exposure to perc.

Group-mean perc levels in urine were more than an order of magnitude higher than published background values (Table 2). The correlation of perc levels in urine, breath, and blood were low because of failure to detect perc in some urine samples, indicating that perc in urine may not be as sensitive an indicator as breath or blood for assessing recent exposure. However, 1 month follow-up samples found that perc concentrations decreased to < 0.53–< 2.5 μg/g creatinine in all urine samples. The perc levels in urine from building A study participants did not remain elevated for as long as perc levels in air, breath, and blood.

Background values for urinary perc metabolite levels in the general population were unavailable. For comparison to metabolite levels seen in the exposed study participants, Table 2 shows levels observed in 21 nonexposed control children from the NYSDOH/U.S. CDC investigation of the day care students (*49*). Group-mean levels of urinary TCA and TCEtOH from the exposed participants ranged from below to about twice as high as the levels observed in the control children. The metabolite from the recently identified glutathione conjugation pathway, N-ac-TCVC, was identified in urine samples from three of four exposed participants.

Two exposed participants were breast-feeding mothers who provided breast milk samples for analysis. The first participant had been lactating for about 6 weeks when the first late day and early morning samples were collected, and for about 23 weeks when sampling was repeated. All samples were collected while the facility was operating dry cleaning machines and mean airborne perc levels ranged from 60 to 2,800 μg/m^3 in the apartment. Her mean concentrations of perc in breast milk ranged from 13 to 75 μg/L and were elevated compared to the mean background level of perc in breast milk of 6.2 μgL (*54*). The second participant was exposed to perc in her home throughout her pregnancy and provided breast milk samples beginning several days postpartum. These samples were collected 1 and 4 months after active dry cleaning ceased. One month after dry cleaning ceased, mean breast milk perc concentration was 31 μg/L and mean airborne perc concentration was 575 μg/m^3. Three months later, mean perc concentration in breast milk was 2.2 μg/L and mean airborne perc concentration was 65 μg/m^3. For both participants, lipid content could not be determined because of small sample volume, and no perc metabolites were detected (<0.5 μg/L).

Vision. Matched-pair t-tests showed no significant group difference [t(16) = 1.67, p = 0.12)] between visual acuity scores (control group mean = 20:22.8 ± 1.1 SEM, exposed group mean = 20:27.7 ± 2.7 SEM). However, group-mean VCS (Figure 1A) was significantly lower (worse) in the exposed than the control group across spatial frequencies [F(16,144) = 19.38, p < 0.001]. Lower VCS scores in the exposed than the control group at each spatial frequency, in combination with the lack of a significant group-by-spatial frequency interaction [F(4,144) = 1.22, p = 0.31], indicated that VCS was lower at each spatial frequency in the exposed than the control group. Mean VCS scores in at least one eye of 11 of the 17 exposed participants (65%; all 4 children, both adults ≥ 60 years of age, 5 other adults) were ≤ the lower 12th percentile score of control participants, whereas this was true for visual acuity in only 5 of 17 exposed participants.

Results from the Lanthony Desaturated 15 Hue Color Discrimination test, shown in Figure 2A, indicated that the mean color-confusion index (CCI) score in the exposed group (CCI = 1.33 ± 0.09 SEM) was higher than that of the control group (1.20 ± 0.07 SEM). However, a two-tailed test of the mean CCI for both eyes of each participant, using matched-pair techniques, indicated that the group difference was nonsignificant [t(16) = 1.16, p = 0.26]. Exploratory analyses (*67*) using less conservative approaches, a one-tailed test (p = 0.13) and a two-tailed test using all control participants as individuals and an unpaired technique [t(39) = 1.76, p = 0.04], were suggestive of a possible tread toward worse color discrimination in the exposed group.

Neither the Pearson correlation coefficient nor multiple regression analyses revealed statistically significant dose–response relationships between environmental perc levels or biologic perc doses and deficits in visual perception.

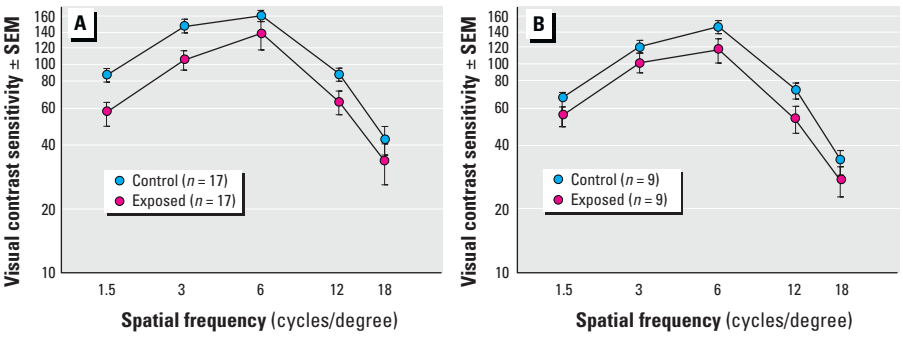

Figure 1. Group-mean visual contrast sensitivity values (± SEM) for populations with chronic, environmental exposure to airborne perc and for matched-control populations. (*A*) VCS was significantly lower across all spatial frequencies in residents of apartments in two buildings that had active dry-cleaning facilities on the ground floor, than in control participants. (*B*) VCS was significantly lower across all spatial frequencies in workers at a day care center that was located adjacent to, and in the same building as, an active dry-cleaning facility, than in control participants.

Day care investigation. **Questionnaires.** Analyses of the questionnaire data indicated that the exposed and control groups did not differ significantly in age, and none of the participants had direct occupational or avocational exposure to perc. Alcohol consumption was low or moderate in all participants. Neither the exposed nor control participants had known exposures to other neurotoxicants, ongoing illness, current use of neuroactive drugs, or a medical history indicative of neurologic dysfunction.

Exposure. The nine female staff members had worked at the day care center for a mean = 8,248 hr, a median = 3,735 hr, and a range = 475–30,084 hr. The mean number of hours spent at work was equivalent to a mean of approximately 4 years during which time the staff spent approximately 23% of their time in the center. The director of the day care was considerably older than the other workers and had worked considerably longer at the center than the other staff members.

Airborne perc concentrations were measured twice on one day in each of the three rooms of the day care center, the main, infant, and toddler rooms, and ranged from 1,800 to 2,400 μg/m^3, with a mean = 2,150 ± 84.7 SEM and median = 2,150 μg/m^3 during active dry cleaning. Perc concentrations in two samples from outside the building under the soffits were 180 and 200 μg/m^3. Six weeks after the facility operator ceased using and removed the dry cleaning machines, levels of airborne perc in the day care center ranged from 8 to 55 μg/m^3.

Vision. Matched-pair *t*-tests showed no significant group difference [$t(8) = 1.56$, $p = 0.16$) between visual acuity scores (control group mean = 20:26.4 ± 2.4 SEM, exposed group mean = 20:22.2 ± 0.8 SEM). However, group-mean VCS (Figure 1B) was significantly lower in the exposed than the in control group across spatial frequencies [$F(8,72) = 21.01$, $p < 0.001$]. Lower VCS scores in the exposed than the control group at each spatial frequency, in combination with the lack of a significant group-by-spatial frequency interaction [$F(4,72) = 1.01$, $p = 0.41$], indicated that VCS was significantly lower at each spatial frequency in the exposed than the control group. Among the nine participants in the exposed group, VCS scores were lower than the control group mean for 7 of 9 at the lowest spatial frequency of 1.5 cpd, for 9 of 9 at 3 cpd, 6 of 9 at 6 cpd, 6 of 9 at 12 cpd, and 6 of 9 at 18 cpd.

Mean CCI scores (Figure 2B) did not differ significantly [$t(8) = 0.91$, $p = 0.39$] between the exposed (CCI = 1.22 ± 0.07 SEM) and control (CCI = 1.18 ± 0.08 SEM) groups.

Discussion

The residential study and the day care investigation both indicated that operating dry-cleaning facilities generated perc emissions to air that spread throughout the buildings in which they were contained. Although the dry-cleaning facilities did not operate at night, indoor and personal air levels remained well above background values (Table 2) over night. The dry-cleaning machines and dry-cleaned fabrics in the facilities likely continued to emit some perc to air at night (*68*). Furthermore, materials in apartments may have acted as sinks, absorbing perc when air concentrations were higher in the daytime and as emission sources via desorption when air concentrations were lower at night (*69*). The elevated perc levels in apartment air were strongly associated with elevated levels in residents' personal air, breath and blood. Perc levels in breast milk from two nursing mothers not only exceeded background values, but were far above the U.S. EPA maximum contaminant level (MCL) for perc in drinking water of 5 μg/L (*70*). Urinary perc levels were well above background values in the residents but correlated weakly with airborne levels. Perc metabolite levels in urine only slightly exceeded background values in the exposed study participants and did not change substantially in follow-up testing, even though room air levels decreased after dry cleaning ceased. Although the number of samples is small and the metabolite background values were from the NYSDOH/U.S. CDC study control children (*49*), urinary perc and metabolite measures may not be as sensitive or as reliable indicators as breath or blood for assessing recent perc exposure.

Measurements of VCS indicated that chronic, environmental perc exposure may adversely affect neurobehavioral function. VCS was significantly lower in the exposed groups than matched-control groups in both the residential study and day care investigation. The VCS deficits were likely of neurologic origin because the exposed and control groups did not differ in visual acuity, indicating that the groups did not different in optical refraction or in the ability to focus images on the retina (*40,48*). The VCS deficits spanned the spatial frequency spectrum in both exposed groups, similar to the VCS deficit profiles seen in other solvent exposed populations (*21–26*) and in contrast to the VCS spatial-frequency profiles observed in populations exposed to methyl mercury (*44,45*) and inorganic mercury (*46,47*). Differences between the shapes of altered VCS spatial-frequency profiles can indicate differential effects of various toxic exposures (*40–48*).

VCS deficits are clearly nonspecific indicators of alterations in neurobehavioral function, having been observed in a number of clinical conditions. A variety of alterations in the VCS spatial-frequency profile have been observed in ocular diseases such as glaucoma, which manifests a low spatial-frequency deficit (*70–72*), macular disease (*73,74*), retinitis pigmentosa (*75–78*), type 1 diabetes before observable retinopathy (*79–81*), and other distal visual conditions (*82,83*). With damage more proximal to the visual cortex, VCS deficits have been observed in cases of optic nerve neuropathy (*84*), optic nerve compression (*85*), and cerebral lesions (*86*). Patients that have recovered from optic neuritis with normal visual acuity retain severe deficits in VCS (*87*). Neurodegenerative diseases that are not well known for their effects on vision also manifested VCS deficits. Multiple sclerosis patients displayed VCS deficits that were orientation specific, suggesting cortical rather than retinal or optic nerve damage (*88,89*). A primarily low spatial-frequency VCS deficit was present in Parkinson (*83*) and Alzheimer (*90–93*) patients, the latter of whom showed an extent of cognitive impairment predicted by VCS scores (*93*). AIDS patients displayed

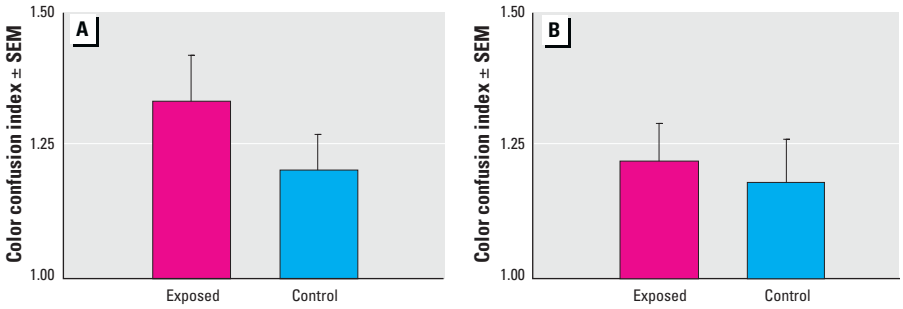

Figure 2. Group-mean color-confusion index values (CCI; ± SEM) for populations with chronic, environmental exposure to airborne perc, and for matched-control populations. (*A*) Apartments in two buildings that had active dry-cleaning facilities on the ground floor; CCI scores in residents were nonsignificantly higher than control scores. (*B*) A day care center located adjacent to and in the same building as an active dry-cleaning facility; there was no significance difference between CCI scores in control participants and workers.

marked color vision and VCS deficiencies (*94*), and cystic fibrosis patients showed a VCS deficit across spatial frequencies (*95*) that was thought to be a primary manifestation of disease in patients taking vitamin A supplements (*96*). Micronutrient deficiencies, including the vitamin B complex, were associated with reversible VCS deficits, as seen in the "Cuban epidemic optic neuropathy" cases of the early 1990s (*97,98*). These observations suggest that VCS is a sensitive indicator of CNS susceptibilities to chemical and physiologic abnormalities.

Color discrimination ability has been among the most sensitive indicators of solvent-induced neurotoxicity to date (*99*). Results, also obtained using the Lanthony Desaturated 15 Hue Color Discrimination Test, from studies of dry-cleaning workers exposed for longer durations to much higher concentrations of airborne perc have indicated exposure-induced deficits (Table 1). No significant group differences in color discrimination were observed in the current studies. The possible trend toward worse color discrimination seen in the residential study, but not in the day care investigation, may have been caused by chance or a higher lifetime perc exposure (based on study mean perc concentration; Table 2) in the residential study (3,400 μg/m^3 years) than in the day care investigation (1,978 μg/m^3 years). In either case, the current results suggested that VCS may surpass color discrimination in sensitivity, perhaps caused by higher variability in color discrimination scores from control populations (*99*) than in VCS scores (*40,42–48*).

Although the similar VCS deficits in both the residential study and day care investigation were apparently associated with chronic low-level environmental perc exposures, methodologic limitations preclude a definitive attribution of causation. The limitations included: *a*) the relatively small numbers of participants may have resulted in group differences due to chance; *b*) a geographic mismatch in residence city between the residential study exposed and control cohorts; *c*) possible unidentified group differences in socioeconomic factors, although no such influences on VCS have been reported; and *d*) possible unidentified group differences in medical conditions, alcohol consumption, medication, or illicit drug use and exposure to other neurotoxicants, although the self-reported questionnaire data indicated no such differences.

In addition, dose–response relationships were not observed. This may be attributable to a lack of such relationships, a relatively small perc exposure range, small sample sizes, or changes in exposure levels before dose and VCS were measured. Measurements of airborne perc levels in the residential study did not definitively establish the concentration that may have caused the VCS deficits. Preliminary daytime indoor-air perc levels in the study apartments were about twice as high as those measured during the study (Table 2). This difference may have resulted from *a*) improvements in perc containment required by regulatory authorities during the intervening period; and *b*) study measurements in two of the six study apartments being obtained about 1 month after on-site cleaning ceased. The study mean indoor air perc concentration, therefore, may underestimate the level associated with the VCS deficit.

It is also possible that the VCS deficits, if attributable to perc, were caused by repeated higher-level perc exposures, rather than by chronic lower-level exposures. Some participants reported previous occasional detections of an odor that, if attributable to perc, would likely indicate higher airborne concentrations. A reliable and detailed report on perc odor threshold measurements obtained using natural breathing conditions has not been published in peer-reviewed literature. One source, however, indicates that the perc odor threshold may be between 8,160 and 12,240 μg/m^3 (*100*), above the highest concentration observed in the residential study preliminary measurements. The hypothesis of persistent neurobehavioral deficits from repeated higher-level exposures to airborne trichloroethylene (*101,102*), styrene (*103*), and mineral spirits (*104*), however, has not been supported by rodent studies. These results suggest that the VCS deficit was more likely associated with cumulative perc exposure than short-term peak exposure levels.

If the residential study and day care investigation group differences in VCS were caused by chronic perc exposure, the mean indoor air perc levels associated with adverse health effects are much lower than those in occupational study reports and lower than those observed by Altmann and colleagues (*20*) in the only previous environmental exposure study (Table 1). High levels of airborne perc in occupational exposure studies (280,060–83,080 μg/m^3) have been associated with increased neurologic symptoms (*19*) and deficits on cognitive and motor-speed tasks (*16–18*) that depend heavily on visual system function (*48*). Deficits in color discrimination have been reported at lower-level (41,741–29,245 μg/m^3) occupational exposures (*14,15*). Altmann and colleagues (*20*) reported deficits in visual memory, simple visual reaction times and complex visual reaction times in residents near dry-cleaning facilities where mean indoor air perc concentration was 4,980 μg/m^3 (median = 1,360 μg/m^3). A deficit in VCS was observed in the residential study when preliminary daytime mean airborne perc concentration was 2,408 μg/m^3 (median = 1,450 μg/m^3) and the mean measured during the study was 778 μg/m^3 (mean of daytime and overnight values in Table 2; median = 350 μg/m^3). A similar VCS deficit was observed in the day care investigation where workers were exposed to a daytime mean of 2,150 μg/m^3 perc in air. The VCS deficit in the day care investigation was measured about 6 weeks after on-premises cleaning ceased, suggesting that the effect is persistent or permanent, as reported in previous solvent exposure studies (*23–26*). Taken together, these data suggest that the lowest observable adverse effect level (LOAEL) for airborne perc exposure may lie within the range of indoor air perc concentrations bracketed by the Altmann and colleague (*20*) study (mean = 4,980 μg/m^3; median = 1,360 μg/m^3) and the residential study (mean = 778 μg/m^3; median = 350 μg/m^3). These concentrations are surprisingly low in that they are less than 3 orders of magnitude above background or ambient indoor air perc levels (5–6 μg/m^3) and the NYSDOH air quality guideline (100 μg/m^3). Neither our data nor those collected by Altmann and colleagues (*20*) were sufficient to identify a no-observable adverse effect level (NOAEL).

Replication of the current results and extension with emphasis on susceptible populations is needed. Interindividual differences in susceptibility were indicated by the observation that not all exposed participants scored below control values on the visual function tests. For example, the exercising participant noted in Table 2 was a younger adult who had excellent VCS and color discrimination. On the other hand, both participants > 60 years in age and all five children in the residential study had VCS scores ≤ the 12th percentile of the control population and showed deficiencies in color discrimination (data not shown). Susceptibility factors may include age and interindividual differences in perc absorption rates, metabolism, and elimination rates, as well as molecular mechanisms involved in damage, repair, and compensatory processes.

These results suggest that chronic exposure to perc in buildings with operating dry-cleaning facilities may be an important public health concern. Although the VCS deficits are subclinical in that alone they are not diagnostic of illness and are not known to indicate a progressive disease process, they do represent a long-lasting, adverse alteration in neurobehavioral function. Further research is needed to determine whether VCS deficits induced by perc or other volatile organic compound exposures are risk factors for the development of clinical conditions such as age-related macular degeneration.

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