TETRACHLOROETHYLENE (PERC) EXPOSURE AND VISUAL CONTRAST SENSITIVITY (VCS) TEST PERFORMANCE IN ADULTS AND CHILDREN RESIDING IN BUILDINGS WITH OR WITHOUT A DRY CLEANER

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TEXT ABBREVIATIONS

ADHD	attention deficit hyperactivity disorder
ANOVA	analysis of variance
BMC	benchmark concentrations
BMCL	benchmark concentration lower limits
CCI	color confusion index
cd/m^2	candles per square meter
CDC	U.S. Centers for Disease Control
CNS	central nervous system
CO_2	carbon dioxide
cpd	cycles per degree
ELDARS	Environmental Laboratory Data Accessioning and Reporting System
F.A.C.T.	Functional Acuity Contrast Test
FF-CATS	Frankfurt-Freiburg Contrast and Acuity Test System
GFAAS	graphite furnace atomic absorption spectrometry
max	maximum
< max	less than maximum
MSSM	Mt. Sinai School of Medicine
NIST SRM	National Institute of Standards Technology Standard Reference Material
NYC	New York City
NYCDOHMH	New York City Department of Health and Mental Hygiene
NYC Perc Project	New York City Per Project
NYS DEC	New York State Department of Environmental Conservation
NYS DOH	New York State Department of Health
OR	odds ratio
PCE	tetrachloroethylene
perc	perchloroethylene
perc	tetrachloroethylene
ppb	parts per billion
QC	quality control
SPME/GC/MS	solid phase microextraction/gas chromatography/mass spectrometry
std. dev.	standard deviation
TCDS	Total Color Distance Scores
TWA	time weighted average
US EPA	United States Environmental Protection Agency
VCS	visual contrast sensitivity
VEP	visual evoked potential
VOC	volatile organic compounds

SUMMARY

This report presents research findings obtained as part of the New York City (NYC) Perc Project (funded through U.S. EPA STAR Grant #R827446 to the New York State Department of Health (NYS DOH)). Households in residential buildings (with and without a co-located dry cleaner using tetrachloroethylene (perc)) in the NYC Borough of Manhattan with at least one adult and one school-age child, were enrolled in the NYC Perc Project. Adults were about 35–45 years old, and children were 9–11 years old. Perc exposures (indoor air, exhaled breath, and blood perc levels) and measures of visual function (visual contrast sensitivity (VCS) and color vision) were obtained for each participant and associations between all measures of perc exposure and visual function were assessed. The main body of this report describes observed associations between perc exposure and VCS. (No associations were observed between perc exposure and color vision as summarized in Appendix 1 of this report.)

Visual contrast sensitivity (VCS) describes the ability to distinguish visual images of variable light-dark contrast. VCS is dependent upon both the optical components of the eye which focus images on the retina (e.g., the cornea, pupil, lens, ciliary muscle) and upon visual pathways of the central nervous system (CNS) which transmit and integrate neural signals in the brain (e.g., retina, optic nerve, lateral geniculate nucleus, striate cortex). Each eye and its associated CNS neural pathways functions independently and is characterized by its own VCS. In this study, optical components of vision were controlled prior to VCS testing allowing an assessment of whether perc exposure may have influenced the CNS.

VCS differs depending upon the size of the image focused on the retina. The Functional Acuity Contrast Test (F.A.C.T.) used in this study assesses VCS for a range of five images consisting of patches filled with parallel dark and light bars within a circle (sinusoidal gratings). The number of bars per match (referred to as cycles per degree (cpd) of visual arc within the retina) varies from 1.5 to 18 cpd.

Each eye was tested monocularly, and analyses of participants' worse performing eyes are highlighted to focus on participants' eyes and associated visual pathways potentially most affected by perc. Analyses of individuals' better performing eyes are also presented to assess the minimum possible effect of perc on VCS. Study participants performed very well on the F.A.C.T. exhibiting a marked ceiling effect at most spatial frequencies. Hence, analytical approaches appropriate for truncated data were applied. This included categorizing VCS as being either the maximum (max) or less than maximum (<max) score possible and application of non-parametric trend analyses and logistic regression to assess associations between increasing perc exposure and VCS. Actual VCS scores were used in non-parametric analysis of variance (ANOVA) for matched pairs to assess child-adult differences in VCS scores for adults and children residing in the same household

Indoor air perc levels were significantly elevated in households in buildings with co-located dry cleaners. Based on their indoor air perc levels, participants were grouped into one of the following three exposure categories: residence in a reference building; residence in a dry cleaner building with indoor air perc < 100 $\mu g/m^3$; or residence in a dry cleaner building with indoor air perc > 100 $\mu g/m^3$. Geometric mean indoor air perc levels for adults in these three categories were about 3, 12, and 480 $\mu g/m^3$, respectively; and for children were about 3, 12, and 340 $\mu g/m^3$,

respectively. Effects of perc exposure on VCS test performance is the subject of this report. No measure of perc exposure was significantly associated with decreased color vision performance among either adults or children.

Overall, children performed better on the F.A.C.T. than adults, adult and child worse performing eyes performed more poorly than their better eyes, and both eyes of adults and children performed more poorly at the highest exposure level. However, differences were observed between adults and children in how VCS may have been affected by perc exposure. Analyses of relationships between perc exposures and F.A.C.T. performance for worse performing eyes suggested that increasing levels of perc exposure decreased children's VCS, specifically at the spatial frequency of 12 cpd. Analyses were less suggestive that increasing perc exposure affected adults' VCS at any spatial frequency.

Decreasing trends in proportions of children's worse eyes achieving the maximum possible score occurred across increasing perc exposure categories at spatial frequencies of 12 cpd ($p < 0.05$) and 6 cpd ($0.05 < p < 0.10$). In the highest exposure group (residence in a dry cleaner building and perc > 100 $\mu g/m^3$), no child achieved the maximum VCS score at 12 cpd. Also, increased odds for children's worse eyes to score < max was significantly associated with increasing levels of perc in children's indoor air, breath or blood ($p< 0.05$), specifically at 12 cpd and no other spatial frequency. Although decreasing trends in proportions of adults' worse eyes achieving the maximum possible scores were observed across increasing exposure categories at some spatial frequencies, the odds for adults' worse eyes to have decreased VCS were not increased for any measure of perc exposure at any frequency. As noted above, when optical and other confounding influences on VCS are controlled for, as they were in this study, alterations in VCS can indicate the occurrence of a CNS effect. Decreased VCS test performance observed here among perc-exposed children, may therefore reflect altered CNS function.

In residences of 11 children with the highest indoor air perc levels (i.e., those residing in dry cleaner buildings with indoor air perc levels > 100 $\mu g/m^3$) indoor air perc levels ranged from 127 to 700 $\mu g/m^3$ (25^{th}–75^{th} percentile: 220–700 $\mu g/m^3$) with a geometric mean of about 340 $\mu g/m^3$. These levels are below average residential indoor air perc levels of 700 and 1400 $\mu g/m^3$ perc in indoor air previously reported to be associated with visual and CNS effects, respectively. Benchmark concentrations (BMCs) associated with extra risks of 40–50 percent (i.e., above the background risk of 60 percent) for children to have decreased VCS at 12 cpd were estimated to range from 14 (95 percent Confidence Interval 7–120 $\mu g/m^3$) to 26 (95 percent Confidence Interval 10–420 $\mu g/m^3$) $\mu g/m^3$ perc. Although highly uncertain, these analyses also suggest that some children may be vulnerable to the effects of perc at levels below previously suggested effect levels.

In summary, the results presented here suggest that increased perc exposures in residences in buildings with co-located dry cleaners using perc are associated with decreased VCS test performance in children's worse performing eyes, at a single spatial frequency (12 cpd). Trend analyses and adjusted logistic regression suggested that increased residential indoor air levels of perc, as well as increased perc levels in children's breath and blood, were statistically significantly associated with decreased VCS test performance at 12 cpd. Although trend analyses of adult VCS test performance suggested that increased residential indoor air perc levels were associated with decreased VCS test performance at 12 cpd among minority or non-low

income adults, adjusted logistic regression found that no measure of perc exposure was associated with increased odds for decreased VCS among adults. These analyses suggest that children in the highest exposure group, (gemmetric mean: 336 μg/m^3, range: 127–710 μg/m^3, may be more vulnerable to the effect of perc on VCS than adults were. Paired analyses of differences in worse eye VCS scores between matched children and adults (child-adult pairs residing in the same household) were consistent with the notion that children's VCS at 12 cpd was more affected by increased perc exposure than adults' VCS.

INTRODUCTION

Tetrachloroethylene (perc) remains the most frequently used solvent by dry cleaning facilities (US EPA, 2006; Earnest, 1996). In many urban areas, dry cleaners using perc are often co-located with residences, and fugitive perc emissions sometimes contaminate indoor air within these residences, raising concern that occupants may experience long-term and possibly harmful, perc exposures (Wallace et al., 1995; Schreiber et al., 1993; 2002; Garetano and Gochfeld, 2000; McDermott et al., 2005).

Elevated perc levels in residential indoor air due to fugitive perc emissions from nearby dry cleaners have been associated with neurobehavioral and visual function effects. Residents (n=14) exposed to a median of 1400 $\mu g/m^3$ perc had slower response times or made more errors on three neurobehavioral tests (simple reaction time, continuous performance, visual retention) than matched control subjects (Altmann et al., 1995). Visual contrast sensitivity (VCS) and color discrimination ability were reported to be decreased among 13 adult residents of buildings with dry cleaners where residential indoor air perc levels averaged about 700 $\mu g/m^3$ perc (geometric mean) compared to unexposed adults, although the decreases were not statistically significant and both groups still performed within the normal ranges reported for the VCS test administered (NYS DOH, 2000; Schreiber et al., 2002; Storm and Mazor, 2004). Effects of perc exposure on the central nervous system (CNS), including the visual system, have also been reported among workers although exposure levels were considerably higher – about 30,000 $\mu g/m^3$ perc or more (Spinatonda et al., 1997; Ferroni et al., 1992; Echeverriea et al., 1995; Cavalleri et al., 1994; Gobba et al., 1998). Based on these observations there is concern that elevated residential indoor air perc levels associated with co-located dry cleaners may adversely effect the CNS and/or visual system. Of additional concern is the possibility that child residents may be more vulnerable than their parents to perc in indoor air since they may experience greater internal exposures and/or greater health consequences than adults in the same exposure environment (Needham & Sexton, 2000; Stein et al., 2002; Schwenk et al., 2003).

Considering the effects of perc on the CNS and visual system and other health effects associated with perc exposure, the New York State Department of Health (NYS DOH) derived a health-based guideline of 100 $\mu g/m^3$ perc for residential air, considering continuous lifetime exposure and potentially sensitive people, including children (NYS DOH, 1997; 2003). NYS DOH currently considers this level to be a useful guideline in aiding decisions about the nature and urgency of efforts to reduce residential exposures to perc when it is present in indoor air. NYS DOH recommends actions to reduce exposure if perc levels are above background even if they are below 100 $\mu g/m^3$, but an increase in the scale and urgency of such actions is recommended when air levels are above 100 $\mu g/m^3$. NYS DOH recommends immediate action when an air level is 1000 $\mu g/m^3$ or more.

When establishing the guideline, NYS DOH recognized uncertainties associated with assessing the likelihood that effects, particularly on vision, might occur among residents experiencing elevated perc levels in their indoor air. To continue to evaluate residential exposures to perc and the possible occurrence of associated vision effects, especially among children, the NYS DOH received funding through the U.S. Environmental Protection Agency (US EPA) (STAR Grant #827446010) to conduct the New York City (NYC) Perc Project. Objectives of the NYC Perc Project were to: assess perc exposures among residents of buildings with co-located dry cleaners;

evaluate whether living in a building with a dry cleaner was associated with vision effects; evaluate relationships between measures of perc exposure and vision effects; and assess whether children were disproportionately exposed to, and/or affected by, perc exposure compared to adults. NYC Perc Project participants included children and adults residing in the same household in buildings with or without a co-located dry cleaner using perc on-site.

VCS and color vision of participants were the health outcomes assessed given evidence that these measures of visual function appear to be sensitive health endpoints for perc and other similar solvent compounds (Gobba, 2000; Iregren et al., 2002; Schreiber et al., 2002). Vision and performance on vision tests is dependent on the optical components of the eye which focus visual images on the retina (e.g., the cornea, pupil, lens, ciliary muscle) and on the CNS components of vision which generate and transmit neural signals from the retina to the brain where visual images are interpreted (e.g., retina, optic nerve, lateral geniculate nucleus, striate cortex) (Purves et al., 1997). CNS components of the visual system are sensitive to luminance contrast within images as well as to orientation, movement, and length of light-dark edges. Thus, when optical components of vision are well controlled during vision testing, alterations in test performance might be ascribed to an effect in the CNS.

When inhaled, perc is absorbed into the blood stream, widely distributed throughout the body especially to adipose tissue, and largely eliminated unchanged in breath (ATSDR, 1997; ACGIH, 2001; Monster et al., 1979; Chiu et al., 2006). In both occupational and residential settings, perc levels in exhaled alveolar breath and blood are directly correlated with perc levels in inhaled air and are widely accepted biologic indices of individual perc exposure (ATSDR, 1997; ACGIH, 2001; Gobba et al., 2003; Solet et al., 1990). Hence, the measures of perc exposure evaluated in the NYC Perc Project include individual exhaled alveolar breath and blood perc levels as well as residential indoor air perc levels.

This report summarizes perc exposures (indoor air, breath, blood perc levels) of child and adult participants in the NYC Perc Project, and relates those exposures to participants' VCS and color vision test performance. Several types of statistical analyses of VCS test results were performed, including correlation analyses, trend analyses, logistic regressions, and exploratory exposure-response analyses. Relationships between perc exposure and VCS test performance are discussed in detail in the body of this report since some statistically significant associations between perc exposure and VCS test performance were found.

Statistically significant relationships between increasing residential perc exposure and color vision test performance were not observed among either adults or children in this study. Analyses of relationships between measures of perc exposure and color vision test performance are provided in Appendix 1 to this report.

METHODS

Study design and all protocols were under continuous approval by Institutional Review Boards at the NYS DOH (Study Number 99–212) and other collaborating institutions (Mt. Sinai Medical Center (Project #99–920 0001 05 CM); U.S. Centers for Disease Control and Prevention (CDC) (Protocol #2597).

Study Area and Building Selection. The study area was an area in NYC characterized by: a high number of residential buildings with dry cleaners; the presence of some buildings where residential perc levels up to 5500 $\mu g/m^3$ had been previously documented (NYS DOH, unpublished data); and proximity to the ophthalmology clinic where vision evaluations were scheduled. Dry cleaners in residential buildings were identified from New York State Department of Environmental Conservation (NYS DEC) regulatory compliance records and internet-based yellow pages (ReferenceUSA^{SM}, InfoSpace^{R}) as described more fully in McDermott, et al. (2005). Each identified dry cleaner building was characterized to verify that the dry cleaner was in operation and using perc on-site, that occupied residences were present in the building, and that no other businesses using volatile organic compounds (VOCs) (e.g., nail salons, shoe repair stores, photography developing) were present in the same building. At least three other residential buildings with no dry cleaner or other business possibly using VOCs, and located at least one city block away from each dry cleaner building meeting inclusion criteria were selected as reference buildings for each dry cleaner building identified.

Participant Recruitment. Households in identified buildings were contacted through mail and/or telephone (mail/telephone) or door-to-door contact as described in McDermott et al. (2005). Eligible households included at least one adult (20–55 years old) and one or more children (5–14 years old) residing full-time in their building for at least one year. Participants meeting the above inclusion criteria and willing to participate were screened to exclude those with known current or previous exposures to VOCs and/or medical conditions that could possibly interfere with visual function evaluation (e.g., substance abuse, diabetes, cataracts, glaucoma). During screening, participants were asked to categorize household race/ethnicity into one or more (up to four) of the following categories: White, African American, American Indian, Chinese, Japanese, Korean, Native Hawaiian, Samoan, Hispanic, or Other. Adult participants were also asked to categorize their annual household income into one of the following ranges: < $15,000; $15,000–$30,000; $30,000–$45,000; $45,000–$60,000; or > $60,000.

Considering the possible greater vulnerability of children's VCS to perc and the matched study design, desirable sample size estimates were based on the ability to detect a statistically significant difference in child-adult differences in VCS scores among matched child-adult residents of reference and dry cleaner buildings. It was assumed that children's VCS scores would be decreased compared to adult scores among residents of dry cleaner buildings; and, that a 20 percent decrease in scores would be meaningful (Amler and Gibertini, 1996). Hence, minimum sample sizes required to detect a difference in adult-child differences in VCS scores were based on the null hypothesis $d_1=d_2$ and the alternative hypothesis $d_1>d_2+d_2(0.20)$, a significance level of alpha (α) = 0.05 and power of 1-beta (β) = 80 percent, where d_1 is the child-adult difference in scores between matched child-adult residents in dry cleaner buildings and d_2 is the difference between matched child-adult residents in reference buildings. VCS score mean and standard deviation values for spatial frequencies 6, 12, and 18 cpd (see below for VCS explanation) used in these calculations were as reported in Amler and Gibertini (1996). Desired child-adult pair sample sizes for accepting the alternative hypothesis at 6, 12, and 18 cpd were 30, 40, and 50 respectively.

Participant Activities. All adult and child participants volunteered and signed consent or child assent forms approved by the Institutional Review Board of the NYS DOH and collaborating institutions.

Participating households were asked to allow collection of indoor air samples to determine levels of perc and a suite of other VOCs. During an initial home visit, adult participants were asked to complete a residential/occupational/medical history questionnaire for themselves and for their child(ren), and organic vapor monitors were deployed. Questionnaires included requests for information on years of education (adults and children) and on alcohol and tobacco use (adults only). Both adult(s) and child(ren) provided exhaled alveolar breath samples for determination of breath carbon dioxide (CO_2) and perc level approximately 24 hours later when the organic vapor monitor was retrieved. During a home visit or by telephone, participants were scheduled at the medical school affiliated ophthalmology research clinic where they completed comprehensive eye examinations, VCS, and color vision assessments. They also provided blood samples for the determination of levels of perc, other VOCs, lead and mercury, and another alveolar breath sample for determination of perc and CO_2 immediately after vision testing.

Participants received $50 for completion of home visit activities and $50 for completion of ophthalmology research clinic visit activities to compensate for the inconvenience associated with participation. Screening for glaucoma, other eye diseases, and a prescription for corrective lenses were also provided to each participant, if warranted, at no cost.

Analytical Methods. Indoor air samples were collected using 3M (Minnesota Mining and Manufacturing Co., Minneapolis, MN) organic vapor monitors deployed in duplicate in main living areas. Monitors were placed approximately six feet high and away from any direct sources of ventilation such as windows, air conditioners, fans, or heating/cooling vents. Air sampling occurred for 21–27 hours during weekdays starting between 3:00 PM and 9:00 PM and ending around the same times the following day. A hard plastic, impermeable lid provided by the manufacturer was affixed to each monitor at the end of the collection period.

Monitors were analyzed for perc and 10 other VOCs (1,1,1-trichloroethane, 1,4-dichlorobenzene, benzene, carbon tetrachloride, ethylbenzene, trichloroethene, toluene, m- and p-xylene, o-xylene, styrene) at the NYS DOH Wadsworth Center in Albany, NY as described by Amin et al. (1998). Detection limits varied slightly by analytical run and were generally about 1 $\mu g/m^3$ for all VOCs including perc. Analytical results were reviewed at the laboratory in accordance with approved Quality Assurance/Quality Control procedures and entered into the NYS DOH Environmental Laboratory Data Accessioning and Reporting System (ELDARS). Results from duplicate indoor air samples were averaged. Average percent difference in perc levels of duplicate badges was 10 percent (upper 75^{th} percentile 11 percent). Both the participating household and the NYC Department of Health and Mental Hygiene (NYCDOHMH) were notified as soon as possible when apartment perc levels were above 10 $\mu g/m^3$ perc. The NYCDOHMH initiates follow-up activities with other governmental agencies, with the dry cleaner, and/or with the resident when elevated residential levels of perc are found.

Breath samples were analyzed for perc and CO_2 as described by Stein et al. (1996). Volumes (0.1–1 mL) of breath samples were withdrawn from breath tubes using a gas tight syringe (0.5 or 1.0 mL) and injected into a gas chromatograph (Hewlett-Packard 5890). The gas chromatograph was fitted with a Rt_x-volatiles fused silica capillary column (60 m, 0.53 mm ID, Restek Corp.) and a Carboxen-1000 stainless steel packed column (15 ft., 1/8" id) connected to an electron capture detector for determination of perc and to a separate pulsed discharge detector for

determination of CO_2. Standards were generated using a Dynacalibrator for volatiles (perc) and a 5 percent commercially prepared standard of permanent gases for CO_2.

CO_2 levels were normally distributed. Breath samples outside of 1.5 interquartile ranges of the mean (for the samples being analyzed) were excluded from analysis in accordance with recommendations for excluding outliers (Rosner, 1995). As recommended by Guillemin and Gubéran (1982), alveolar breath perc levels were corrected by a proportional adjustment assuming that perc levels varied directly with CO_2 levels, and that average alveolar breath CO_2 partial pressure was that observed at sea-level: 40.0 mm Hg or 5.3 percent (Guyton and Hall, 1996).

Blood samples were collected and forwarded to the CDC for analysis as previously described for perc and other VOCs (Ashley et al., 1992). Briefly, two whole human blood samples were collected by venipuncture into vacutainers (Becton Dickinson, Franklin Lakes, NJ) specially prepared for VOC analysis (Cardinali et al., 1995). These samples were shipped chilled to the CDC and stored at 4° C until analysis. Analysis of perc and other VOCs involved analysis of a 3 mL aliquot from each vacutainer using solid phase microextraction/gas chromatography/mass spectrometry (SPME/GC/MS) as previously described (Cardinali et al., 2000). Isotope dilution mass spectrometry was used for calculation of analyte levels based on relative response compared with an internal standard (perc-^{13}C1, Cambridge Isotope Labs, Andover, MA). This method had a limit of detection of 0.048 ng perc/mL blood, and was able to measure perc in most of the blood samples tested. This analysis involved rigorous quality control (QC) procedures including evaluation for: contamination, absolute sensitivity, confirmation ion ratios, accuracy, and precision. Blind QC samples were evaluated by an independent QC officer according to Westgard QC rules (Westgard et al., 1981). If a QC sample exceeded QC limits for an analyte, then all results for that analyte on that day were rejected.

Lead was measured by graphite furnace atomic absorption spectrometry (GFAAS) using a modification of the method of Miller et al. (1987). The GFAAS utilized an aqueous calibration and Zeeman background correction with a resulting blood lead limit of detection of 0.3 µg/dL. The reported lead result was the average of two measurements.

Whole blood specimens 0.2 mL, were analyzed for total mercury by an automated cold vapor atomic absorption spectrophotometry system (Flow Injection Mercury System 400 Perkin-Elmer, Shelton, CT) with an AS-91 autosampler and a Maxidigest MX 350, (Prolabo, Fontenay-sous-Bois, Cedex, France) in-line microwave digester connected to the FIMS-400 system. Matrix matched calibration methods were used (Chen et al., 1998). The method has a detection limit of 0.14 µg/L for total mercury. National Institute of Standards Technology Standard Reference Material (NIST SRM 966) was used as a bench quality control material as well as 3 levels of in-house blood pools traceable to NIST SRM 966 for daily quality control.

Visual Function. Evaluations of visual function were conducted in a controlled clinical setting under standardized testing conditions at the Mt. Sinai School of Medicine (MSSM) Department of Ophthalmology Research Clinic. All clinicians conducting evaluations were unaware of whether participants resided in buildings with dry cleaners or not. Spanish-speaking clinicians administered tests to participants whose preferred language was Spanish.

Each participant was given a thorough ophthalmologic examination which included determination of past ocular and medical history, measurement of visual acuity, pupil size, extraocular motility, and intraocular pressure; and anterior (slit-lamp) and posterior (fundus) segment exams. For participants whose uncorrected acuity was worse than 20/25, manifest refraction was performed. If best corrected visual acuity was not better than or equal to 20/25 or if VCS was abnormal, a dilated fundus exam and automated visual field test of the central 30 degrees was performed to document foveolar sensitivity and retinal function. Participating ophthalmologists discussed individual findings with each case. Participants with abnormalities or taking medications that could influence VCS and/or color vision (e.g., glaucoma, diabetes, cataracts, and astigmatism) were excluded from further consideration.

VCS was determined using the Functional Acuity Contrast Test (F.A.C.T.) distance chart (Stereo Optical Co., Inc., 1993) placed 10 feet from the participant under light conditions specified by the manufacturer (i.e., 68–240 cd/m^2). This chart (37" x 27") consists of five rows of nine different patches filled with sinusoidal gratings (parallel dark and light bars within a circle) oriented at +15°, 0°, or -15°. Spatial frequency (number of bars per patch; referred to as cycles per degree [cpd] of visual arc) is constant within rows but increases from the top to bottom row. Contrast of bars against background decreases within rows from left to right. At different spatial frequencies, different degrees of contrast are required to reach threshold visibility. VCS is reflected in a function which relates the threshold stimulus for spatial vision in terms of spatial frequency and contrast.

For each eye, each participant was asked to indicate the orientation of bars in each patch as the test administrator called out each patch from left to right, row by row, beginning at the top row, left patch. If orientation was misidentified, the participant was instructed to view each succeeding 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. This procedure was repeated for each row in descending order. Scores for each eye were recorded on a graph showing a normal range (90 percent confidence interval) provided by the F.A.C.T. manufacturer and typically used for clinical interpretation of VCS. For each participant, the examining ophthalmologist made a judgment as to whether or not VCS was normal or abnormal based on these graphs. Specific contrast values for each frequency, contrast sensitivity combination provided with the F.A.C.T. were recorded.

The F.A.C.T., the quantitative contrast sensitivity threshold values possible using the F.A.C.T., and responses on the F.A.C.T. reported by the manufacturer as normal are described in Appendix 2.

Data Analyses. Non-working and non-residential telephone numbers identified during mail/telephone recruitment and vacant households identified during door-to-door recruitment were eliminated to provide the total number of households identified. Identified households were categorized into contacted (presence of adult-child pair determined) and not contacted (presence of adult-child pair not determined) groups. Contacted households were further categorized as not eligible (households without an age-eligible adult-child pair); potentially eligible (households with an age-eligible adult-child pair); or, eligible (households meeting all inclusion criteria (i.e., no other VOC exposures, residence duration > 1 year, no excluding

medical conditions) based on the screening questionnaire. All eligible adult-child pairs were asked to participate.

All statistical analyses were performed using SAS software (Release 9.1, SAS Institute, Cary, NC). Findings were deemed significant when $p < 0.05$ and nearly significant when $p < 0.10$ but > 0.05. Indoor air perc levels obtained from main living areas were averaged for each household. VOC indices were estimated for each household by summing VOC concentrations (other than perc) expressed as parts per billion (ppb). Categorical household and participant characteristics identified from the screening questionnaire were summarized by percent and compared between exposure groups using the chi-square test. Continuous household and participant variables were summarized by mean ± standard deviation (std. dev.) and compared between exposure groups using Analysis of Variance (ANOVA) and Student-Newman-Keuls test. Spearman correlation coefficients were used to assess associations between socioeconomic and other individual characteristics (e.g., VOC indices, mercury and lead levels in blood, age, gender, etc.), levels of perc in indoor air, breath, and blood, and VCS scores.

Analyses were done on VCS observations associated with individuals' "worse" and "better" performing eyes. VCS testing was done monocularly since neural signals from each eye are independent of the other eye (although signals from both eyes are integrated in the visual cortex of the brain for interpretation), and visual function associated with individuals' different eyes is commonly different (Purves et al. 1997). Further, decreased visual function associated with either only one or both eyes has been associated with VOC exposure suggesting that vision of a single eye can be independently affected by VOC exposure (e.g., Donoghue et al., 1995; Grandjean et al., 2001). Analyses based on "worse" eyes highlight maximum possible effect of perc on VCS test performance in each individual. Thus, analyses based on detectable effect on "worse" performing eyes provides a better chance of detecting an effect of perc on VCS than analyses based on "better" performing eyes. Analyses based on "better" performing eyes highlight minimum differences in VCS across exposure categories. Also, an alteration in VCS for only one eye may be important for individuals dependent upon only one for vision.

Reference and dry cleaner building resident group VCS functions for both worse and better eyes obtained with the F.A.C.T. exhibited marked ceiling effects as illustrated in Figure 1a and b, respectively. Given this unexpected finding, two types of statistical analyses suitable when the dependent variable is truncated were applied: trend analyses based on categorization of exposures and responses, and non-parametric ANOVA followed by post-hoc t-tests (Rosner, 2006). Differences in child-adult differences in VCS scores were assessed using ANOVA for matched pairs. For analyses based on categories, each participant's VCS at each spatial frequency was categorized as being either the maximum (max) or less than maximum (< max) score possible for each eye. Exposure categories for trend and ANOVA analyses were residence in: a reference building, dry cleaner building with indoor air perc $< 100\ \mu g/m^3$ (below NYS DOH guideline); or a dry cleaner building with indoor air perc $> 100\ \mu g/m^3$ (above NYS DOH guideline). For trend analyses the proportion of participants achieving the maximum score was evaluated for decreasing trends across increasing exposure categories using the Cochran-Armitage Exact trend test. For ANOVA, differences in VCS scores among exposure categories were evaluated using Kruskall-Wallace ANOVA based on ranks followed by post-hoc Bonferroni t-tests.

Elevated perc levels were detected more often in dry cleaner buildings located in low income and/or minority neighborhoods, and other analyses indicated that being a member of a minority group and/or having lower annual income were significantly associated with increased indoor air levels of perc as well as increased breath and blood perc levels (McDermott et al., 2005; Mazor et al., unpublished/under review). Therefore, participants were also stratified by race/ethnicity and annual income for trend analyses and ANOVA. To attain sufficient sample sizes for analyses within race/ethnicity groups, households and participants were categorized as non-minority, minority, or other. The non-minority category included participants identifying themselves as non-Hispanic White only. The minority category included participants identifying themselves as African American only, Hispanic only, or as African American or Hispanic in combination with any other category. The other category included participants not falling into either of these defined categories; these participants were not included in trend analyses stratified by race/ethnicity. For analyses stratified by income categories, participants were categorized as having annual incomes of < $30,000, $30,000–$60,000, or > $60,000. Participants who chose not to provide this information were categorized as "non-responders" (see Results) and were not included in analyses.

Mean differences in VCS scores (for worse and better performing eyes at each spatial frequency) between children and adults residing in the same household were evaluated using Kruskall-Wallis ANOVA for matched pairs. The possibility that *in utero* perc exposure may have contributed to decreased VCS among child residents of dry cleaner buildings was explored by comparing VCS of children whose mothers had lived in the sampled building during pregnancy with VCS of children whose mothers had not lived in the sampled building during pregnancy.

Logistic regression was applied to model the probability of scoring < max at each VCS spatial frequency as a function of each measure of perc exposure (perc level in indoor air, breath at home, breath at the clinic, blood) for all participants meeting inclusion criteria. Both unadjusted and adjusted regressions were performed. Unadjusted regression assesses only the effect of perc exposure on VCS test performance, and an unadjusted odds ratio (OR) associated with a (log) unit increase in perc exposure is determined. Adjusted regressions assess the effect of potential confounders as well as perc exposure on VCS test performance, and an adjusted OR is determined. Confounders included were identified through correlation analyses and review of scientific literature which indicated that age, smoking, and alcohol use may influence performance on VCS and/or other neurobehavioral tests (Krieg et al., 2001; Amler et al., 1995; Amler and Gibertini, 1996). Neither race/ethnicity (minority/non-minority) nor income (low income/non-low income) were treated as confounders in the regression as neither varied independently of exposure (i.e., minority and low-income participants had the greatest perc exposures).

Exposure-Response Analyses. The probability of worse performing eyes to score < max at the spatial frequency of 12 cpd appeared to be most clearly increased among children as perc exposure (indoor air, breath at home, blood) increased. Hence, a logistic regression model was applied to estimate indoor air perc levels associated with a range of extra risks for scoring < max at 12 cpd (above a background risk) according to the following relationship:

$$Extra\ Risk = \frac{P(d) - P(bkgd)}{1 - P(bkgd)}$$

In these estimates, the background risk is the probability associated with scoring < max at 12 cpd when indoor air perc levels are at a background level. The background level is defined as either the 50^{th} or 90^{th} upper percentile of indoor air perc levels present in reference households sampled in this study.

Modeling was performed using SAS NLMIXED procedure as described by Wheeler (2005) which applies the same methods as the U.S. EPA's Benchmark Dose Software (see http://www.epa.gov/ncea/bmds (accessed May 2008)). In these analyses concentrations (termed benchmark concentrations (BMC)) along with their 95 percent confidence intervals were derived for a range of extra risks (10–50 percent) above background in the proportion of children scoring < max at 12 cpd. This process is described in greater detail in Appendix 3.

We also assessed exposure–response for children's VCS at 12 cpd by evaluating whether a no observed effect level (NOEL) or low observed effect level (LOEL) could be identified from indoor air perc levels associated with each of the three exposure categories: residence in a reference building; residence in a dry cleaner building with indoor air perc < 100 $\mu g/m^3$; and, residence in a dry cleaner building with indoor air perc > 100 $\mu g/m^3$.

RESULTS

Table 1 summarizes numbers of households in dry cleaner and reference buildings enrolled. A total of 1261 households in dry cleaner buildings were contacted; 89 met inclusion criteria, and 65 agreed to participate. A total of 1252 households in reference buildings were contacted; 80 met inclusion criteria, and 61 agreed to participate.

Some adults and children did not complete some or any of the visual function assessment portions of the study for a variety of reasons. Other adults and children completed some or all visual function assessments but their test results were excluded prior to analyses due to the presence of medical or eye conditions known to influence the measures evaluated (which were identified during ophthalmologic examination), indication of past or present exposure to perc or other VOCs outside the home, or a residence time of less than one year. Visual function tests for some children were excluded from analyses because of their young age (less than 6 years old) or because they were noted by their parents as learning disabled or having attention deficit hyperactivity disorder (ADHD). Children 6 years old or younger often had difficulty maintaining attention during testing. Children with learning disabilities or ADHD not only often paid poor attention during testing, but have also been shown to perform poorly on the F.A.C.T. (Storm and Mazor, 2004) and on other tests of visual function (Farrar et al., 2001). Hence, the study population evaluated in this report includes only those individual participants completing the VCS test that were not excluded based on these criteria, and child-adult pairs in which neither the child nor the adult met exclusion criteria and both completed the VCS test. These populations are summarized by residence building type and exposure category in Table 2. Total numbers of child-adult pairs residing in reference and on-site dry cleaner buildings met original recruitment goals for assessing group differences in child-adult differences in VCS scores at 6 and 12 cpd of 30 and 40, respectively, but fell slightly short of the goal of 50 at 18 cpd.

Participant Characteristics and VCS Test Performance. Socioeconomic characteristics of households and individuals (adults, children, child-adult pairs) completing the VCS test are summarized by exposure category in Table 3. More households in dry cleaner buildings where

perc > 100 $\mu g/m^3$ were categorized as minority ($p < 0.05$), and fewer were categorized as high income (> $60,000 annual income) ($p < 0.05$) compared to households in reference buildings, or dry cleaner buildings where perc < 100 $\mu g/m^3$. Nearly 25 percent of the households in the > 100 $\mu g/m^3$ exposure category did not provide income range. Also, adults in the highest exposure group were younger ($p < 0.05$) and had fewer years of education ($p < 0.05$) than adults in the other exposure categories.

Correlations between socioeconomic and individual characteristics and VCS scores for worse and better performing eyes of reference participants are summarized in Table 4. Among adults, correlations were observed between increased smoking and decreased VCS scores for worse eyes at 6 ($0.05 < p < 0.10$), 12 ($p < 0.05$) and 18 cpd ($0.05 < p < 0.10$), and for better eyes at 6 cpd ($p < 0.05$). Correlations were observed between minority race/ethnicity and increased VCS scores at 12 cpd for worse eyes ($p < 0.05$), and at 18 cpd for better eyes ($p < 0.05$). Increasing alcohol use correlated with decreased VCS scores at 18 cpd for better eyes ($0.05 < p < 0.10$).

Among children, correlations were observed between increased worse eye VCS score at 6 cpd and more years of school ($p < 0.05$) and increasing age ($0.05 < p < 0.10$). Decreased VCS score for better eyes at 12 cpd correlated with more years of school ($0.05 < p < 0.10$) and increasing age ($p < 0.05$). A correlation between increased child residence duration and decreased VCS scores at 18 cpd was observed for worse performing eyes ($p <0.05$). Blood lead level correlated with increased VCS scores at 12 and 18 cpd for better eyes ($p < 0.05$).

Perc Exposures and VCS Test Performance. Tables 5a (individual adults, children) and 5b (matched adults and children, i.e., child-adult pairs) summarize perc exposures for participants with VCS test results. Adult and child residents of both categories of dry cleaner buildings (< 100 $\mu g/m^3$ and > 100 $\mu g/m^3$) had greater indoor air perc levels ($p < 0.05$) and greater breath and blood perc levels ($p < 0.05$) than residents of reference buildings. Residents in the > 100 $\mu g/m^3$ category had higher indoor air, breath, and blood perc levels than residents in the < 100 $\mu g/m^3$ category ($p < 0.05$).

Spearman correlation coefficients between measures of perc exposure and VCS scores of worse and better performing eyes for all residents of reference and dry cleaner buildings are summarized in Table 6. Most correlation coefficients are small (i.e., close to zero) suggesting that, for the entire study population, VCS scores and perc exposures are neither negatively nor postively correlated. Among adults, increased perc in breath at the clinic correlated with increased VCS score at 1.5 and 12 cpd for better eyes ($p < 0.05$), whereas increased levels of perc in breath obtained at home correlated with decreased VCS scores at 3 cpd for worse eyes ($0.05 < p < 0.10$). Among children, increased perc in indoor air and breath obtained at home correlated with lower VCS scores at 12 cpd for worse eyes ($p < 0.05$), whereas increased perc in indoor air and breath at home and the clinic correlated with increased VCS scores at 3 cpd for better eyes ($p < 0.05$). Increased perc in breath at the clinic correlated with decreased VCS scores at 6 cpd for children's better eyes ($p < 0.05$).

Figures 2a and b illustrate responses of adults and children in each exposure category at each spatial frequency for worse and better performing eyes, respectively. Tables 7a and b summarize proportions of worse and better performing eyes achieving the max VCS score at each spatial frequency across perc exposure categories, respectively. Together, Figures 2a and b and Tables

7a and b illustrate that children tended to perform better than adults (i.e., at most spatial frequencies higher proportions of children's worse and better performing eyes achieved the max VCS score when compared to adults). Figures 2a and b and Tables 7a and b also show that worse and better eyes of adults and children in the highest exposure group (perc > 100 $\mu g/m^3$) performed more poorly (i.e., lower proportions achieve the max VCS score) than eyes of those in the reference and lower exposure groups (perc < 100 $\mu g/m^3$). For worse eyes, in the highest exposure group (> 100 $\mu g/m^3$) no child achieved the maximum VCS score at 12 cpd and no adult achieved the maximum VCS score at 18 cpd. Decreasing trends for worse eyes are significant at spatial frequencies of 6 cpd among adults and 12 cpd among children ($p < 0.05$) and nearly significant at 18 cpd among adults and at 6 cpd among children ($0.05 < p < 0.10$) (Table 7a). VCS test performance for adults' better eyes did not show any decreasing trends (Table 7b) but children's better eyes showed a decreasing trend for VCS test performance at 1.5 cpd ($p < 0.05$) and 6 cpd ($0.05 < p < 0.10$).

Tables 8a and b summarize decreasing trends in achieving the max VCS score for participants stratified by race/ethnicity and by income categories. Minority race/ethnicity and low income households comprised greater percentages of those in the highest exposure category (Table 3). Stratified analyses controls for the possible influence of these characteristics on VCS. Trends in achieving the max VCS score for worse performing eyes decreased significantly across exposure categories at spatial frequencies 1.5, 6, and 12 cpd for minority children ($p < 0.05$), and at 6 and 12 cpd for low-income children ($p < 0.05$). Decreasing trends in VCS occurred at 1.5 cpd among low-income children ($0.05 < p < 0.10$). VCS test performance for worse eyes decreased among minority adults at 18 cpd ($p < 0.05$), among non-minority adults at 3 and 6 cpd, and among low-income adults at 12 cpd ($0.05 < p < 0.10$). Trends in VCS test performance for better performing eyes decreased at 1.5 cpd among minority and low income children ($p < 0.05$), and at 6 and 12 cpd among minority children ($0.05 < p < 0.10$). Among adults, trends in VCS test performance for better performing eyes decreased at 1.5 and 6 cpd among minority adults ($0.05 < p < 0.10$), and at 1.5, 3 and 6 cpd among low income adults ($0.05 < p < 0.10$).

Kruskall-Wallis ANOVA of differences in VCS scores across exposure categories (followed by post-hoc Bonferroni t-tests) were performed since ANOVA allows consideration of the range of VCS scores apparent at the highest spatial frequencies (cf., VCS scores at 12 and 18 cpd, Figure 2a and b). As illustrated in Figures 3x and y, perc exposure was associated with altered VCS test scores at 6 cpd for adults' better eyes ($p < 0.05$) and at 1.5 and 12 cpd ($0.05 < p < 0.10$) for children's worse and better eyes, respectively. When participants were stratified by race/ethnicity, perc exposure was associated with group differences in VCS scores of better eyes of non-minority adults at 6 cpd ($p < 0.05$) and 12 cpd ($0.05 < p < 0.10$) (Figure 3x). Perc exposure as also associated with group differences in VCS scores of better eyes of minority children at 1.5 cpd ($0.05 < p < 0.10$). When participants were stratified by income, perc exposure was associated with group differences in VCS scores of non-low income adults' better eyes at 6 cpd ($p < 0.05$) and 12 cpd ($p < 0.05$) (Figure 3y). Among children, perc exposure was associated with group differences in VCS scores of low income children's worse eyes at 1.5 cpd ($0.05 < p < 0.10$), 6 cpd ($0.05 < p < 0.10$) and 12 cpd ($p < 0.05$), and VCS scores of low income children's better eyes at 12 cpd ($0.05, p < 0.10$).

Mean differences in VCS scores for worse and better performing eyes (child VCS score – adult VCS score = difference in VCS score) for matched children and adults residing in the same

household (child-adult pairs) are summarized in Table 9. Mean differences at all spatial frequencies except 1.5 cpd and in all three exposure categories are positive, consistent with the tendency of children to perform better than adults (cf., Figures 1a and b, 2a and b). Mean difference in child-adult differences of worse eye VCS scores at 12 cpd across exposures categories was decreased ($0.05 < p < 0.10$). The comparatively smaller mean child-adult difference in VCS scores at 12 cpd in the highest exposure category compared to the lower exposure and reference categories suggests that at this specific spatial frequency the advantage of chlidren over adults may be smaller than in the other two exposure groups. Mean child-adult differences in better performing eye VCS scores differed across exposure categories at 6 cpd ($p < 0.05$). However, the negative difference in the < 100 $\mu g/m^3$ group (indicating that adults performed better than children) followed by the large positive difference in the > 100 $\mu g/m^3$ group (indicating that children performed substantially better than adults) indicate group differences are not related to perc exposure. Additional analyses indicated that child residents of dry cleaner buildings with possible *in utero* perc exposures did not perform any worse than children without possible *in utero* exposures (data not shown). Both categories of children had equivalent proportions scoring < max at every spatial frequency.

Results of logistic regression assessing the effect of each measure of perc exposure (perc level in indoor air, breath, and blood) on the odds for scoring < max at each VCS spatial frequency for worse and better performing eyes are summarized in Tables 10a and b (adults) and 11a and b (children). In these analyses, perc exposure is a continuous rather than categorical independent variable. VCS test performance of participants in all exposure categories are included. Among adults' worse or better eyes, increases in perc exposure were not associated with any increased adjusted or unadjusted odds for scoring < max VCS (Tables 10a and b). Among children, increased perc levels in indoor air ($p < 0.05$), breath at home ($p < 0.05$), and blood ($0.05 < p < 0.10$) were associated with increased adjusted odds for worse eyes to score < max at 12 cpd (Table 11a). Adjusted odds for worse eyes to score < max were also increased as perc level in blood increased at 6 cpd ($0.05 < p < 0.10$) and 18 cpd ($0.05 < p < 0.10$). Increased adjusted odds for better eyes to score < max were associated with increased perc in breath at the clinic at 6 cpd ($p < 0.05$).

Exposure-Response Analyses. Trend tests (Tables 7a and b; 8a and b), ANOVA's (Figures 3x and y) and logistic regression (Table 11a and b) suggested that children's worse eye VCS test performance at 12 cpd was the outcome most consistently associated with perc exposure. Not only increased indoor air perc levels, but also increased individual breath and blood levels, increased the odds for decreased worse eye VCS test performance at 12 cpd among children. Hence, the relationship between perc exposure and children's worse eye VCS test performance at 12 cpd was selected as the basis for exploratory exposure-response analyses to estimate an indoor air perc effect level. Indoor air perc level was used as the measure of perc exposure in these analyses rather than breath or blood perc level to allow for comparison of the estimated effect level estimated here with indoor air perc effect levels reported elsewhere.

Using the benchmark concentration method described in Appendix 3, indoor air perc effect levels associated with a range of extra risks above the risk existing at background levels of indoor air perc for scoring < max at 12 cpd of 10–50 percent were estimated. This is generally illustrated in Figure 4. These indoor air perc effect levels and their 95 percent confidence intervals are termed benchmark concentrations (BMC_{10}–BMC_{50}) and benchmark 95 percent

confidence intervals, respectively, and are summarized in Table 12. Although these analyses suggest that residential indoor air perc levels (i.e., benchmark concentrations) in the 3–73 $\mu g/m^3$ range may be associated with a 10–50 percent extra risk for not achieving the maximum VCS score at 12 cpd among children, 95 percent confidence intervals for these estimates are quite large, reflecting considerable uncertainty in these estimates.

Another way to estimate an effect level is to identify a NOEL and/or the LOEL for decreased VCS test performance. Visual inspection of Figure 4 shows that perc levels above 100 $\mu g/m^3$ are always associated with eyes scoring < max; whereas perc levels between 10 and 100 $\mu g/m^3$ are associated with most eyes scoring < the max (n=20) but some eyes scoring the max (n=5). The highest indoor air perc level associated with a maximum score was 92 $\mu g/m^3$. Thus, a LOEL for altered VCS among children may be close to 100 $\mu g/m^3$.

DISCUSSION

In this report, visual contrast sensitivity (VCS) test performance at five different spatial frequencies was assessed monocularly in adult and child residents of buildings with or without a dry cleaner using perc. Contrast refers to the light-dark transition at borders or edges of viewed images and is an important characteristic the visual system relies upon to identify objects. The level of contrast normally required to detect an object is termed the contrast threshold. In clinical and other research, contrast threshold is usually expressed as contrast sensitivity, which is the reciprocal of the threshold. Thus, a better ability to detect contrast is associated with lower contrast threshold and greater contrast sensitivity (Bodis-Wollner and Camisa, 1980; Owsley, 2003). Contrast sensitivity differs depending upon the size of the object viewed, and may also differ for each eye.

Everyday activities such as driving or reading can be adversely affected if an individual's ability to detect contrast is impaired (i.e., if their contrast sensitivity is reduced). Reduced contrast sensitivity can indicate an effect on, or damage to, centrally mediated visual pathways in the brain even when VCS is still within a normal range (Bodis-Wollner and Camisa, 1980; Owsley, 2003). For these reasons, tests of VCS are often included in clinical evaluations of the CNS as well as of vision. On VCS tests like the Functinal Acuity Contrast Test (F.A.C.T.) administered in this study, subjects are presented with a series of circular visual images containing gratings of variable contrast and width. The number of gratings subtending one degree of visual angle on the observer's retina is referred to as cycles per degree (cpd) or spatial frequency. Smaller size gratings, or widths, have higher cpd or spatial frequency. On the F.A.C.T., spatial frequencies range from 1.5 to 18 cpd and possible detectable contrast sensitivities range from a minimum of 0.60 to a maximum of 2.26 depending upon the spatial frequency (see Appendix 2). The shaded areas of Figures 1-2 represent the full range of VCS detectable with the F.A.C.T.

In this study, individual's eyes were categorized as being either the worse or better performing eye, and relationships between perc exposure and VCS were assessed in several ways. Analyses of worse eyes made detection of an effect of perc exposure, if present, more likely since each individual's worse eye VCS test performance (either max or < max) reflects the greatest possible impact of perc exposure on that individual's eyes. Analyses were also performed using VCS of participants' better performing eye to assess the minimum possible impact of perc exposure on VCS.

Figures 1 and 2 illustrate that in this study a marked ceiling effect was observed at nearly all spatial frequencies, with many subjects scoring as well as possible at each spatial frequency. In this study, 51, 34, 28, 13, and 8 percent of reference adults' worse eyes (n=47; mean age = 44 years) achieved the maximum score at 1.5, 3, 6, 12, and 18 cpd, respectively (cf., Figure 1a; Table 8a). Adults' better eyes scored even higher than worse eyes with 81, 64, 55, 30, and 30 percent achieving the maximum score at 1.5, 3, 6, 12 and 18 cpd, respectively. The ceiling effect was even more evident among children. Sixty-three, 44, 43, 37, and 37 percent of children's worse eyes and 85, 74, 76, 67, and 68 percent of children's better eyes achieved the maximum score at 1.5, 3, 6, 12 and 18 cpd, respectively. Ceiling effects on the F.A.C.T. have been reported by other investigators using or evaluating the usefulness of the F.A.C.T. in outcomes research and having similar exclusion criteria. Pesudovs et al. (2004), for example, reported that 19, 26, 11, 4, and 11 percent of normal adult subjects (n=27; mean age=39 years) achieved the maximum VCS score on the F.A.C.T. at 1.5, 3, 6, 12, and 18 cpd, respectively. Bühren et al. (2006) also noted a ceiling effect at 1.5 cpd, the only spatial frequency tested, among normal subjects (n=10; median age=29 years).

Ceiling effects have also been observed on an earlier version of the F.A.C.T., the Vistech test (Stereo Optical Co., Inc., 1993), even though maximum detectable contrast sensitivity scores exceed those of the F.A.C.T. (Pesudovs et al., 2004). Maximum detectable contrast sensitivity scores at 1.5, 3, 6, 12, and 18 cpd are 2.23, 2.34, 2.41, 2.23, and 1.95 on the Vistech test, respectively, compared to only 2.00, 2.20, 2.26, 2.98, and 1.81 on the F.A.C.T. (Pesudovs et al., 2004). Bühren et al. (2006) also found that a different, more recently developed test (the Frankfurt-Freiburg Contrast and Acuity Test System (FF-CATS)) was able to measure contrast sensitivity as high as 2.50 at 1.5 cpd (the only spatial frequency evaluated). Thus, the high proportions of participants achieving maximum scores in this study (i.e., the ceiling effect) is due at least in part to limitations in measuring contrast sensitivity associated with the F.A.C.T. itself. Exclusion of participants with acuity worse than 20/25 or with medical or eye conditions known to interfere with vision likely also contributed.

Because of the marked ceiling effect, actual VCS scores were used only in non-parametric ANOVA and correlation analyses. For other analyses, VCS scores were categorized as being the maximum or less than the maximum achievable score and the influence of perc exposure on whether participants achieved the maximum score (max) or less than the maximum score (< max) at each spatial frequency was assessed.

Table 13 summarizes associations observed between increased indoor air perc and VCS test performance when participants are stratified and not stratified by race/ethnicity or income ($p < 0.05$ or $0.05 < p < 0.10$). Stratified analyses were performed because minority and low income participants were over-represented in the highest exposure category and stratified analyses would tend to provide the most support for concluding that perc exposure may have altered VCS independent of race/ethnicity or income. Table 14 summarizes perc exposure related increased risks for decreased VCS test performance based on the adjusted logistic regressions. These analyses considered together present the strongest evidence from this study that residential perc exposure may have influenced VCS at the specific spatial frequency of 12 cpd, especially among children.

Because residential perc exposure appeared to be associated with children's worse eye VCS test performance at the spatial frequency of 12 cpd, the exposure-response relationship between residential indoor air perc level and VCS test performance at 12 cpd among children was to estimate possible perc effect levels associated with decreased VCS test performance.

These main study findings are described and discussed in greater detail below.

Residential Perc Exposure and Adult VCS Test Performance. Trend analyses suggested that adults' worse and better performing eyes VCS test performance may have been influenced by perc exposure (Table 13). However, ANOVA based on VCS scores suggested that only better eyes were affected. Moreover, adjusted logistic regression, which related all adult participants' individual indoor air, breath, and blood perc levels to their categorical VCS test performance (i.e., < max or max score), and which controlled for age, smoking, and alcohol use, suggested that perc exposure did not increase the risk for decreased VCS for either worse or better performing eyes (Table 14). (Although the odds for decreased VCS was increased for adults' worse eyes at 18 cpd, the confidence interval was very large.)

Indoor air perc air levels, which are 24-hour time weighted averages, for the highest exposure adults in this study ranged from 216 to 2183 $\mu g/m^3$ with an average of 478 $\mu g/m^3$ and a median of 376 $\mu g/m^3$. Decreased group VCS scores averaged across all spatial frequencies were reported among adults with residential indoor air perc levels ranging between 65–5,300 $\mu g/m^3$ and a geometric mean of about 700 $\mu g/m^3$ perc (based on 3–18 hour daytime samples) or with indoor air perc exposures ranging between 1800–2400 $\mu g/m^3$ and a median of 2150 $\mu g/m^3$ (based on six 4-hour daytime samples) while working at a day care center (NYS DOH, 2000; Schreiber et al., 2002; Storm and Mazor, 2004). Decreased VCS, specifically at spatial frequencies 6 and 12 cpd, has been reported among adults exposed to various volatile organic solvents while working at microelectronics, furniture, or reinforced plastics factories, although levels of exposure are much higher than those found here (Mergler et al., 1991; Frenette et al., 1991; Gong et al., 2003; Campagna et al., 1995; Castillo et al., 2001). Thus, both median and geometric mean indoor air levels of perc experienced by adult participants in this study appear lower than levels associated with VCS effects by other investigators.

Residential Perc Exposure and Children's VCS Test Performance. Both trend analyses and ANOVA suggest that children's VCS test performance was influenced by perc exposure (Table 13). This was most apparent for worse eyes at 12 cpd, where increasing indoor air perc level was associated with decreasing trends in achieving the maximum VCS score, and differences in VCS scores among the three categorical exposure groups (i.e., ANOVA) among minority and low income children. Adjusted logistic regression, which relates all children's categorical VCS test performance (i.e., < max or max score) to their individual indoor air, breath, and blood perc levels while controlling for age, also suggested that increasing perc (in indoor air, breath or blood) increased the risk for decreased VCS for children's worse performing eyes at 12 cpd (Table 14). Although significant associations were sometimes observed at other spatial frequencies for better as well as worse eyes, the most consistent association with perc exposure was observed at the specific spatial frequency of 12 cpd.

It is not known why VCS might be more vulnerable to an effect of perc at any specific spatial frequency. Visual inspection of VCS functions in Figures 1 and 2 indicates a stronger ceiling

effect at lower spatial frequencies than higher spatial frequencies. This may have limited the ability to detect an effect of perc at mid- and lower spatial frequencies. Alternatively, as discussed below, centrally mediated visual pathways associated with detecting contrast at 12 cpd may have been selectively affected.

We know of no other evidence linking residential perc exposure to altered VCS test performance specifically in children. However, there are some reports that VCS may be altered in young children exposed prenatally to perc or to organic solvents. A single 2 ½ year old toddler exposed prenatally to perc as a result of his mother's occupational exposure to perc in a dry cleaning shop during pregnancy exhibited decreased VCS compared to three unexposed toddlers when VCS was assessed using a sweep visual evoked potential (VEP) (Till et al., 2003). Also, using sweep VEP to assess contrast sensitivity at spatial frequencies of 0.5 to 6 cpd, VCS at a spatial frequency of 0.5 cpd was reported to be statistically significantly reduced in 21 infants or toddlers (age 6–40 months) of organic solvent exposed mothers. However, in this study infant exposures were unknown and performance was not compared to matched adults (Till et al., 2005).

Further, we know of no other effects that have been associated with the comparatively low levels of residential perc exposure in this study. Median indoor air perc level for children in the > 100 $\mu g/m^3$ category was about 340 $\mu g/m^3$. The overall median for all children residing in dry cleaner buildings was about 27 $\mu g/m^3$. These are below average or median residential indoor air perc levels previously associated with CNS or visual system effects. As noted above, decreased overall VCS and color discrimination ability were reported among adults with residential indoor air perc levels of about 700 $\mu g/m^3$ perc (geometric mean) compared to unexposed adults (NYS DOH, 2000; Schreiber et al., 2002); and, slower response times and more errors on three neurobehavioral tests (simple reaction time, continuous performance, visual retention) compared to matched control subjects, were reported among adult residents exposed to a median of 1400 $\mu g/m^3$ perc (Altmann et al., 1995).

Vulnerability of Children. Enrollment of child-adult pairs in this study was intended to support assessment of whether children might be more vulnerable to an effect of perc exposure on VCS than adults residing in the same household. Children as a group tended to perform better than adults (cf., Figures 1, 2). Hence, if adult VCS scores were decreased more than children as perc exposure increased, child-adult differences would have increased as perc exposure increased across exposure categories. Conversely, if child VCS scores were decreased more than adults as perc expsoures increased, child-adult differences would have decreased as perc exposure increased across exposures categories. If child-adult VCS scores were affected to an equivalent degree, adult-child differences would remain constant across exposure categories. Mean child-adult differences in VCS scores at nearly all spatial frequencies for worse and better eyes are > 1 (Table 9). The mean child-adult difference in VCS scores for worse eyes at 12 cpd in the highest exposure group is smaller at 12 cpd than at other spatial frequencies, and also smaller than child-adult differences in the low exposure and reference groups ($0.05 < p < 0.10$), suggesting a greater effect of perc exposure on children's VCS than on adults' VCS at this spatial frequency. (Child-adult differences in VCS scores of better performing eyes initially appear to indicate that VCS was affected at 6 cpd among adults with greater perc exposure as the mean child-adult difference was negative (Table 9). However, child-adult differences in better eye VCS scores at 6 cpd actually decreased at < 100 $\mu g/m^3$ and then increased at > 100 $\mu g/m^3$, showing no exposure-

response relationship. Hence, although the differences in child-adult differences were significant across exposure categories, they were not exposure-related.

A vulnerability of children's VCS to perc is also suggested by the increased odds for worse eyes to have decreased VCS at 12 cpd as perc level in indoor air and breath at home increases (Table 13). For adults' worse eyes, increasing perc exposure was not associated with increased odds for decreased VCS at any spatial frequency. (For adults, the odds for decreased VCS was increased at 18 cpd but the very large confidence interval indicates a high degree of uncertainty and instability in the estimate).

Possible bases for greater vulnerability of children's VCS test performance to perc exposure compared to adults are unknown. Considerable evidence about perc and other chlorinated solvents indicates that perc, rather than any of its metabolites, is most likely to be responsible for CNS effects (reviewed in Bushnell et al., 2005). Levels of perc in children's breath and blood are not greater than levels in adults (Tables 5a, 5b), suggesting that children participating in this study did not have higher internal perc exposures (i.e., breath, blood levels) than adults. In fact, among children and adults residing in the same household (child-adult pairs), levels of perc in adult blood and breath obtained at the clinic were greater than levels of perc in child blood ($p < 0.01$) and breath obtained at the clinic ($p < 0.01$) (Mazor et al., in preparation). Assuming equivalent residential exposures, these observations, that children did not have greater internal perc exposures than adults, raises the possibility that VCS of children's worse eye may have been more vulnerable to perc than adults' worse eye due to greater susceptibility of children's CNS to perc compared to adults.

VCS Test Performance, Vision and CNS. Tests of VCS assess both vision (i.e., the ability of the optical components of the eye to detect contrast) and CNS function (i.e., the ability of visual pathways in the CNS to detect and interpret images of variable contrast transmitted to and from the retina). Thus, VCS results are interpreted in terms of both vision and CNS function.

Clinically abnormal VCS based on the F.A.C.T. administered in this study is defined by the manufacturer and others as scoring below the "normal" range specified for the F.A.C.T. at any spatial frequency (Stereo Optical Co., Inc., 1993). As clearly illustrated in Figures 1 and 2, most participants performed as well as possible on the VCS test, especially at low and mid-spatial frequencies with children as a group performing even better than adults. Very few worse eyes (Figure 1a) and only one better eye (Figure 1b) had any VCS scores at any spatial frequency below the 90 percent confidence interval noted by the F.A.C.T. manufacturer as "normal." For those few who did score below normal an association with perc exposure was not indicated, as they were mostly in the reference or low exposure group (cf., Figures 1, 2). Thus, VCS would not be considered clinically abnormal for any group of adults or children in this study.

Decreased VCS at one or more spatial frequencies, even if still within a normal range, may also indicate an effect on the CNS component of the visual system. The ability to detect and interpret images of variable contrast and spatial frequency reflects the functioning of separate, sequentially arranged groups of neurons, referred to as "channels," in the central visual system (Purves et al., 1997). Each channel is most sensitive to a relatively narrow range of spatial frequencies. The general shape of the VCS function in Figures 1 and 2 reflects the overlapping function of multiple vision channels which together tend to have greater sensitivity to contrast at intermediate (6, 12 cpd) spatial frequencies and less sensitivity to contrast at larger (18 cpd) or

smaller (1.5, 3 cpd) spatial frequencies. The shape of an individual's VCS function indicates whether these neuronal channels of the visual system are performing normally. An alteration in the VCS function at specific spatial frequencies is an indication to clinicians that there may be a localized abnormality somewhere within the centrally mediated, or CNS, visual pathways (e.g., Kupersmith et al., 1982; 1984; Leguire et al., 1991; Billock and Harding, 1996). An example is that decreased VCS among children with the condition of phenylketonuria is a consequence of decreased function of retinal neurons (Diamond and Herzberg, 1996). Even though a specific lesion may not be identifiable, subtle interference at any point in a vision "channel" may be sufficient to disrupt the overall integrative process of vision and to be reflected as a change in the VCS function (Ginsburg, 1996; Owsley, 2003; Bodis-Wollner and Camis, 1980). For example, alterations in contrast sensitivity thresholds at specific spatial frequencies associated with nervous system conditions such as multiple sclerosis have been documented even though specific lesions in the visual system have not been identified (Regan et al., 1980; 1981).

Viewed in the above context, it is biologically plausible that the perc exposures found in this study had an effect on the CNS that only became evident through specialized testing, e.g., VCS testing. Such an effect can be described as a subclinical effect, i.e. an effect that occurs at lower levels of exposure along the exposure-response continuum than a clinically obvious effect (Grandjean and Landrigan, 2006). Given these considerations, altered VCS test performance as found here may indicate the occurrence of a CNS effect among children due to residential perc exposure.

Exposure-Response Analyses. The indoor air perc level(s) observed in this study suggest that an effect on children's CNS may occur at levels of perc lower than levels previously associated with any other effect. Median indoor air perc level for the eleven children in the highest exposure category was 338 $\mu g/m^3$ (25–75th percentiles of about 215–700 $\mu g/m^3$) which is lower than average residential indoor air perc levels of about 700 and 1500 $\mu g/m^3$ previously reported to be associated with visual and CNS effects, respectively (Schreiber et al., 2002; Altmann et al., 1995). We explored the relationship between perc exposure and VCS test performance using both an approach which estimates benchmark concentrations and a NOEL/LOEL approach, which identifies the NOEL and/or LOEL from summary statistics of perc levels associated with exposure category groups.

A logistic regression model describing the relationship between indoor air perc level and the probability for children to score < max at 12 cpd, was applied to explore indoor air perc levels (i.e., benchmark concentrations) associated with a range of extra risks above the risk at a background perc level. Visual inspection of the resulting regression curve along with the distribution of max and < max scores with respect to perc exposure suggests that 100 $\mu g/m^3$ may be close to LOEL. Above this level no child achieved the maximum score; whereas below this level about 36 percent of children achieved the maximum score. Although calculated benchmark concentrations suggested a 10–50 percent extra risk for decreased VCS (Table 12) at residential indoor air perc levels in the 3–26 $\mu g/m^3$ range, 95 percent confidence intervals for these estimates are quite large, reflecting considerable uncertainty in these estimates. Moreover, it is uncertain what level of extra risk for decreased VCS is meaningful given the very high probability of scoring < max (about 60 percent) already present at the median background level of 2.5 $\mu g/m^3$ perc.

Consideration of indoor air perc levels associated with exposure categories used in trend analyses, which (unlike ANOVA) considers the exposure-response relationship, is another way of estimating indoor air perc effect levels. For example, increasing percentages of children not achieving the maximum score at 12 cpd across exposure categories used in trend analyses (reference building; dry cleaner building and < 100 $\mu g/m^3$; dry cleaner building and > 100 $\mu g/m^3$) suggest that children were affected by perc in an exposure-related way (Table 9a, b). Consideration of the percentage of children not achieving the maximum score in the highest exposure group suggest a level associated with a LOEL. This group of 11 children had indoor air perc levels with a geometric mean of 336 $\mu g/m^3$ (median 338 $\mu g/m^3$) and ranging from 127–700 $\mu g/m^3$ (25^{th}–75^{th} percentile 215–700 $\mu g/m^3$). This information suggests that indoor air perc levels in this general range may be associated with decreased VCS, and hence CNS, effects in children.

STRENGTHS/LIMITATIONS

Strengths. A strength of this study is the ability to link multiple individual measures of perc exposure with individual measures of VCS. Not only were residential indoor air levels of perc obtained as a measure of exposure for each adult and child participant, but levels of perc in each participant's exhaled breath and blood were also obtained. Demonstration that increased perc levels in children's breath and blood, as well as in their indoor air, was associated with decreased VCS increased confidence in concluding that perc exposure was probably a causative factor in decreased VCS at 12 cpd. A lack of consistency in associations between indoor air perc levels and VCS and between breath and blood perc levels and VCS would have decreased confidence in concluding that perc exposure was causative. Hence, the ability to consider the influence of indoor air as well as internal measures of perc exposure on VCS test performance enhanced confidence in conclusions drawn about the influence of increased perc exposure on VCS test performance.

Another strength of this study was that adults and children residing in the same household (child-adult pairs) were enrolled. Enrollment of child-adult pairs allowed for an evaluation of whether children were more vulnerable than adults to equivalent residential indoor air perc exposures. Paired analyses of differences in VCS scores between matched children and adults suggested that children's VCS test performance at 12 cpd was more affected than adults by increasing perc exposure ($0.05 < p < 0.10$).

Finally, in this study the VCS testing environment was well-controlled and potential confounders and/or covariates were documented, assessed, and controlled in analyses where appropriate. Participants were administered the VCS test in an ophthalmology research clinic where testing conditions were consistent, well controlled, and in accordance with test manufacturer recommendations. Test administrators were "masked" to participant's perc exposures, and test administrators able to speak Spanish conducted testing of participants for whom Spanish was preferred. Also, participants with optical or other medical conditions known to influence VCS or with other VOC exposures that could possibly influence VCS were excluded. Information on numerous socioeconomic and personal characteristics known to influence neurobehavioral function and/or testing was obtained and addressed in analyses where appropriate. Thus, the likelihood that alterations in VCS test performance reflect alterations in VCS associated with factors other than perc exposure was reduced.

Limitations. Interpretation of the results reported here is limited by the nature of the outcome variable. It was not possible to assess the absolute differences in VCS scores associated with perc exposures because high proportions of participants scored the maximum possible on the VCS test, and therefore sample distributions of VCS scores were truncated at the maximum achievable score at most spatial frequencies. In trend and regression analyses, VCS was categorized as being either the maximum or less than the maximum possible score (i.e., dichotomized), rather than as a specific VCS score. Some non-parametric analyses of exposure category differences based on ranking VCS scores were performed. Although these types of analyses can identify group differences in VCS scores, they cannot demonstrate an exposure-response relationship, nor can they convey the absolute difference in VCS scores among exposure groups. Thus, because of limitations associated with the VCS test administered, these results do not convey the possible quantitative magnitude of alterations in VCS associated with perc exposure.

Another outcome related limitation is that participants were tested only once. In a study of 33 individuals, mean age 32 years, who were administered the F.A.C.T. twice with a test-retest time of approximately one week, intraclass correlation coefficients (i.e., the correlation between two replicates from the same subject) at 1.5, 3, 6, 12 and 18 cpd were 0.18, 0.28, 0.44, 0.36, and 0.45, respectively (Pesudovs et al., 2004). Intraclass correlation coefficients of <0.4 indicate poor reproducibility; correlations between 0.4 and 0.75 indicate fair to good reproducibility; and, correlations $\geq$ 0.75 indicate excellent reproducibility (Rosner, 2006). These observations tend to decrease confidence that single measurements of VCS using the F.A.C.T. are reliable.

A limitation associated with the analyses upon which some conclusions are based include the very small number of both adults and children experiencing the highest perc exposures (e.g., indoor air levels > 100 $\mu g/m^3$) especially when results were stratified by race/ethnicity or income. Even though correlation analyses indicated that neither race/ethnicity nor income significantly influenced VCS in this study, it is not possible to conclusively determine whether the observed effects are completely independent of race/ethnicity or income as most of the highest exposed participants were minority and/or low income participants; and, very few were non-minority or higher income. Relative risks for scoring < max at 12 cpd among those exposed to > 100 $\mu g/m^3$ compared to those exposed to $\leq$ 100 $\mu g/m^3$ did not suggest that race/ethnicity or income level were confounders (e.g., neither was significantly associated with either outcome or exposure) (data not shown). However, sample sizes of the > 100 $\mu g/m^3$ group were always very small (n=4–8) limiting confidence in these analyses. The small number of participants in the highest exposure group and the possible confounding of exposure and race/ethnicity or income also limit generalizability of these findings to other populations.

A limitation related to analyses of associations between perc exposure and VCS is that a number of exploratory analyses were performed. These analyses were helpful in understanding factors possibly contributing to the VCS changes observed, but multiple analyses on the same set of data increases the possibility of calculating a statistically significant difference that occurred by chance alone.

Uncertainty in interpretation of the effects on VCS observed or in interpreting the "meaningfulness" of the differences in VCS observed is another limitation. It is plausible, as

noted in the discussion above, that worse performance on the VCS test administered may reflect an underlying alteration in the function of centrally mediated visual pathway(s). However, to our knowledge, VCS has not been evaluated as an indicator of alterations in any aspect of CNS function other than vision with the exception of the work on children with phenylketonuria (Diamond and Herzberg, 1996). The lack of information in these areas limits the ability to link significant effects on VCS test performance observed to any adverse or functional CNS effect.

Limitations associated with the exposure-response analyses contribute uncertainty to the perc effect levels estimated using the data obtained in this study. For example, a limitation associated with the outcome variable of scoring < max at 12 cpd is that a very high proportion of children (60–70 percent) score < max at 12 cpd even when levels of perc are at a background level (i.e., the 50^{th} or 90^{th} upper percentile of indoor air perc levels in reference households). This raises the question of whether comparatively small increases in the probability of scoring < max 12 cpd (or extra risks of 10–50 percent) are meaningful.

A limitation associated with the exposure variable of indoor air perc level is that it is a single 24 hour, time-weighted average estimate of current exposures – other 24 hour perc levels occurring within the study period timeframe are likely to have varied from this measure. Also, indoor air perc levels in dry cleaner buildings in the past could have been higher or lower than those found during this study. A related limitation is uncertainty associated with whether the effect, if it exists, is a consequence of short-term exposure only, short-term in combination with chronic exposure, or chronic exposure only. Additionally, exposures other than perc that could potentially affect VCS were not assessed. Although residents of households where some VOCs were elevated were eliminated from analysis, it is not known whether other VOCs may have been present and/or whether other VOCs, even at low levels, may have interacted with perc to effect VCS.

Recommendations. The suggestion of a subtle effect of perc on VCS in this study indicates the desirability of additional research to better understand the quantitative relationships between indoor air perc exposure and VCS. Ideally, additional study should involve children and/or adults with a range of perc exposures similar to those observed here, but with a much larger number of participants having indoor air exposures to > 100 $\mu g/m^3$ and exposures above background but < 100 $\mu g/m^3$. In such a study, an alternative to the F.A.C.T. that captures the full quantitative range of VCS should be used for assessing VCS. A larger sample size of those with clearly elevated perc exposures and a better test of VCS would address two of the major limitations associated with this study.

Another recommendation is to utilize the VCS, perc exposure, and other data gathered in this study to support development of physiologically-based pharmacokinetic (PBPK) models which can relate indoor air perc exposures to individual levels of perc in blood and/or brain. PBPK models could conceivably be applied to relate outcome (e.g., VCS/CNS effects) to target tissue (e.g., brain) dose. In the absence of additional epidemiological research, such PBPK models might be useful in estimating indoor air perc effect levels.

More generally, as recently emphasized in a review of the use of VCS tests in occupational and environmental neurotoxicology, a universally accepted definition of clinically meaningful VCS deficits in terms of both functional vision and CNS function is needed (Waksman and Brody,

2007). Also, additional research to better understand whether and how changes in VCS reflect changes to CNS function is warranted, and conversely, whether and what changes in CNS function are reflected as changes to VCS. Understanding these relationships is fundamental to determining whether subtle VCS changes like those observed here are meaningful.

CONCLUSIONS

In summary, the results presented here suggest that increased perc exposures in residences in buildings with co-located dry cleaners using perc are associated with decreased VCS test performance in children's worse performing eyes at 12 cpd. Trend analyses and adjusted logistic regression suggested that increased residential indoor air levels of perc, as well as increased perc levels in children's breath and blood, were statistically significantly associated with decreased VCS test performance at 12 cpd. Although trend analyses of adult VCS test performance suggested that increased residential indoor air perc levels were associated with decreased VCS test performance at 12 cpd among minority or non-low income adults, adjusted logistic regression found that no measure of perc exposure was associated with increased odds for decreased VCS. Consideration of these child and adult analyses suggest that children in the highest exposure group, i.e., with more than 127 $\mu g/m^3$ indoor air perc, were more vulnerable to the effect of perc on VCS than adults were. Paired analyses of differences in worse eye VCS scores between matched children and adults (child-adult pairs residing in the same household) were consistent with the notion that children's VCS at 12 cpd was more affected by increased perc exposure than adults' VCS. Although exploratory exposure-response analyses of the data obtained in this study also suggest that elevated levels of perc in residential indoor air may alter children's VCS test performance, these analyses are very uncertain, primarily due to questions about the meaningfulness of the small changes in VCS observed in a small number of children.

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FIGURES

Figure 1a. Percentages of VCS scores (worse eye) for adults living in (a) reference buildings (n=47) and (b) onsite dry cleaner buildings (n=54), and children living in (c) reference buildings (n=54) and (d) onsite dry cleaner buildings (n=50). The shaded area denotes the normal range of scores, as given by the manufacturer (Stereo Optical, 1993). Larger circles reflect higher percentages. :: reflects other achievable contrast sensitivity scores.

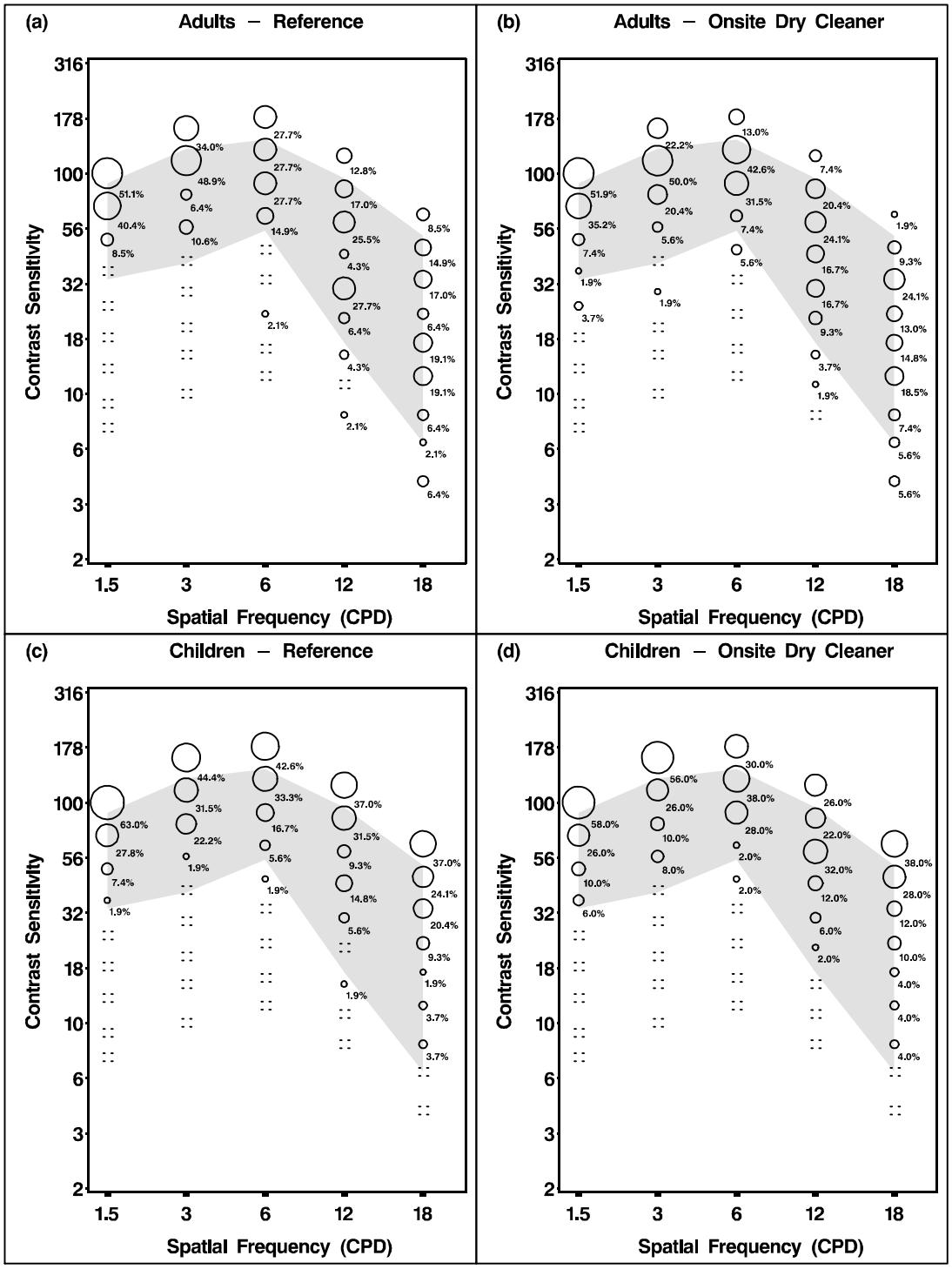


Figure 1b. Percentages of VCS scores (better eye) for adults living in (a) reference buildings (n=47) and (b) onsite dry cleaner buildings (n=54), and children living in (c) reference buildings (n=54) and (d) onsite dry cleaner buildings (n=50). The shaded area denotes the normal range of scores, as given by the manufacturer (Stereo Optical, 1993). Larger circles reflect higher percentages. :: reflects other achievable contrast sensitivity scores.

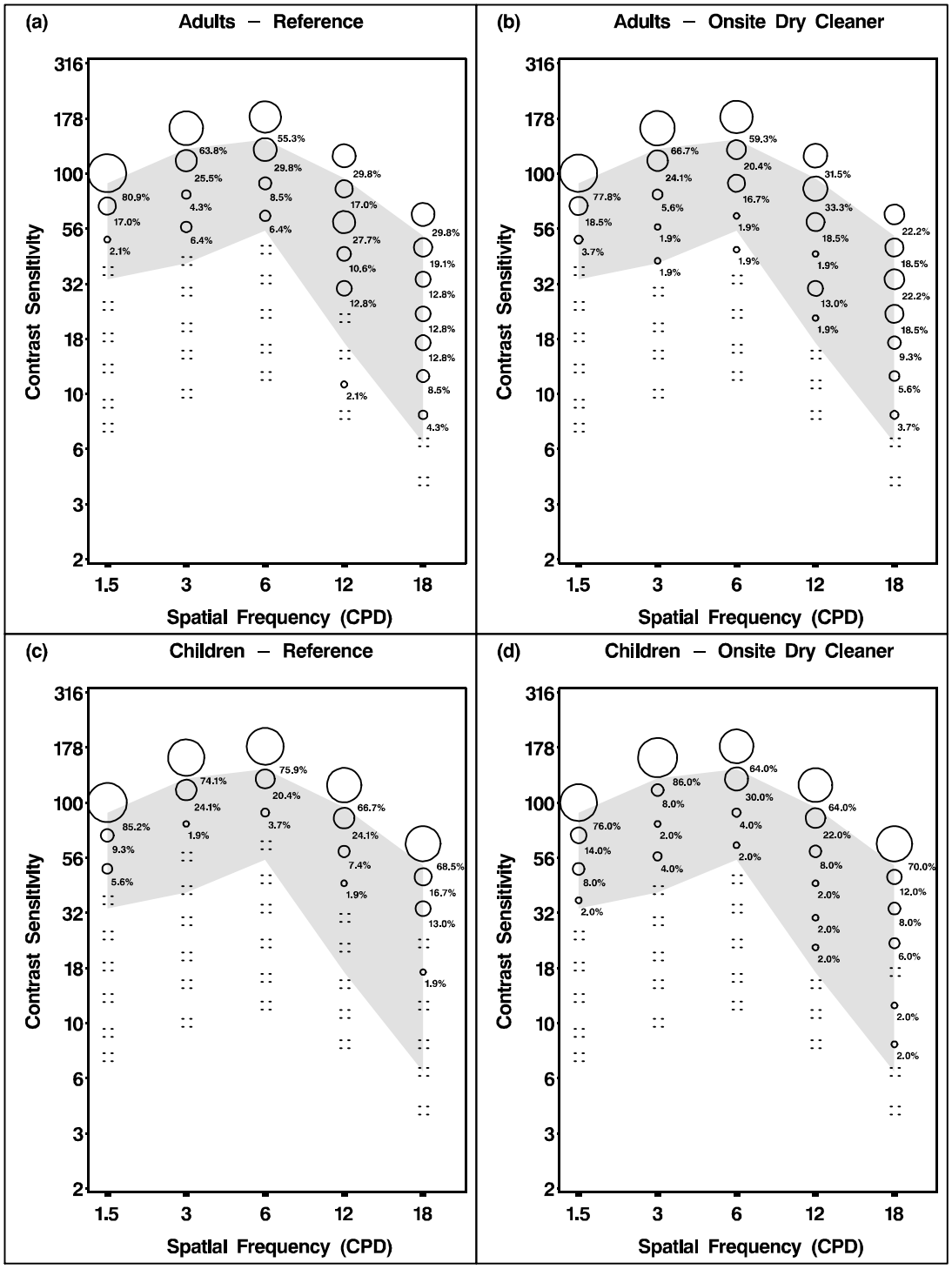


Figure 2a. Numbers of VCS scores (worse eye) for adults living in (a) reference buildings (n=47), (b) onsite dry cleaner buildings with an indoor air level less than 100 μg/m^3 (n=42), and (c) onsite dry cleaner buildings with an indoor air level greater than 100 μg/m^3 (n=12), and children living in (d) reference buildings (n=54), (e) onsite dry cleaner buildings with an indoor air level less than 100 μg/m^3 (n=39), and (f) onsite dry cleaner buildings with an indoor air level greater than 100 μg/m^3 (n=11). The shaded area denotes the normal range of scores, as given by the manufacturer (Stereo Optical, 1993). Larger circles reflect larger numbers of participants with that contrast sensitivity. :: reflects other achievable contrast sensitivity scores.

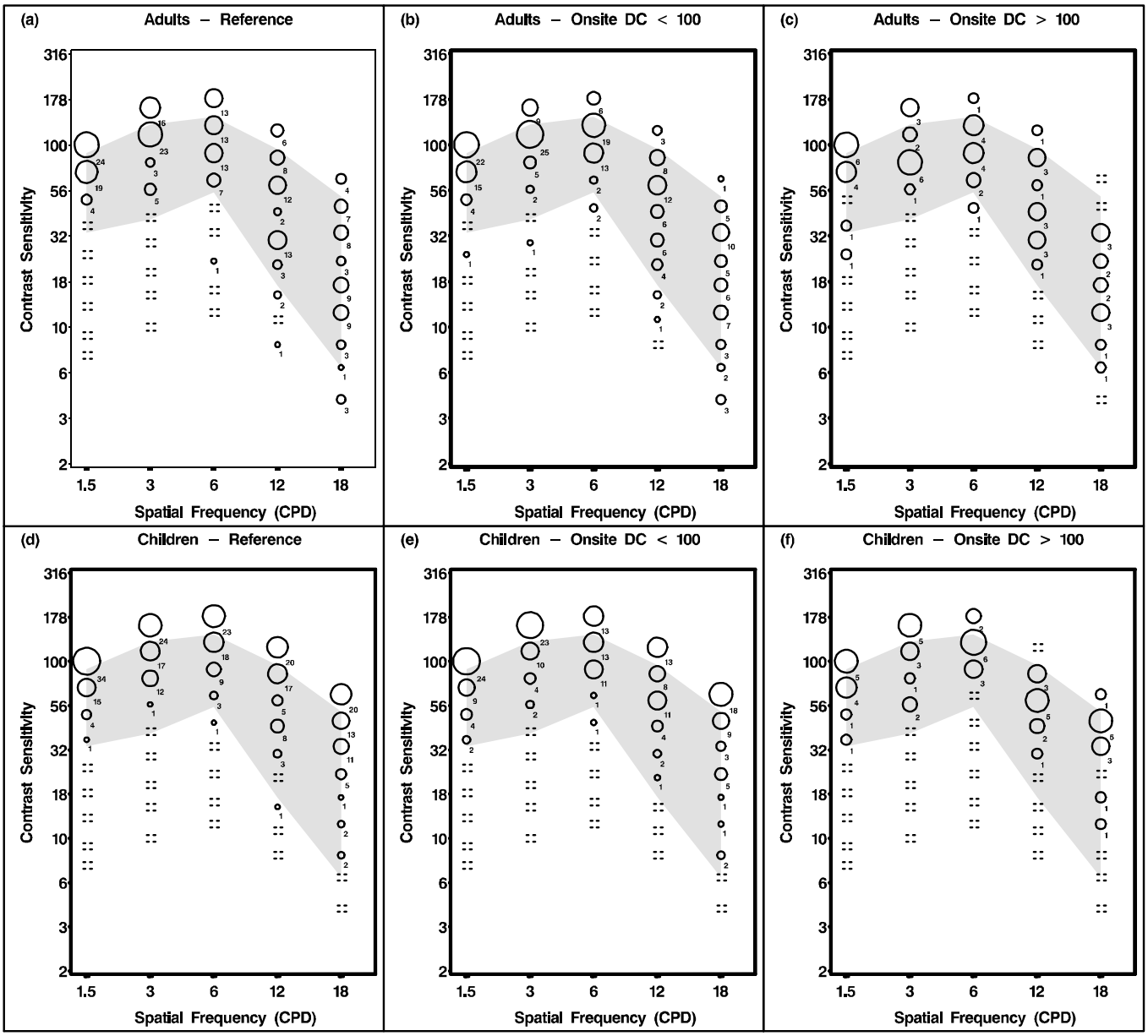


Figure 2b. Numbers of VCS scores (better eye) for adults living in (a) reference buildings (n=47), (b) onsite dry cleaner buildings with an indoor air level less than 100 μg/m^3 (n=42), and (csz) onsite dry cleaner buildings with an indoor air level greater than 100 μg/m^3 (n=12), and children living in (d) reference buildings (n=54), (e) onsite dry cleaner buildings with an indoor air level less than 100 μg/m^3 (n=39), and (f) onsite dry cleaner buildings with an indoor air level greater than 100 μg/m^3 (n=11). The shaded area denotes the normal range of scores, as given by the manufacturer (Stereo Optical, 1993).). Larger circles reflect larger numbers of participants with that contrast sensitivity. :: reflects other achievable contrast sensitivity scores.

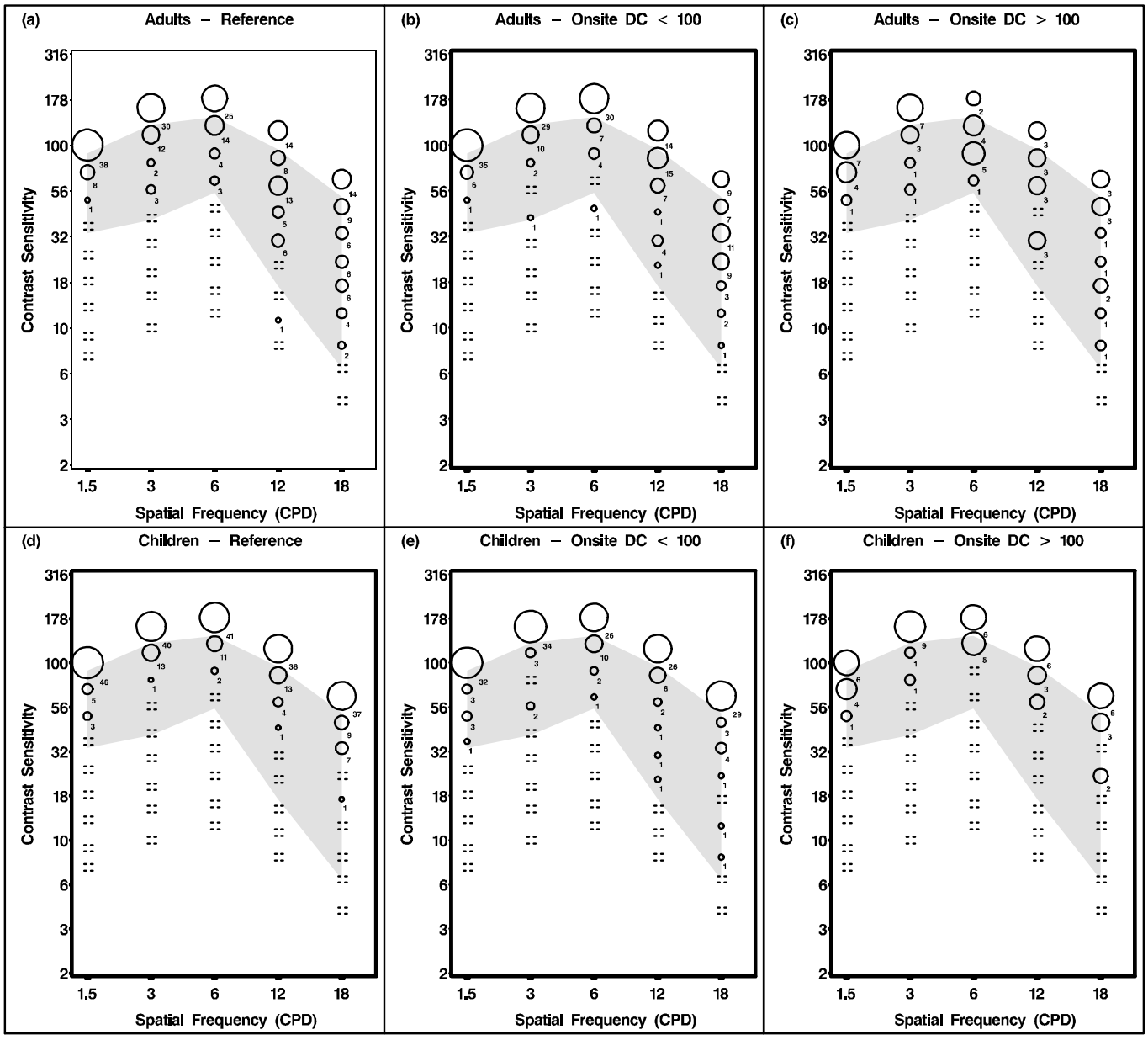
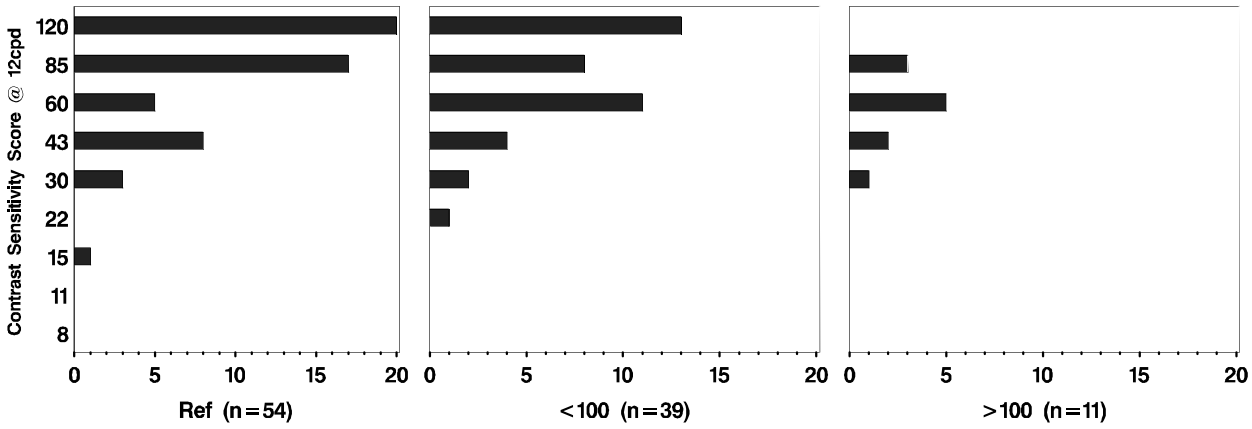
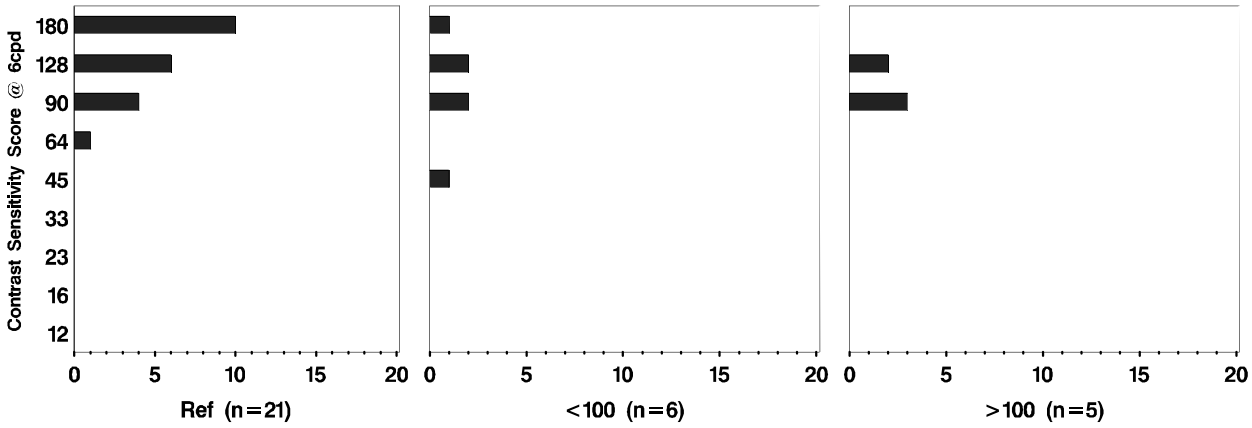


Figure 3a. Significant Group Differences in VCS Score for Worse Eyes (Kruskal-Wallis ANOVA with Bonferroni t tests). Subtitle indicates the groups included in analyses, the p-value for ANOVA, and significant group differences resulting from post-hoc analyses, if found.

All Children at 12 cpd ($p < 0.10$); reference & >100 $\mu g/m^3$



Low-Income Children at 6 cpd ($p < 0.10$)



Low-Income Children at 12 cpd ($p < 0.05$); reference & <100 $\mu g/m^3$

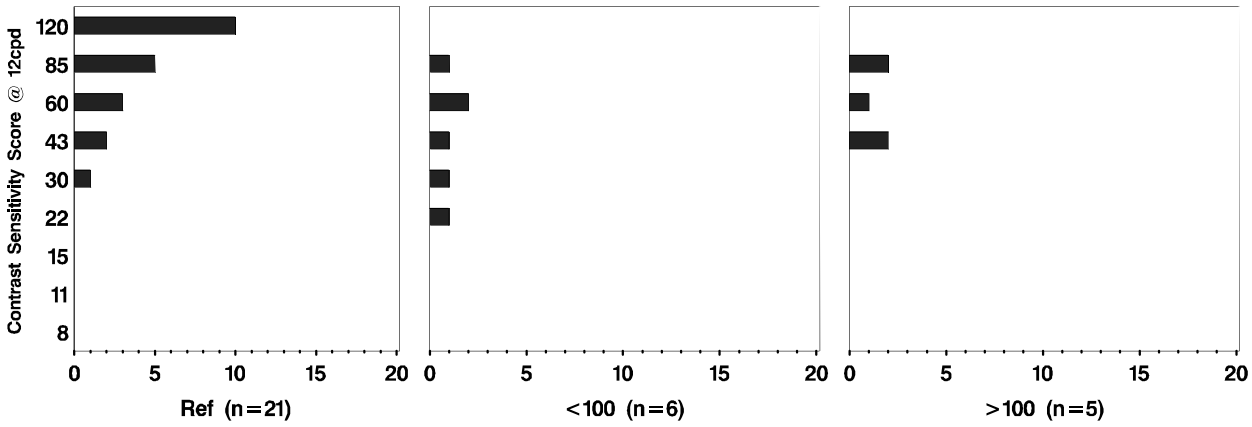
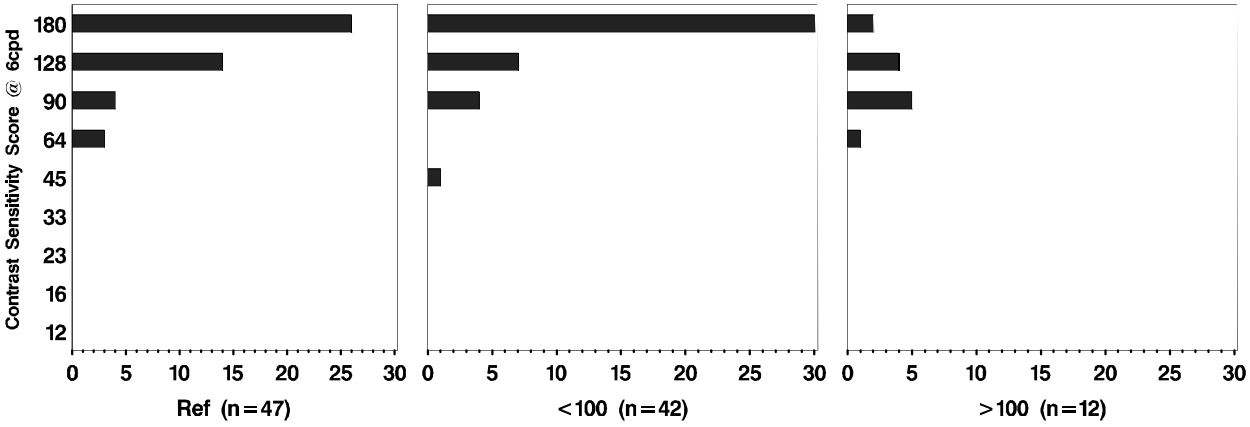
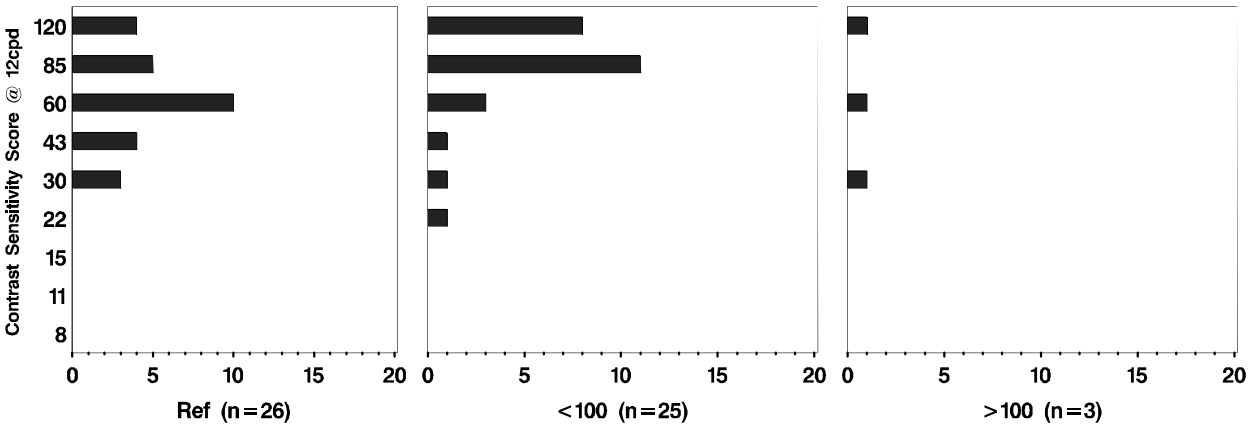


Figure 3b. Significant Group Differences in VCS Score for Better Eyes (Kruskal-Wallis ANOVA with Bonferroni t tests). Subtitle indicates the groups included in analyses, the p-value for ANOVA, and significant group differences resulting from the post-hoc analyses, if found.

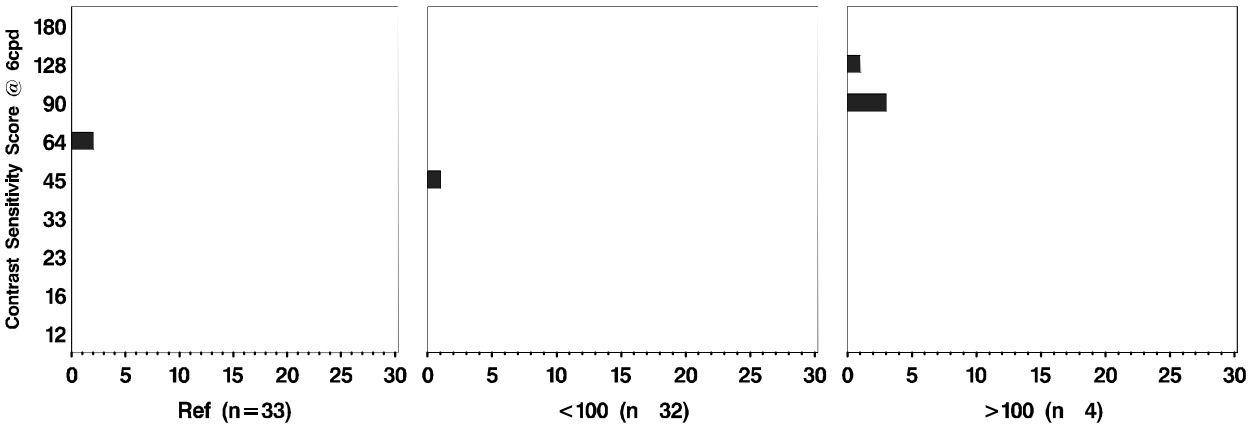
All Adults at 6 cpd ($p < 0.05$); <100 $\mu g/m^3$ & >100 $\mu g/m^3$; reference & >100 $\mu g/m^3$



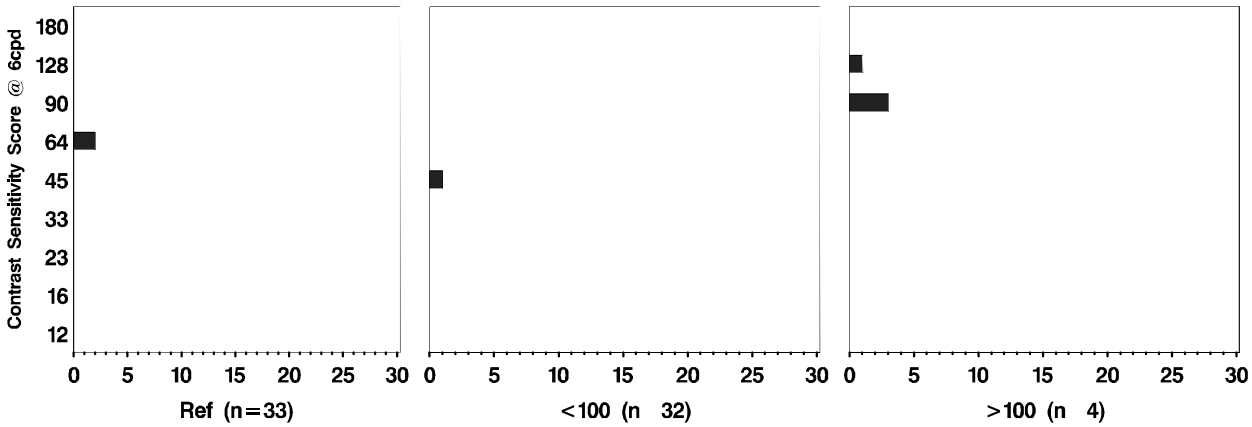
Non-Minority Adults at 12 cpd ($p < 0.10$)



Non-Low Income Adults at 6 cpd ($p < 0.05$); <100 $\mu g/m^3$ & >100 $\mu g/m^3$; reference & <100 $\mu g/m^3$



Non-Low Income Adults at 12 cpd ($p < 0.05$); reference & <100 $\mu g/m^3$



Low Income Children at 12 cpd ($p < 0.10$)

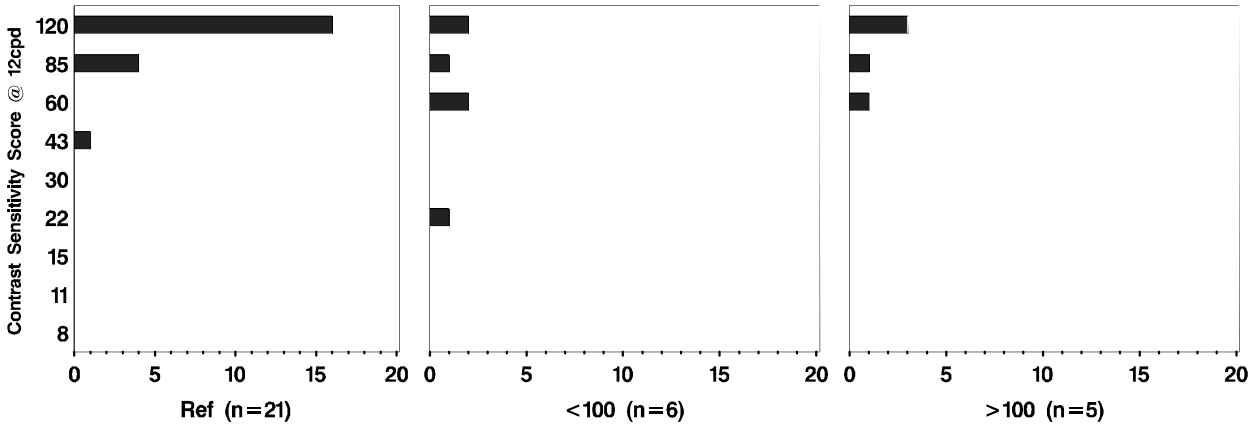
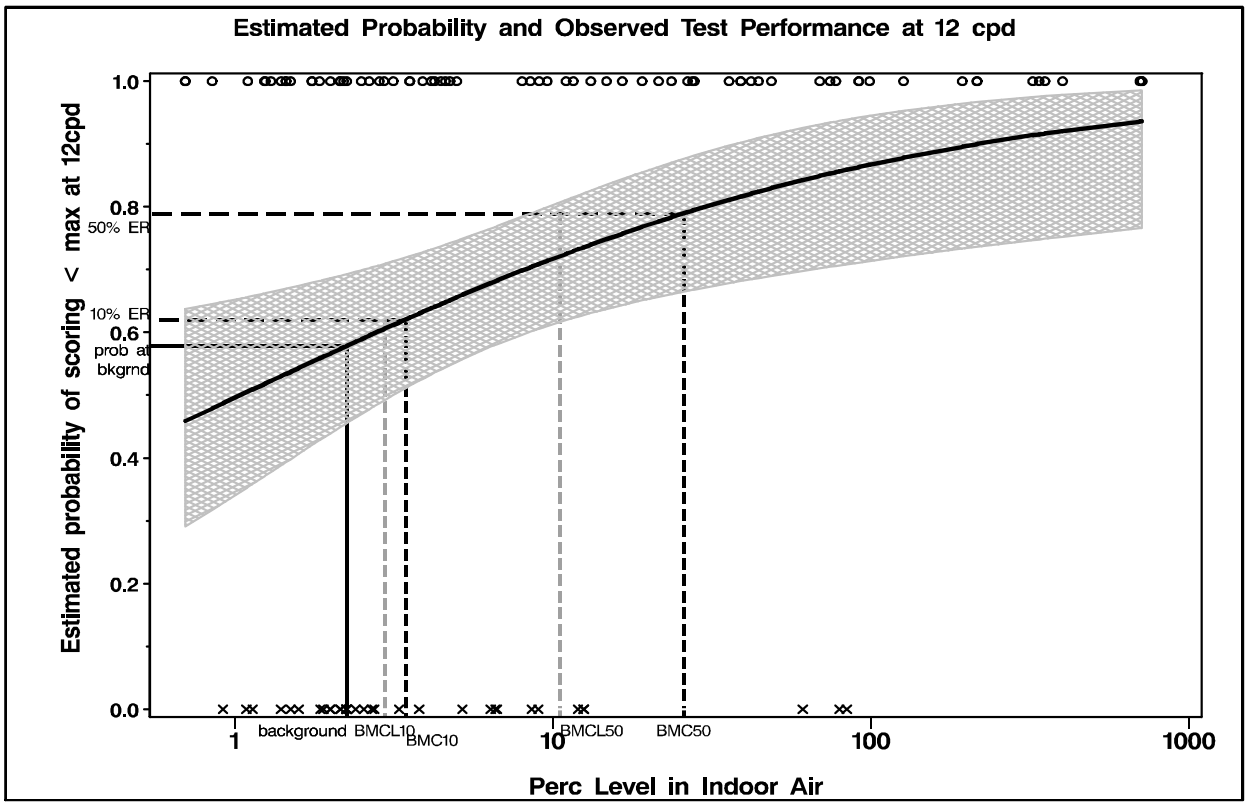


Figure 4. Logistic regression of the estimated probability for children to score < max at 12 cpd as a function of the indoor air perc level. Shaded area denotes the 95% confidence interval for the model. Dotted lines indicate BMCs and BMCLs associated with 10% and 50% extra risk.

o = individual scoring < max
x = individual scoring the max



ER = Extra Risk
BMC10 = Benchmark Concentration for 10% Extra Risk
BMCL10 = Benchmark Concentration 95% Lower Confidence Limit for 10% Extra Risk
BMC50 = Benchmark Concentration for 50% Extra Risk
BMCL50 = Benchmark Concentration 95% Lower Confidence Limit for 50% Extra Risk

TABLES

Table 1. NYC Perc Project - Recruitment Summary.

	Reference Buildings	Onsite Dry Cleaner Buildings
Buildings:		
Identified [a]	--	180
Characterized [b]	--	136
Met Criteria [c]	293	83
Contacted [d]	--	67
Sampled [e]	36	24
Apartments:		
Identified [f]	3215	2780
Contacted [g]	1252	1261
Potentially Eligible [h]	175	132
Eligible [i]	80	89
Participated [j]	61	65

-- Not applicable.
[a] Dry cleaners reporting using perc on-site.
[b] Dry cleaner buildings surveyed for presence of occupied residences; absence of other VOC sources.
[c] Dry cleaner buildings with occupied residences; no other VOC sources.
[d] Dry cleaner building where household recruitment was attempted.
[e] Dry cleaner building where at least one apartment was sampled.
[f] Estimated total apartments present.
[g] Presence of age-eligible child(ren) determined.
[h] Age-eligible adult and child present.
[i] Met screening NYC Perc Project household inclusion criteria.
[j] Apartment indoor air sampled for perc.

Table 2. Number of Adult and Child Residents and Child-Adult Pairs Completing Vision Tests.

	Reference Buildings	Onsite Dry Cleaner Buildings	
		< 100 μg/m^3	> 100 μg/m^3
Adults			
Enrolled in NYC Perc Project	60	48	19
Excluded from VCS analyses:			
- did not visit clinic	7	2	4
- less than 1 year at residence	0	1	0
- part-time resident	0	0	1
- medical condition	2	1	1
- eye condition	2	0	0
- high VOCs in residence	0	1	1
- did not take test (no reason given)	1	1	0
- pilot data (different VCS test)	1	0	0
Valid F.A.C.T. VCS Test Results	47	42	12
Children			
Enrolled in NYC Perc Project	71	49	18
Excluded from VCS analyses:			
- did not visit clinic	8	3	1
- less than 1 year at residence	0	2	0
- part-time resident	0	0	2
- autism	0	0	1
- ADHD/learning disability	3	3	0
- <6 years old	2	1	2
- low attention	2	0	0
- eye condition	0	1	0
- high VOCs in residence	0	0	1
- did not finish (per request)	1	0	0
- pilot data (different VCS test)	1	0	0
Valid F.A.C.T. VCS Test Results	54	39	11
Child-Adult Pairs			
Valid F.A.C.T. VCS Test Results	46	38	10

Table 3. Demographic and Socioeconomic Characteristics – Participants with VCS Results.

	Individual Participants			Child-Adult Pairs		
	Reference Buildings	Onsite Dry Cleaner Buildings		Reference Buildings	Onsite Dry Cleaner Buildings	
		< 100 μg/m^3	> 100 μg/m^3		< 100 μg/m^3	> 100 μg/m^3
Households	n=54	n=43	n=13	n=44	n=36	n=9
Race/Ethnicity						
Minority	25 (46.3%)	10 (23.3%)	9 (69.2%)	17 (38.6%)	9 (25.0%)	5 (55.6%)
Non-Minority	27 (50.0%)	26 (60.5%)	3 (23.1%)	25 (56.8%)	20 (55.6%)	3 (33.3%)
Other	2 (3.7%)	7 (16.3%)	1 (7.7%)	2 (4.6%)	7 (19.4%)	1 (11.1%)
No Response	–	–	–	–	–	–
Annual Income						
< $30,000	20 (37.0%)	6 (14.0%)	5 (38.5%)	13 (29.6%)	5 (13.9%)	4 (44.4%)
$30,000–$60,000	7 (13.0%)	7 (16.3%)	3 (23.1%)	7 (15.9%)	7 (19.4%)	1 (11.1%)
> $60,000	26 (48.2%)	26 (60.5%)	2 (15.4%)	24 (54.6%)	21 (58.3%)	2 (22.2%)
No Response	1 (1.9%)	4 (9.3%)	3 (23.1%)	–	3 (8.3%)	2 (22.2%)
Individual Participants						
Adults	n=47	n=42	n=12	n=46	n=38	n=10
Age (yrs ± std. dev.) *	44.1 ± 7.8 [a]	44.9 ± 5.6 [a]	35.0 ± 9.5 [b]	44.1 ± 8.2 [a]	44.9 ± 5.8 [a]	35.4 ± 10.3 [b]
Gender (female)	40 (85.1%)	33 (78.6%)	9 (75.0%)	39 (84.8%)	30 (79.0%)	6 (60.0%)
Currently Employed	34 (72.3%)	28 (66.7%)	8 (66.7%)	33 (71.7%)	27 (71.1%)	7 (70.0%)
Residence Duration (yrs ± std. dev.)	9.7 ± 7.0	10.5 ± 8.0	9.7 ± 7.6	10.1 ± 6.9	11.7 ± 7.8	10.9 ± 7.7
Years of Education (yrs ± std. dev.) *	15.4 ± 3.0 [a]	16.0 ±2.8 [a]	12.3 ± 4.6 [b]	15.4 ± 3.0 [a]	15.9 ±3.1 [a]	12.0 ± 5.2 [b]
Smoking Category						
Non-Smoker	21 (44.7%)	19 (45.2%)	7 (58.3%)	20 (43.5%)	15 (39.5%)	7 (70.0%)
Former Smoker	16 (34.0%)	18 (42.9%)	2 (4.9%)	16 (34.8%)	18 (47.4%)	1 (10.0%)
Current Smoker	9 (19.2%)	4 (42.9%)	3 (18.8%)	9 (19.6%)	4 (10.5%)	2 (20.0%)
No Response	1 (2.1%)	1 (2.4%)	–	1 (2.2%)	1 (2.6%)	–
Alcohol Use						
Does not Drink	14 (29.8%)	9 (21.4%)	5 (41.7%)	14 (30.4%)	9 (23.7%)	4 (40.0%)
2 or less drinks/wk	20 (42.6%)	14 (33.3%)	7 (58.3%)	18 (39.1%)	14 (36.8%)	6 (60.0%)
3 or more drinks/wk	12 (25.5%)	19 (45.2%)	–	13 (28.3%)	15 (39.5%)	–
No Response	1 (2.1%)	–	–	1 (2.2%)	–	–
Children	n=54	n=39	n=11	n=46	n=38	n=10
Age (yrs ±std)	10.8 ± 2.8	10.4 ± 2.7	9.5 ± 2.4	10.8 ± 2.8	10.3 ± 2.7	9.5 ± 2.6
Gender (female)	23 (42.6%)	22 (56.4%)	6 (54.6%)	19 (41.3%)	22 (57.9%)	5 (50.0%)
Residence Duration (yrs ± std. dev.)	8.5 ± 3.7	8.5 ± 3.2	7.0 ± 3.2	8.3 ± 3.7	8.5 ± 3.2	7.0 ± 3.4
Years of Education (yrs ± std. dev.)	4.9 ± 2.9	4.6 ± 2.6	3.7 ± 2.4	4.8 ± 2.8	4.6 ± 2.6	3.7 ± 2.5

Minority = African-American, Hispanic, or either in combination with another race; Non-minority = non-Hispanic White; Other = excluded from race/ethnicity analyses. * means with different letters are different ($p < 0.05$).

Table 4. Spearman Correlation Coefficients between VCS Score (Worse & Better Performing Eye) and Socioeconomic and Other Characteristics for Residents in Reference Buildings.

		VCS Spatial Freqeuncy									
		1.5 cpd		3 cpd		6 cpd		12 cpd		18 cpd	
	N	worse eye	better eye	worse eye	better eye	worse eye	better eye	worse eye	better eye	worse eye	better eye
Adults											
Income Category	47	0.16	0.07	-0.07	-0.04	-0.06	0.00	-0.20	-0.19	-0.18	-0.22
Minority Status	47	-0.06	-0.12	0.09	0.06	0.11	0.06	0.27 **	0.23	0.19	0.34 **
Years of School	47	0.20	0.12	0.19	0.14	0.04	0.21	0.01	0.07	0.01	0.04
Years in Residence	47	0.00	-0.02	-0.09	0.17	0.06	-0.05	-0.01	-0.11	0.00	-0.14
Age	47	-0.17	-0.06	0.08	0.08	0.04	-0.05	-0.06	-0.02	-0.16	-0.15
Drinks/week Category	46	-0.06	0.01	0.02	0.01	-0.04	-0.01	-0.26	-0.03	-0.24	-0.26 *
Cigarettes/day Category	46	-0.18	-0.21	0.13	-0.08	-0.30 *	-0.30 **	-0.29 **	-0.11	-0.36 *	-0.22
Lead in blood (µg/L)	38	-0.02	0.02	0.00	-0.15	0.02	-0.03	-0.11	0.07	-0.15	-0.17
Mercury in blood (µg/L)	38	-0.02	0.22	-0.01	0.02	0.15	0.25	0.08	0.15	0.03	0.04
VOC index (ppb) (without perc)	34	0.18	-0.16	-0.11	-0.12	-0.24	-0.22	-0.08	-0.17	-0.09	-0.20
Children											
Income	53	-0.01	0.04	-0.05	0.15	-0.04	-0.05	-0.10	-0.13	-0.05	0.00
Minority Status	54	0.12	0.09	0.18	-0.01	0.01	0.12	0.17	0.22	0.09	0.05
Years of School	54	0.13	0.04	-0.02	-0.09	0.25 **	-0.06	-0.12	-0.26 *	-0.13	-0.14
Years in Residence	54	0.01	0.00	-0.04	-0.13	0.06	-0.19	-0.13	-0.08	-0.23 **	-0.12
Age	54	0.16	0.04	-0.03	-0.09	0.27 *	-0.05	-0.11	-0.27 **	-0.11	-0.09
Lead in blood (µg/L)	33	-0.20	-0.05	-0.06	0.11	-0.19	-0.24	0.16	0.37 **	0.27	0.38 **
Mercury in blood (µg/L)	29	0.06	-0.15	-0.02	0.11	-0.03	-0.07	0.11	-0.04	0.17	0.05
VOC index (ppb) (without perc)	41	-0.06	0.02	0.05	0.02	0.07	0.02	-0.03	0.02	0.12	0.10

* $(0.05 < p < 0.10)$.

** $(p < 0.05)$.

Table 5a. Perc and Exposures – All Adult and Child Participants with VCS Results.

	Adult Residents			Child Residents		
	Reference Buildings	Onsite Dry Cleaner Buildings		Reference Buildings	Onsite Dry Cleaner Buildings	
		< 100 μg/m^3	> 100 μg/m^3		< 100 μg/m^3	> 100 μg/m^3
Perc						
Indoor Air (μg/m^3)	n=47	n=42	n=12	n=54	n=39	n=11
Geometric mean *	2.9 [a]	12.4 [b]	477.9 [c]	3.2 [x]	12.4 [y]	335.8 [z]
Median	2.3	12.5	375.9	2.3	12.5	337.5
25th and 75th percentile	1.5–4.2	4.6–42.0	268.9–735.3	1.8–4.5	4.3–44.3	215.0–699.5
Alveolar Breath (μg/m^3)						
Taken at home	n=42	n=36	n=12	n=47	n=35	n=9
Geometric mean *	4.6 [a]	19.2 [b]	141.4 [c]	3.7 [x]	12.2 [y]	159.5 [z]
Median	5.0	17.5	172.3	3.9	14.3	176.4
25th and 75th percentile	2.2–8.5	10.2–30.5	92.6–213.9	1.9–6.3	5.2–25.4	128.6–192.5
Taken at clinic	n=34	n=37	n=11	n=39	n=36	n=10
Geometric mean *	4.8 [a]	13.3 [b]	70.2 [c]	3.3 [x]	8.2 [y]	50.0 [z]
Median	5.6	12.9	57.3	3.3	8.1	55.3
25th and 75th percentile	2.4–8.6	8.0–24.8	48.3–114.5	2.1–5.3	4.2–14.5	23.0–64.5
Blood (μg/L)	n=37	n=38	n=11	n=32	n=28	n=7
Geometric mean *	0.05 [a]	0.13 [b]	1.3 [c]	0.04 [x]	0.11 [y]	0.51 [z]
Median	0.05	0.13	1.3	0.02	0.11	0.57
25th and 75th percentile	0.02–0.08	0.08–0.21	0.53–1.9	0.02–0.05	0.07–0.16	0.37–0.89

* means with different letters (for adults or children) are significantly different ($p<0.05$).

Table 5b. Perc Exposure – Pairied Child-Adult Residents with VCS Results.

	Matched Adult Residents			Matched Child Residents		
	Reference Buildings	Onsite Dry Cleaner Buildings		Reference Buildings	Onsite Dry Cleaner Buildings	
		< 100 μg/m^3	> 100 μg/m^3		< 100 μg/m^3	> 100 μg/m^3
Perc						
Indoor Air (μg/m^3)	n=46	n=38	n=10	n=46	n=38	n=10
Geometric Mean *	3.0 [a]	12.1 [b]	351.1 [c]	3.0 [x]	12.1 [y]	351.1 [z]
Median	2.3	12.5	344.7	2.3	12.5	344.7
25th and 75th percentile	1.6–4.2	4.3–44.3	215.5–699.5	1.6–4.2	4.3–44.3	215.5–699.5
Alveolar Breath (μg/m^3)						
Taken at home	n=40	n=32	n=10	n=41	n=34	n=9
Geometric Mean *	4.8 [a]	18.6 [b]	129.2 [c]	3.7 [x]	12.0 [y]	159.5 [z]
Median	5.0	17.5	137.3	3.9	14.0	176.4
25th and 75th percentile	2.3–8.6	10.2–27.5	102.2–183.5	1.9–6.3	5.2–25.4	128.6–192.5
Taken at clinic	n=35	n=34	n=9	n=32	n=36	n=9
Geometric Mean *	4.7 [a]	13.4 [b]	44.8 [c]	3.3 [x]	8.2 [y]	55.8 [z]
Median	5.5	12.5	54.0	3.3	8.1	58.4
25th and 75th percentile	2.4–8.6	8.7–24.8	48.3–57.3	2.1–5.5	4.2–14.5	33.1–64.5
Blood (μg/L)	n=36	n=35	n=9	n=27	n=27	n=6
Geometric Mean *	0.05 [a]	0.13 [b]	0.73 [c]	0.04 [x]	0.11 [y]	0.50 [z]
Median	0.04	0.13	0.58	0.02	0.11	0.55
25th and 75th percentile	0.02–0.08	0.07–0.27	0.53–1.3	0.02–0.06	0.07–0.16	0.37–0.89

* means with different letters (for adults or children) are significantly different ($p<0.05$).

Table 6. Spearman Correlation Coefficients between VCS Score (Worse & Better Performing Eye) and Perc Exposures for Residents in Reference Buildings or Onsite Dry Cleaner Buildings.

		Indoor Air	Exhaled Breath at Home	Exhaled Breath at Clinic	Blood at Clinic
Adults		(n=101)	(n=90)	(n=82)	(n=86)
1.5	worse eye	0.04	-0.01	0.14	0.00
	better eye	0.06	0.02	0.28 **	0.10
3	worse eye	-0.03	-0.18*	0.03	0.00
	better eye	0.03	0.05	0.16	0.05
6	worse eye	-0.14	-0.10	0.09	-0.05
	better eye	-0.08	-0.07	0.15	0.05
12	worse eye	-0.04	-0.07	0.09	0.04
	better eye	0.04	-0.07	0.25 **	0.16
18	worse eye	-0.03	-0.05	0.13	0.03
	better eye	-0.04	-0.09	0.13	0.02
Children		(n=104)	(n=91)	(n=85)	(n=67)
1.5	worse eye	0.04	-0.04	-0.07	0.02
	better eye	0.01	-0.03	-0.04	-0.08
3	worse eye	0.10	0.04	0.03	0.16
	better eye	0.24 **	0.25 **	0.20 *	0.17
6	worse eye	0.03	-0.06	-0.13	-0.15
	better eye	0.06	0.02	-0.26 **	-0.14
12	worse eye	-0.23 **	-0.35 **	-0.15	-0.17
	better eye	0.05	-0.09	-0.05	-0.09
18	worse eye	0.01	-0.02	-0.10	-0.14
	better eye	0.02	0.01	0.00	-0.10

* $(0.05 < p < 0.10)$.

** $(p < 0.05)$.

Table 7a. Significance of Decreasing Trend (Cochran-Armitage Exact Trend Test) in Percent of Residents of Buildings With or Without a Dry Cleaner (Indoor Air Perc < 100 μg/m^3 or > 100 μg/m^3) Scoring the Maximum VCS Score (Worse Performing Eye).

Spatial Frequency (cpd)	Maximum VCS Score	Percent of Worse Performing Eyes with Maximum Score							
		Adult Residents				Child Residents			
		Reference Buildings (n=47)	Onsite Dry Cleaner Buildings		p	Reference Buildings (n=54)	Onsite Dry Cleaner Buildings		p
			< 100 μg/m^3 (n=42)	> 100 μg/m^3 (n=12)			< 100 μg/m^3 (n=39)	> 100 μg/m^3 (n=11)	
1.5	100	51.1	52.4	50.0	0.50	63.0	61.5	45.5	0.19
3	160	34.0	21.4	25.0	0.14	44.4	59.0	45.5	0.77
6	180	27.7	14.3	8.3	0.03 **	42.6	33.3	18.2	0.06 *
12	120	12.8	7.1	8.3	0.23	37.0	33.3	0.0	0.02 **
18	65	8.5	2.4	0.0	0.06 *	37.0	46.2	9.1	0.19

* $(0.05 < p < 0.10)$.
** $(p < 0.05)$.

Table 7b. Significance of Decreasing Trend (Cochran-Armitage Exact Trend Test) in Percent of Residents of Buildings With or Without a Dry Cleaner (Indoor Air Perc < 100 μg/m^3 or > 100 μg/m^3) Scoring the Maximum VCS Score (Better Performing Eye).

Spatial Frequency (cpd)	Maximum VCS Score	Percent of Better Performing Eyes with Maximum Score							
		Adult Residents				Child Residents			
		Reference Buildings (n=47)	Onsite Dry Cleaner Buildings		p	Reference Buildings (n=54)	Onsite Dry Cleaner Buildings		p
			< 100 μg/m^3 (n=42)	> 100 μg/m^3 (n=12)			< 100 μg/m^3 (n=39)	> 100 μg/m^3 (n=11)	
1.5	100	80.9	83.3	58.3	0.12	85.2	82.1	54.6	0.03 **
3	160	63.8	69.1	58.3	0.48	74.1	87.2	81.8	0.88
6	180	55.3	71.4	16.7	0.12	75.9	66.7	54.6	0.06 *
12	120	29.8	33.3	25.0	0.47	66.7	66.7	54.6	0.28
18	65	29.8	21.4	25.0	0.25	68.5	74.4	54.6	0.35

* $(0.05 < p < 0.10)$.
** $(p < 0.05)$.

Table 8a. Significance of Decreasing Trend (Cochran-Armitage Exact Trend Test) in Percent of Residents of Buildings With or Without a Dry Cleaner (Indoor Air Perc < 100 μg/m^3 or > 100 μg/m^3) Scoring the Maximum VCS Score for Worse Performing Eye.

Socio-economic category	Spatial Frequency (cpd)	Percent with Maximum Score							
		Adult Residents				Child Residents			
		Reference Building	Onsite Dry Cleaner Building		p	Reference Building	Onsite Dry Cleaner Building		p
			< 100 μg/m^3	> 100 μg/m^3			< 100 μg/m^3	> 100 μg/m^3	
Stratified by Race/ethnicity									
Non-Minority Adults (n=26, 25, 3) Children (n=27, 21, 3)	1.5	53.9	48.0	66.7	0.49	55.6	61.9	100.0	0.89
	3	26.9	12.0	0.0	0.05 *	33.3	57.1	66.7	0.96
	6	26.9	12.0	0.0	0.05 *	40.7	38.1	66.7	0.66
	12	7.7	4.0	33.3	0.73	25.9	38.1	0.0	0.51
	18	0.0	4.0	0.0	0.76	33.3	47.6	0.0	0.49
Minority Adults (n=19, 10, 8) Children (n=25, 11, 7)	1.5	47.4	60.0	50.0	0.61	68.0	63.6	28.6	0.04 **
	3	36.8	30.0	25.0	0.27	56.0	72.7	42.9	0.41
	6	26.3	10.0	12.5	0.16	48.0	36.4	0.0	0.01 **
	12	21.1	10.0	0.0	0.07 *	44.0	18.2	0.0	0.01 **
	18	21.0	0.0	0.0	0.03 **	40.0	45.5	14.3	0.17
Stratified by Income									
Non-low Income Adults (n=33, 32, 4) Children (n=32, 29, 4)	1.5	48.5	56.3	25.0	0.45	59.4	58.6	75.0	0.63
	3	27.3	15.6	25.0	0.20	40.6	55.2	50.0	0.17
	6	24.2	15.6	0.0	0.10	37.5	34.5	25.0	0.32
	12	6.1	6.3	25.0	0.80	28.1	37.9	0.0	0.43
	18	3.0	0.0	0.0	0.17	31.3	51.7	0.0	0.63
Low Income Adults (n=14, 6, 5) Children (n=21, 6, 5)	1.5	57.1	33.0	60.0	0.43	66.7	83.3	20.0	0.07 *
	3	50.0	50.0	20.0	0.15	52.4	66.7	40.0	0.41
	6	35.7	16.7	20.0	0.20	47.6	16.7	0.0	0.01 **
	12	28.6	16.7	0.0	0.08 *	47.6	0.0	0.0	0.01 **
	18	21.4	16.7	0.0	0.14	42.9	16.7	20.0	0.11

* $(0.05 < p < 0.10)$.

** $(p < 0.05)$.

Table 8b. Significance of Decreasing Trend (Cochran-Armitage Exact Trend Test) in Percent of Residents of Buildings With or Without a Dry Cleaner (Indoor Air Perc < 100 μg/m^3 or > 100 μg/m^3) Scoring the Maximum VCS Score for Better Performing Eye.

Socio-economic Category	Spatial Frequency (cpd)	Percent with Maximum Score							
		Adult Residents				Child Residents			
		Reference Building	Onsite Dry Cleaner Building		p	Reference Building	Onsite Dry Cleaner Building		p
			< 100 μg/m^3	> 100 μg/m^3			< 100 μg/m^3	> 100 μg/m^3	
Stratified by Race/ethnicity									
Non-Minority Adults (n=26, 25, 3) Children (n=27, 21, 3)	1.5	84.6	84.0	100.0	0.65	81.5	90.5	100.0	0.87
	3	61.5	58.0	33.3	0.40	74.1	90.5	100.0	0.95
	6	50.0	76.0	0.0	0.61	70.4	76.2	66.7	0.58
	12	15.4	32.0	33.3	0.91	55.6	76.2	33.3	0.69
	18	19.2	16.0	0.0	0.24	66.7	76.2	33.3	0.40
Minority Adults (n=19, 10, 8) Children (n=25, 11, 7)	1.5	79.0	80.0	50.0	0.08 *	88.0	72.7	42.9	<0.01 **
	3	63.2	70.0	62.5	0.52	72.0	90.9	71.4	0.65
	6	57.9	50.0	25.0	0.07 *	80.0	54.6	57.1	0.06 *
	12	47.4	30.0	25.0	0.11	76.0	45.5	57.1	0.08 *
	18	36.8	30.0	37.5	0.48	72.0	63.6	71.4	0.42
Stratified by Income									
Non-low Income Adults (n=33, 32, 4) Children (n=32, 29, 4)	1.5	75.8	87.5	50.0	0.52	84.4	86.2	75.0	0.43
	3	57.6	71.9	75.0	0.89	75.0	86.2	100.0	0.93
	6	48.5	81.3	0.0	0.75	75.0	75.9	50.0	0.27
	12	15.2	34.4	25.0	0.93	59.4	75.9	50.0	0.74
	18	24.2	18.8	0.0	0.15	65.6	82.8	50.0	0.72
Low Income Adults (n=14, 6, 5) Children (n=21, 6, 5)	1.5	92.9	83.3	60.0	0.05 *	85.7	83.3	40.0	0.02 **
	3	78.6	66.7	40.0	0.06 *	71.4	83.3	60.0	0.40
	6	71.4	50.0	40.0	0.09 *	76.2	33.3	60.0	0.11
	12	64.3	33.3	40.0	0.12	76.2	33.3	60.0	0.11
	18	42.9	50.0	40.0	0.49	71.4	50.0	60.0	0.23

* $(0.05 < p < 0.10)$.

** $(p < 0.05)$.

Table 9. Summary of Significance of Paired Child-Adult Differences in VCS Score (Kruskal-Wallis Test for Matched Pairs).

	Spatial Frequency (cpd)	Mean Difference (Child VCS – Adult VCS = Difference)			P-value
		Reference (n=46)	Onsite Dry Cleaner Buildings		
			< 100 μg/m^3 (n=38)	> 100 μg/m^3 (n=10)	
Worse Eye	1.5	3.3	0.9	-1.0	0.73
	3	6.0	15.6	17.1	0.48
	6	20.3	15.1	27.7	0.80
	12	27.8	26.5	0.8	0.07 *
	18	21.1	24.8	17.7	0.51
Better Eye	1.5	1.4	-3.6	-2.1	0.60
	3	8.5	5.9	22.9	0.34
	6	16.3	-1.2	38.6	0.01 **
	12	31.3	16.6	21.0	0.14
	18	19.7	19.5	15.6	0.74

* $(0.05 < p < 0.10)$.

** $(p < 0.05)$.

Table 10a. Perc Exposure Risk Factors for < Max VCS (Worse Performing Eye) for Adult Residents of Reference or Onsite Dry Cleaner Buildings.

			Unadjusted			Adjusted		
Measure of Perc Exposure	**Indoor Air Perc (log µg/m^3)**	**CPD**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		1.5	101	0.902	0.562–1.433	98	0.909	0.555–1.474
		3		0.869	0.525–1.461		0.830	0.482–1.432
		6		1.794 *	0.940–3.898		1.860	0.939–4.197
		12		0.993	0.478–2.319		1.045	0.487–2.473
		18		2.006	0.612–11.770		2.003	0.668 – 11.701
	Breath Perc - Home (log µg/m^3)	**CPD**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		1.5	90	0.871	0.448–1.671	87	0.841	0.417–1.673
		3		1.441	0.692–3.185		1.170	0.539–2.628
		6		1.919	0.818–4.997		1.848	0.754–5.017
		12		2.362	0.649–10.685		2.552	0.729–11.933
		18		6.342 *	0.964–67.332		8.365	0.915–409.727
	Breath Perc - Clinic (log µg/m^3)	**CPD**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		1.5	82	0.495	0.196–1.155	80	0.445	0.159–1.121
		3		0.776	0.306–1.987		0.628	0.222–1.768
		6		0.792	0.273–2.424		0.819	0.236–3.073
		12		0.460	0.107–2.114		0.398	0.069–2.210
		18		--			--	
	Blood Perc (log ng/mL)	**CPD**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		1.5	86	1.374	0.568–3.382	84	0.907	0.412–1.953
		3		0.945	0.393–2.260		0.779	0.321–1.904
		6		1.944	0.761–5.474		1.434	0.483–4.948
		12		1.564	0.606–4.378		0.632	0.158–2.915
		18		1.672	0.668–4.527		1.783	0.377–21.496

-- computationally invalid estimate.

* increased odds ratios ($0.05 < p < 0.10$).

** increased odds ratios ($p < 0.05$).

Adjusted for: minority status, age, smoking, and alcohol use.

Most covariates were not significant, with the exception of minority race/ethnicity at 3 cpd for all models.

Table 10b. Perc Exposure Risk Factors for < Max VCS (Better Performing Eye) for Adult Residents of Reference or Onsite Dry Cleaner Buildings.

			Unadjusted			Adjusted		
Measure of Perc Exposure	**Indoor Air Perc (log µg/m^3)**	**CPD**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		1.5	101	0.959	0.522–1.672	98	0.795	0.417–1.439
		3		0.822	0.555–1.494		0.855	0.479–1.478
		6		1.320	0.828–2.133		1.245	0.761–2.054
		12		0.984	0.601–1.649		0.925	0.545–1.596
		18		0.997	0.595 – 1.729		1.092	0.636 – 1.913
	Breath Perc - Home (log µg/m^3)	**CPD**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		1.5	90	1.059	0.468–2.320	87	1.019	0.443–2.296
		3		0.899	0.451–1.757		0.826	0.388–1.721
		6		1.261	0.655–2.466		1.210	0.604–2.472
		12		1.341	0.652–2.899		1.182	0.550–2.631
		18		1.584	0.722–3.752		1.627	0.729–3.956
	Breath Perc - Clinic (log µg/m^3)	**CPD**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		1.5	82	0.245 **	0.066–0.763	80	0.091 **	0.017–0.374
		3		0.613	0.236–1.478		0.716	0.261–1.929
		6		0.525	0.208–1.229		0.446 *	0.165–1.128
		12		0.561	0.212–1.433		0.390 *	0.122–1.138
		18		0.710	0.064–1.931		0.728	0.248–2.207
	Blood Perc (log ng/mL)	**CPD**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		1.5	86	0.754	0.273–1.806	84	0.656	0.235–1.619
		3		1.094	0.501–2.328		1.018	0.433–2.440
		6		1.032	0.485–2.159		0.931	0.419–2.083
		12		0.840	0.387–1.875		0.715	0.302–1.702
		18		1.081	0.485–2.623		1.087	0.462–2.715

-- computationally invalid estimate.

* increased odds ratios ($0.05 < p < 0.10$).

** increased odds ratios ($p < 0.05$).

Adjusted for: minority race/ethnicity, age, smoking, and alcohol use.

Most covariates were not significant, with the following exceptions: minority status at 18 cpd for the indoor air model; age at 1.5 and 12 cpd for the breath at clinic model; and alcohol use at 3 cpd for the breath at clinic model and at 6 cpd for the blood at clinic model.

Table 11a. Perc Exposure Risk Factors for < Max VCS (Worse Performing Eye) for Child Residents of Reference or Onsite Dry Cleaner Buildings.

			Unadjusted			Adjusted		
Measure of Perc Exposure	**Indoor Air Perc (log µg/m^3)**	**CPD**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		1.5	104	1.063	0.641–1.750	104	0.975	0.575–1.634
		3		0.898	0.546–1.466		0.927	0.559–1.528
		6		1.319	0.789–2.284		1.230	0.720–2.171
		12		2.583 **	1.382–5.380		2.640 **	1.408– 5.520
		18		1.328	0.796–2.290		1.397	0.829–2.439
	Breath Perc - Home (log µg/m^3)	**CPD**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		1.5	91	1.283	0.652–2.541	91	1.102	0.532–2.274
		3		1.133	0.586–2.225		1.203	0.601–2.447
		6		1.604	0.805–3.402		1.539	0.734–3.497
		12		3.143 **	1.401–8.065		3.372 **	1.443–9.286
		18		1.394	0.704–2.904		1.536	0.756–3.341
	Breath Perc - Clinic (log µg/m^3)	**CPD**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		1.5	85	1.374	0.568–3.382	85	1.164	0.464–2.963
		3		0.945	0.393–2.260		0.996	0.403–2.435
		6		1.944	0.761–5.474		1.917	0.710–5.815
		12		1.564	0.606–4.378		1.602	0.610–4.586
		18		1.672	0.668–4.527		1.853	0.721–5.194
	Blood Perc (log ng/mL)	**CPD**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		1.5	67	0.931	0.319–2.565	67	0.782	0.252–2.242
		3		0.602	0.210–1.604		0.602	0.202–1.660
		6		2.755	0.970–9.006		2.707 *	0.921–9.271
		12		3.626 **	1.052–16.190		3.535 *	0.938–17.788
		18		2.329	0.851–7.127		2.732 *	0.962–8.884

-- computationally invalid estimate.
* increased odds ratios ($0.05 < p < 0.10$).
** increased odds ratios ($p < 0.05$).
Adjusted for: minority race/ethnicity and age.
Most covariates were not significant, with the exception of age at 1.5 cpd for all models, as well as at 6 cpd for the indoor air model.

Table 11b. Perc Exposure Risk Factors for < Max VCS (Better Performing Eye) for Child Residents of Reference or Onsite Dry Cleaner Buildings.

			Unadjusted			Adjusted		
Measure of Perc Exposure	**Indoor Air Perc (log µg/m^3)**	**CPD**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		1.5	104	1.171	0.625–2.125	104	1.010	0.525–1.876
		3		0.510 *	0.226–1.011		0.535 *	0.239–1.057
		6		1.117	0.650–1.888		1.101	0.638–1.871
		12		1.039	0.615–1.728		1.094	0.641–1.845
		18		1.129	0.661 – 1.904		1.172	0.682–1.994
	Breath Perc - Home (log µg/m^3)	**CPD**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		1.5	91	1.554	0.714–3.361	91	1.345	0.598–2.975
		3		0.412 *	0.144–1.006		0.455	0.152–1.126
		6		1.091	0.523–2.216		1.130	0.537–2.325
		12		1.306	0.656–2.607		1.398	0.684–2.878
		18		1.267	0.632–2.533		1.368	0.661–2.834
	Breath Perc - Clinic (log µg/m^3)	**CPD**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		1.5	85	1.706	0.586–4.931	85	1.460	0.483–4.429
		3		0.345 *	0.096–1.246		0.391	0.093–1.343
		6		3.616 **	1.376–10.536		3.847 **	1.441–11.355
		12		1.296	0.523–3.224		1.409	0.558–3.574
		18		1.477	0.579–3.796		1.658	0.639–4.362
	Blood Perc (log ng/mL)	**CPD**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		1.5	67	1.841	0.461–6.922	67	1.666	0.402–6.549
		3		0.315	0.062–1.599		0.396	0.057 – 1.823
		6		1.893	0.627–5.735		1.821	0.590–5.640
		12		1.361	0.493–3.737		1.381	0.490–3.878
		18		1.672	0.534–5.121		1.865	0.579–5.994

-- computationally invalid estimate.
* increased odds ratios ($0.05 < p < 0.10$).
** increased odds ratios ($p < 0.05$).
Adjusted for: minority status and age.
No covariates were significant, with the exception of age at 1.5 for the indoor air model.

Table 12. Estimated Indoor Air Perc Effect Levels (μg/m^3) for Children's Worse Eye to Score < max at 12 cpd.

	Probability of scoring < max at 12 cpd	Benchmark Concentration (BMC)	Benchmark Concentration 95% Confidence Interval
Scenario 1: background defined as median of indoor air levels in reference buildings			
Background = 2.25 μg/m^3	0.58		
10% Extra Risk	0.62	3.4	2.9 – 5.5
20% Extra Risk	0.66	5.4	3.9 – 14
30% Extra Risk	0.71	8.6	5.3 – 39
40% Extra Risk	0.75	14	7.3 – 120
50% Extra Risk	0.79	26	10 – 421
Scenario 2: background defined as 90th percentile of indoor air levels in reference buildings			
Background = 8.5 μg/m^3	0.70		
10% Extra Risk	0.73	12	--
20% Extra Risk	0.76	18	13 – 47
30% Extra Risk	0.79	27	17 – 123
40% Extra Risk	0.82	43	22 – 358
50% Extra Risk	0.85	73	30 – 1204

-- Not calculable.

Table 13. Summary of Associations Between Increased Indoor Air Perc Level (perc exposures are residence in: a reference building; a dry cleaner building with perc < 100 µg/m^3; or, a dry cleaner building with perc > 100 µg/m^3) and Decreased VCS Test Performance.

	Spatial Frequency (cpd)	Adult Residents (unpaired)				Child Residents (unpaired)			
		Trend Analyses (based on proportions with max scores)		Analysis of Variance (based on VCS scores)		Trend Analyses (based on proportions with max scores)		Analysis of Variance (based on VCS scores)	
		Unstrat [a]	Strat [b]	Unstrat [a]	Strat [b]	Unstrat [a]	Strat [b]	Unstrat [a]	Strat [b]
Worse Eye	1.5	–	–	–	–	–	++[2],+[3]	–	+[3]
	3	–	+[1]	–	–	–	–	–	+[1]
	6	++	+[1]	–	–	+	++[2,3]	–	+[3]
	12	–	+[2,4]	–	–	++	++[2,3]	+	+[2],++[3]
	18	+	++[2]	–	–	–	–	–	–
Better Eye	1.5	–	+[2],++[3]	–	–	++	++[2,3]	+	+[2]
	3	–	+[3]	–	–	–	–	–	–
	6	–	+[2,3]	++	++[1,4]	+	+[2]	–	–
	12	–	–	–	+[1],++[4]	–	+[2]	–	+[3]
	18	–	–	–	–	–	–	–	–

– = no effect of increased perc exposure observed.
+ 0.05 < p < 0.10.
++ p < 0.05.
[a] Unstrat = unstratified analyses.
[b] Strat = stratified analyses. Stratifying variables are:
race/ethnicity ([1]non-minority; [2]minority); and,
income ([3]low income; [4]non-low income).

Table 14. Summary of Perc Exposure (perc exposures are continuous) Related Increased Risks for Decreased VCS (scoring the max) Among Residents of Buildings With or Without a Co-Located Dry Cleaner.

	Spatial Frequency (cpd)	All Adult Residents	All Child Residents
		Adjusted Odds Ratio [#] (95% Confidence Interval)	Adjusted Odds Ratio [##] (95% Confidence Interval)
Worse Eye	1.5	–	–
	3	–	–
	6	–	–
	12	–	2.64 (1.41 -5.52) [1] 3.37 (1.44- 9.29) [2] 3.54 (0.94 – 17.79) [3]
	18	–	2.73 (0.96-8.88) [3]
Better Eye	1.5	–	–
	3	–	–
	6	–	3.85 (1.44 - 11.36)
	12	–	–
	18	–	–

[#] Odds ratio adjusted for race/ethnicity, age, smoking, and alcohol use
[##] Odds ratio adjusted for race/ethnicity, age
[1] indoor air perc level (< 1 – 710 mcg/m^3)
[2] home breath perc level (< 1 – 675 mcg/m^3)
[3] blood perc level (0 – 2 ng/L)
[4] clinic breath perc level (1 – 191 mcg/m^3)

APPENDIX 1. TETRACHLOROETHYLENE (PERC) EXPOSURE AND COLOR VISION TEST PERFORMANCE IN ADULTS AND CHILDREN RESIDING IN BUILDINGS WITH OR WITHOUT A DRY CLEANER.

SUMMARY

This Appendix presents research findings on color vision test performance by participants in the New York City (NYC) Perc Project. Color vision test performance on two color vision tests ((Farnsworth (D15) and Lanthony Desaturated (D15d)) was the outcome variable evaluated. Sample distributions of the dependent variable normally assessed by both tests -- color confusion index (CCI) -- were not obtained due to the occurrence of marked floor effects. Consequently, in addition to CCI, each participant's performance on both color vision tests was categorized according to whether or not at least one major error was made. For initial exploratory analyses, participants were grouped into the same three exposure categories used to evaluate visual contrast sensitivity (VCS) test performance: residence in a reference building; in a dry cleaner building with perc < 100 $\mu g/m^3$; or, in a dry cleaner building with perc > 100 $\mu g/m^3$. Associations between increasing perc exposure and both dependent variables (CCI, making a major error(s)) were explored among unpaired adults and children using nonparametric trend and correlation analyses. Mean CCI differences were assessed in a paired chi-square test based on ranks to assess child-adult differences in CCI for adults and children residing in the same household. The odds for making at least one major error on the more difficult Lanthony (D15d) test as perc exposure increased was assessed using logistic regression.

Both CCI and the commission of major errors on both color vision tests were significantly associated with minority race/ethnicity, lower income, fewer years of school and/or younger age for both adults and children. No measure of perc exposure (indoor air, breath, blood perc level) was significantly associated with decreases in color vision test performance. Significant positive correlations between perc exposure and CCI or commission of major errors were not observed. Significantly decreasing trends in commission of major errors as perc exposure increased were not observed. And, increased perc exposure did not significantly increase the odds for either adults or children to make major errors. Additionally, CCIs among study participants were found to be equivalent to CCIs found in several other unexposed populations. Thus, residential perc exposure, at the level present among the study population did not appear to adversely impact color vision test performance of either children or adults.

INTRODUCTION

As noted in the Introduction to the main body of this report, elevated perc levels have been associated with visual function effects among dry cleaner workers exposed to perchloroethylene (perc) (Ferroni et al., 1992; Echeverria et al., 1995; Cavalleri et al., 1994; Gobba et al., 1998). Decreased color vision, specifically, has been reported to be associated with perc exposures of about 30,000–40,000 $\mu g/m^3$ (Cavalleri et al., 1994; Gobba et al., 1998). Color vision was also reported to be decreased among 13 adults exposed to residential indoor air perc levels averaging about 700 $\mu g/m^3$ perc (geometric mean) compared to unexposed adults, although the decrease was not statistically significant (NYS DOH, 2000; Schreiber et al., 2002). In addition, exposures to other volatile organic solvents have been associated with decreased color vision (Mergler et al., 1988; Gong et al., 2003; Bowler et al., 1991).

Based on these observations, it was hypothesized that elevated residential indoor air perc levels might be associated with decreased color vision among New York City (NYC) Perc Project participants. Thus, color vision, in addition to visual contrast sensitivity (VCS), was assessed among both adult and child participants who met all inclusion criteria. As noted in the main body of this report several measures of perc exposure were assessed for each participant (indoor air, breath, and blood perc level), and most participants completed both VCS and color vision testing. Associations between perc exposure and VCS test performance are described in the main body of this report. Associations between perc exposures and color vision test performance are summarized in this Appendix.

METHODS

The study area and building selection, participant recruitment procedures, participant activities, analytical methods, and general visual function assessment are described in the main body of this report.

Color vision assessment. Color vision was assessed binocularly using first the Farnsworth (D15) and then the Lanthony Desaturated (D15d) arrangement tests according to Farnsworth Munsell (Luneau Ophthalmology, Paris France) under light conditions specified by the manufacturer. Colors on the Farnsworth (D15) test are easier to distinguish than those on the Lanthony (D15d) test, and it is used to identify individuals with inherited "color blindness." Data obtained from individuals exhibiting inherited "color blindness" on the Farnsworth (D15) test were excluded from further analyses. Colors on the Lanthony (D15d) test are paler and lighter and more difficult to distinguish than colors on the Farnsworth (D15) test, and it is typically used to detect acquired color vision deficits (Melamud et al., 2004).

For both tests, participants were shown a rectangular box containing 16 colored caps (about the size of a bottle cap) arranged in chromatic order. The test administrator removed 15 caps, leaving the first as a standard, and randomized them in front of the participant. Participants were asked to place the cap which most closely matched the standard in hue (i.e., color) in the box next to the standard, and to continue the process until all colored caps were in the box. When the participant was done, the order of cap placement was recorded and diagrammed on templates provided with the tests.

Based on review of these charts, examining ophthalmologists made judgements as to whether or not color vision was normal or abnormal.

The number of errors for each participant was recorded by noting instances of inversions involving a single cap (a minor error) and instances of inversions involving two or more caps (major errors). Perceptual color distances between colored caps were obtained using the recorded order of color cap placement and published tables of perceptual color distances between caps (Bowman, 1982; Geller, 2001). Total Color Distance Scores (TCDS) were determined and a Color Confusion Index (CCI) was calculated for each participant according to Geller (2001) (Lanthony D15d) and Bowman (1982) (Farnsworth D15). CCI is the ratio of a participant's TCDS and the TCDS associated with errorless performance, which is 116.9 for the Farnsworth test and 56.4 for the Lanthony D15-d test. A perfect score would have a CCI equal to 1.0.

Data Analyses. All statistical analyses were performed using SAS software (Release 9.1, SAS Institute, Cary, NC) as noted in the main body of this report. Findings were deemed significant when $p < 0.05$ and nearly significant when $p < 0.10$. Indoor air perc levels obtained from main living areas were averaged for each household. Volatile organic compounds (VOCs) indices were estimated for each household by summing VOC concentrations (other than perc) expressed as parts per billion (ppb). Categorical household and participant characteristics identified from a screening questionnaire were summarized by percent and compared between exposure groups using the chi-square test. Continuous variables were summarized by mean ± standard deviation (std. dev.) and compared between exposure groups using Analysis of Variance (ANOVA) and Student-Newman Keul's test. Spearman correlation coefficients were used to assess associations between socioeconomic and other individual characteristics, levels of perc in indoor air, breath, and blood, and color vision measures.

Most participants, regardless of residence building type (i.e., reference or dry cleaner), scored perfectly on both color vision tests, i.e., CCI=1, resulting in marked floor effects. Therefore, full sample CCI distributions were not obtainable, and parametric statistical analyses of group CCIs were not possible. Instead, non-parametric statistical analyses were applied to evaluate associations between perc exposure and CCI as well as between perc exposure and a derived measure of color vision test performance. For this measure, participants were categorized according to whether they made no, or one or more major error(s) (e.g., cap inversion spanning at least two cap locations). Individuals with normal color vision commonly make one or two minor errors (e.g., cap inversion spanning only one cap location) and occasionally one major error; whereas individuals with acquired color vision deficits tend to make one or more major errors (Melamud et al., 2004).

For trend and other group analyses, participants were categorized into one of the following three exposure categories, as was done for VCS test performance analyses: residence in a reference building, dry cleaner building with indoor air perc < 100 $\mu g/m^3$ (below NYS DOH guideline), and dry cleaner building with indoor air perc > 100 $\mu g/m^3$ (above NYS DOH guideline).

Associations between perc exposure and performance on the Farnsworth (D15) and Lanthony (D15d) color vision tests were evaluated separately. Using the Cochran-Armitage exact trend test, decreasing trends in the proportion of participants not making major errors across the three exposure categories was evaluated. Spearman correlation coefficients indicated that race/ethnicity

and annual income of sampled households were significantly associated with increased indoor air levels of perc as well as increased breath and blood perc levels. Therefore, within exposure categories, participants were also stratified by race/ethnicity and income for trend analyses, as was done for VCS analyses.

To assess a possible greater vulnerability of children to an effect of perc on color vision test performance compared to adults, differences in CCI between children and adults residing in the same household (child-adult pairs) (child CCI – adult CCI = CCI difference) across the three exposure categories were evaluated using Kruskall-Wallis chi-square test based on ranks.

Logistic regression was used to model the probability of making at least one major error on each color vision test given a unit (log) increase in each measure of perc exposure (perc level in indoor air, breath at home, breath at the clinic, blood). All participants meeting inclusion criteria were included in this regression to utilize all exposure-response data available. Spearman correlation analyses indicated significant associations between race/ethnicity, income, age, and years of education, and test performance on both color vision tests. Hence odds ratios (ORs) adjusted for these known, and other possible (e.g., residence duration; gender; smoking (adults only); alcohol use (adults only); VOC index; and lead and mercury blood levels) confounders are presented.

Residence duration was considered a potential confounder since longer residence duration in a dry cleaner building might reasonably have been associated with a longer duration of residential perc exposure and hence a greater effect on color vision test performance. Age is well recognized to influence color vision (Lomax et al., 2004; Gong et al., 2003; Schaper et al., 2004). Gender was considered a potential confounder given the possibility that it may have influenced color vision test performance, even though there is currently no evidence suggesting this would be so (e.g., Kinnear and Sahraie, 2002; Lomax et al., 2004). Race/ethnicity, income, alcohol use, and tobacco use are recognized potential confounders in cognitive and neurobehavioral tests (Krieg et al., 2001; Amler et al., 1995; Amler and Gibertini, 1996), and there is some evidence that they specifically influence color vision as well (cf., Lomax et al., 2004; Geller and Hudnell, 1997; Mergler et al., 1991). Lead, mercury, and VOC exposures have been shown to influence neurobehavior and, in some cases, specifically color vision (e.g., Ventura et al., 2005; Mergler and Blain, 1987; Mergler et al., 1988; 1991).

RESULTS

Some adults and children did not complete some or any of the visual function assessment portions of the study. Other adults and children completed some or all visual function assessments but their test results were excluded from analyses due to the presence of medical or eye conditions known to influence the measures evaluated, indication of past or present exposure to perc or other VOCs outside the home, or a residence time of less than one year. Visual function tests for some children were excluded from analyses because of their young age (less than 6 years old) or because they were noted by their parents as learning disabled or having attention deficit hyperactivity disorder. Hence, the study population evaluated here includes only those individual adult and child participants completing the Farnsworth (D15) and/or Lanthony (D15d) test that met inclusion criteria and child-adult pairs in which both a child and an adult residing in the same household met

inclusion criteria and completed each test. These populations are summarized by residence building type and exposure category in Table A–1.

Socioeconomic characteristics of households, individuals, and child-adult pairs are summarized in Tables A–2a and A–2b for those completing the Farnsworth (D15) and Lanthony (D15d) color vision tests, respectively. For both tests, more households in dry cleaner buildings where perc > 100 $\mu g/m^3$ were categorized as minority, and fewer were categorized as high income (> $60,000 annual income) compared to households in reference or dry cleaner buildings where perc < 100 $\mu g/m^3$. Also, adults in the highest exposure category were younger and had fewer years of education on average than adults in the other two groups.

Perc exposures for each exposure category are summarized in Tables A–3a (individual adults, children) and A–3b (child-adult pairs) for participants with Farnsworth (D15) color vision test results, and in Tables A–4a (individual adults, children) and A–4b (child-adult pairs) for participants with Lanthony (D15d) color vision test results. Adult and child residents of both categories of dry cleaner buildings (< 100 $\mu g/m^3$ and > 100 $\mu g/m^3$) for whom color vision test results were available had significantly elevated indoor air perc levels and significantly greater exhaled breath and blood perc levels than residents of reference buildings. There were no significant differences in indoor air levels of other VOCs (cf., VOC indices) (data not shown).

CCIs for adult and child residents of reference and dry cleaner buildings are illustrated in Figure A–1 which shows that CCIs for both the Farnsworth (D15) and Lanthony (D15d) color vision tests were characterized by a marked floor effect with most participants achieving a perfect CCI of 1.0 on both tests.

As summarized in Table A–5 both measures of test performance on one or both color vision tests were significantly associated with race/ethnicity, income, years of school, and/or age. On the less difficult Farnsworth (D15) test lower income, minority race/ethnicity, and fewer years of school were significantly or nearly significantly associated with higher CCI among adults. For children, fewer years of school, younger age, and shorter residence duration were significantly, or nearly significantly, associated with higher CCI and making major error(s) on the Farnsworth (D15). On the more difficult Lanthony (D15d) test, lower income, minority race/ethnicity, and fewer years of school were significantly associated with higher CCI and making major error(s) among adults. Lower income, being of minority race/ethnicity, fewer years of school, younger age, and shorter residence duration were significantly or nearly significantly associated with higher CCI and, with the exception of minority membership and lower income, making major error(s) among children. (Significant correlations suggesting that higher blood mercury level is associated with lower CCI (child Farnsworth (D15)) or with not making major error(s) (adult Lanthony (D15d)) appear spurious. Prior studies suggest that increased, rather than decreased, mercury exposure would be likely to impair color vision (Cavalleri et al., 1995; Urban et al., 2003).)

As summarized in Table A–6 no significant positive Spearman correlations were observed between any measure of perc exposure and either measure of adult or child Farnsworth (D15) or Lanthony (D15d) color vision test performance (CCI, one or more major errors). Negative correlations suggesting that increased perc in air, breath, or blood is associated with lower CCIs or not making major errors (i.e., improved color vision) is counterintuitive.

Decreasing trends in proportions of participants in each exposure category making no major errors (summarized in Table A–7) were not significant for either color vision test in stratified or unstratified analyses. This is consistent with results of logistic regression, (summarized in Tables A–8a and A–8b) which suggested that the odds for commission of major errors on the Lanthony (D15d) color vision test were not significantly associated with increases in any measure of perc exposure. Adjusted odds for making major errors on the Farnsworth (D15) test could not be calculated due to characteristics of the data that prevented calculation of maximum likelihood estimates (see discussion of complete or quasi-complete separation in Allison (1999)). The adjusted odds for making major errors were significantly, or nearly significantly, decreased for some measures of increased perc exposure on the Lanthony (D15d) test for both adults and children. These observations may be spurious though given that perc exposure is not expected to have a beneficial effect on color vision test performance.

To explore whether child color vision test performance might be more vulnerable to perc exposure than adult color vision test performance, mean differences in CCI for child-adult pairs (child CCI – adult CCI = CCI difference) were assessed across exposure categories. Assuming that children would tend to have higher CCIs than adults and that increased perc exposure would only increase, and not decrease, CCI, a larger child-adult difference in CCI would indicate a comparatively greater increase in CCI of matched children compared to matched adults. A smaller child-adult difference may indicate a comparatively greater increase in CCI among adults. As shown in Table A–9, a significant effect of perc exposure on mean child-adult CCI difference on the Farnsworth (D15) test was not observed. However, a significant effect of increasing perc exposure on mean child-adult CCI difference on the Lanthony (D15d) test was observed, and post-hoc analysis indicated the mean child-adult CCI difference in the > 100 $\mu g/m^3$ group was significantly greater than the mean difference of the other two exposure groups. This suggests that children in the highest exposure category may have been more affected by perc exposure than adults residing in the same household (although such a conclusion is inconsistent with trend analyses and with logistic regression).

To provide additional perspective on the possibility that color vision test performance of either children or adults, especially in the highest exposure group, might have been influenced by perc exposure, CCIs of study participants are compared with CCIs of unexposed groups reported by other investigators in Table A–10. CCIs for all adult and child exposure categories evaluated in this study are well within the range of CCIs reported for other unexposed populations. Although median and maximum CCIs of children in the > 100 $\mu g/m^3$ exposure category are higher than that of matched adults, they are still less than and within a range, respectively, of what has been observed in a different group of unexposed children of similar age (NYS DOH, 2005). At the same time, median and maximum CCIs of matched adults are equivalent or lower than other available adult reference populations. Thus, although study conditions may differ, CCIs for neither adult nor child participants in the NYC Perc Project appear to differ from other unexposed populations.

DISCUSSION

Most adult and child participants scored perfectly, i.e., had a color confusion index (CCI) of 1.0 or made no major errors on both the Farnsworth (D15) and Lanthony (D15d) color vision tests. The high proportion of perfect scores limited the ability to detect quantitative differences in CCI among exposure groups. A high proportion of perfect scores on these color vision tests is consistent with what has been reported in several other recent reports and reviews (Schaper et al., 2004; Castillo et al., 2001; Gong et al., 2003; Iregren et al., 2002; Lomax et al., 2004; Geller and Hudnell, 1997; Good et al., 2005). The color vision tests administered were therefore not sufficient to reliably quantify differences in CCI, and parametric analyses were not appropriate for evaluating differences in CCI across groups. Hence, non-parametric statistical analyses were applied to assess differences in CCI among adults, children, and child-adult pairs across exposure categories. An additional measure of color vision test performance, whether or not major error(s) (an inversion of at least two caps) were made, was also determined for each participant and used in exploratory trend and in logistic regression analyses as the dependent variable.

Spearman correlations indicated that no measure of perc exposure was positively significantly associated with CCI or making major error(s) on either color vision test among adults or children. Some socioeconomic and personal characteristics were consistently significantly associated with higher CCIs and with committing major error(s) on one or both color vision tests. For example, lower household income (adults only), minority race/ethnicity (i.e., not non-Hispanic White) (adults only), fewer years of education, and younger age (children only) and shorter residence duration (children only) were each significantly associated with increased CCI on the Lanthony (D15d) among adults and/or children. Younger age, fewer years of school, and shorter residence duration were significantly or nearly significantly associated with making major error(s) on the Lanthony (D15d) test among children. We know of no other reports demonstrating that color vision test performance is significantly negatively associated with younger age among children in the age range tested here (e.g., 7–15 years of age). Nor do we know of other reports demonstrating a significant association between race/ethnicity or income on color vision test performance among either adults or children. Given these significant observations, race/ethnicity, income, age, and years of education were considered confounders of color vision test performance in our analyses and should be considered as such by other investigators.

Exploratory trend analyses found no significant effect of increasing residential perc exposure on proportions of participants not making major error(s) among all adults and children, or among adults and children stratified by race/ethnicity or income. This is consistent with logistic regression (adjusted for socioeconomic characteristics and other factors) which indicated that no measure of perc exposure significantly increased commission of major errors on either color vision test among adults or children. The logistic regression appeared to suggest, in fact, that increasing perc exposure was associated with significantly decreased odds for making major error(s) for both adults and children. As it appears unlikely that perc exposure would improve color vision test performance, these findings appear to be spurious.

Paired analysis of mean differences in CCI between children and adults residing in the same household (child-adult pairs) seems to have suggested a significant effect of perc exposure on children's Lanthony (D15d) test CCI. However, confidence that perc exposures were responsible

for this observation is weakened by the possible confounding influence of age on children's CCI in these analyses. Children in the highest exposure category were about a year younger (mean age 9.8 years) than children in the < 100 $\mu g/m^3$ (mean age 10.9 years) and reference (mean age 11.2 years) categories (cf., Table A–2b). Additionally, the apparently significantly decreased mean child-adult difference was likely influenced by the low adult CCIs in the highest exposure group. Median adult CCI value was 1.0 which is at the lower end of median values of 1.0–1.2 reported by other investigators for reference populations (cf., Table 10). A higher median CCI value for adults would have decreased the difference between adults and children in this study.

Comparison of Lanthony (D15d) CCIs found here with CCIs reported for other populations not exposed to perc or other solvents supports the conclusion that color vision test performance was not influenced by perc exposure in this study (cf., Table A–10). Median CCIs for reference, lower exposure (< 100 $\mu g/m^3$ perc), and higher exposure (> 100 $\mu g/m^3$ perc) adults were 1.00, 1.06, and 1.00, respectively. These medians are within or even below the range of medians for adult reference populations (Iregren et al., 2002; Lomax et al., 2004), and for controls in 15 studies assessing the influence of toluene, styrene, or mixed solvents on Lanthony (D15d) color vision (Paramei et al., 2004). For children, median CCIs for reference, lower exposure (< 100 $\mu g/m^3$ perc), and higher exposure (> 100 $\mu g/m^3$ perc) were 1.10, 1.00, and 1.16, respectively. These CCI values are actually slightly lower than the median CCI values of 1.22 and 1.26 observed among a group of unexposed children of the same age (NYS DOH, 2005).

Interpretation of the study results presented here as indicating that perc exposure (at the levels found) did not influence color vision test performance is not inconsistent with other reports of the effect of perc on color vision. A recent comprehensive review summarized and evaluated the published scientific literature (Nakatsuka et al., 1992; Cavalleri et al., 1994; Gobba et al., 1998; Schreiber et al., 2002) relating altered color discrimination to perc exposure and concluded that "there is so little information on the effects of tetrachloroethylene on color discrimination that no reliable conclusions can be drawn" (Lomax et al., 2004). Nor are these results inconsistent with the findings of a NYS DOH study of 17, 8–10 year old children who had been exposed to about 1800–400 $\mu g/m^3$ perc while attending a day care center when they were about 4–5 years old (NYS DOH, 2005). Color vision among these children did not differ significantly from color vision of 17 age- and gender matched children who had never been exposed to perc.

STRENGTHS/LIMITATIONS

Strengths. A strength of this study was that several previously unidentified confounding influences on color vision test performance were identified and also included in analyses of the effect of perc exposure on the odds for making color vision test errors. In particular, among adults, minority race/ethnicity and lower income significantly influenced color vision test performance. Among children, younger age and the related characteristics of shorter residence duration and fewer years of school significantly influenced color vision test performance. Recognition of the influence of these socioeconomic and personal characteristics on color vision test performance led to more defensible assessment of the possible relationship(s) between perc exposure and color vision test performance in the study population. Adjustment for these, and other potential confounding variables (e.g., tobacco and alcohol use), in logistic regression analyses contributed confidence to the finding that

increased perc exposure did not increase the odds for making major error(s) on the Lanthony (D15d) test.

Another strength of this study is that individual levels of perc in each participant's exhaled breath and blood, as well as in their indoor air, were obtained and evaluated for their relationship with color vision test performance. The observation that no measure of internal perc exposure of either adults or children significantly increased the adjusted odds for making major error(s) on the Lanthony (D15d), contributes confidence to the conclusion that, in this study, increased perc exposures did not adversely influence color vision test performance.

Another strength of this study was that adults and children residing in the same household (child-adult pairs) were enrolled. Enrollment of child-adult pairs was intended to allow for an evaluation of whether children were more vulnerable than adults to equivalent residential indoor air perc exposures. Paired analyses of differences in CCI between matched children and adults suggested that children's Lanthony (D15d) test performance was more affected than adults by increasing perc exposure. This observation encouraged further review of the possible effect of perc exposure on children's Lanthony (D15d) test performance in the context of other data in the scientific literature. Comparison of CCI values of the matched adults in the study population with CCIs of other unexposed adults supported the conclusion that their CCIs were in the lower range of what has been observed among unexposed adults. Thus, the greater difference in CCIs observed among the highest exposed child-adult pairs was most likely due to better adult test performance rather than worse child test performance, and was consistent with other negative study findings (e.g., no significant decreasing trend; no significantly increased odds for making error(s)).

Finally, in this study the color vision testing environment was well controlled and potential confounders were assessed in analyses. Participants were administered the color vision tests in an ophthalmology research clinic where testing conditions were consistent, well controlled, and in accordance with test manufacturer recommendations. Test administrators were "masked" to participants' perc exposures, and test administrators able to speak Spanish conducted testing of participants for whom Spanish was preferred. Also, participants with optical or other medical conditions known to influence color vision, or with other exposures that could possibly influence color vision were excluded. Information on numerous socioeconomic and personal characteristics known to influence neurobehavioral function and/or testing was obtained and included in analyses. Thus, in this study color vision test performance was most likely accurately assessed, and despite limitations in the color vision tests administered to assess the full range of color vision, there is confidence in the conclusion that increased perc exposure did not adversely influence color vision.

Limitations. Interpretation of the results reported here is limited by the nature of the outcome variable. It was not possible to assess quantitative differences in CCI associated with perc exposures, as planned, because high proportions of participants scored as well as possible on the color vision tests (i.e., had CCI=1.0). Instead, differences in performance on the color vision tests administered, rather than differences in CCI, were assessed by categorizing each participant's performance according to whether major errors were made or not. The relationship between this measure of color vision test performance and CCI is unknown. Thus, the observation that perc exposure did not increase the proportions of individuals making major errors or the odds for making

major errors on the color vision tests administered cannot necessarily be interpreted as indicating that color vision was unaffected.

Another possible limitation associated with the outcome variable is that color vision was assessed binocularly, rather than monocularly. Some investigators have argued that eyes can respond differently to toxicants and that color vision should therefore be assessed for each individual eye. By testing color vision binocularly, possible effects of perc exposure on color vision by an affected eye may have been masked by good performance of the other eye.

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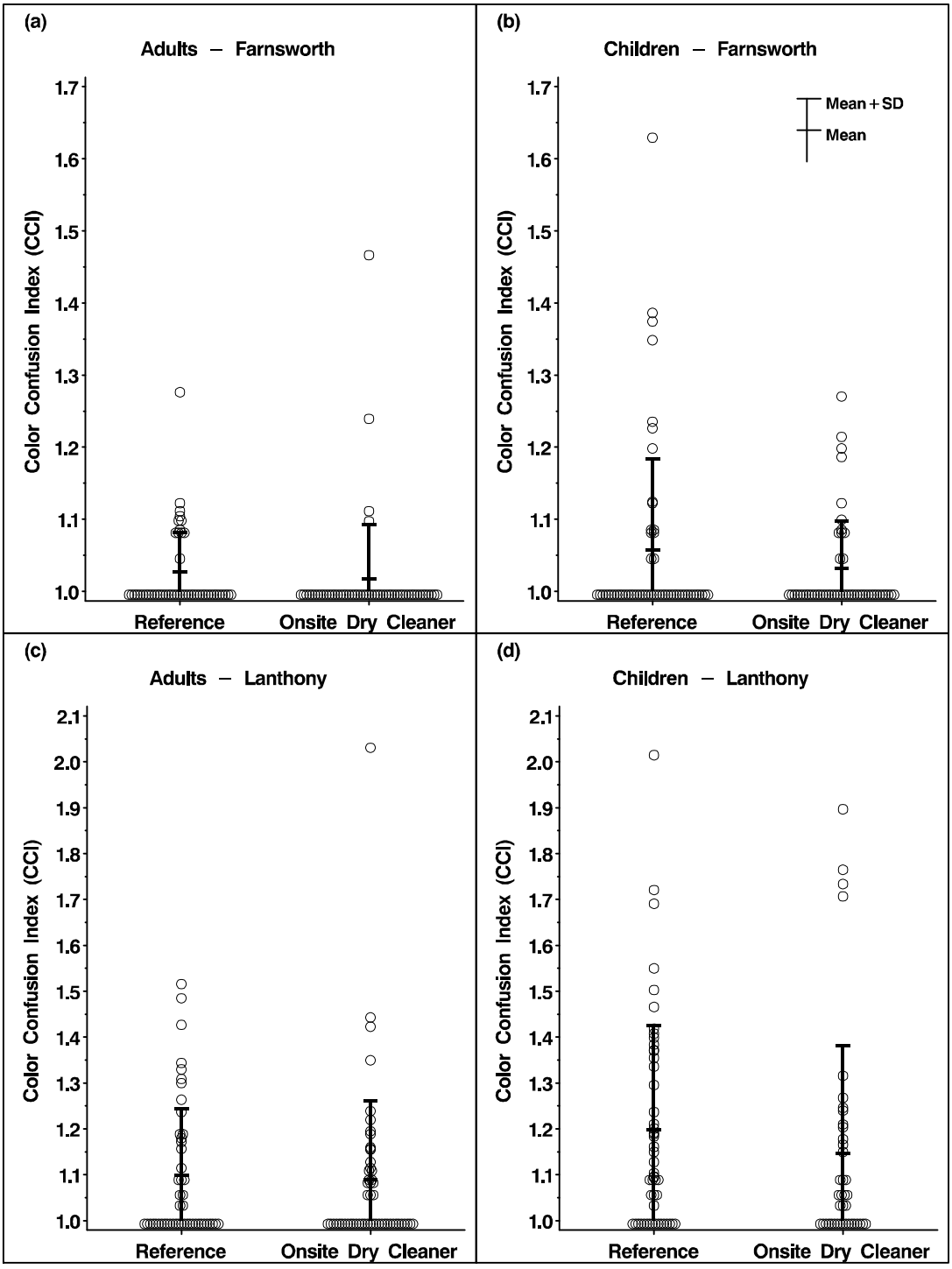
Appendix 1, Figure A-1. CCI values for the Farnsworth test for (a) adults and (b) children, and for the Lanthony test for (c) adults and (d) children.



Appendix 1, Table A–1. Number of Adult and Child Residents and Child-Adult Pairs Completing Color Vision Tests.

	Reference Buildings	Onsite Dry Cleaner Buildings	
		< 100 μg/m^3	> 100 μg/m^3
Adults			
Enrolled	60	48	19
- did not visit clinic	7	2	4
- less than 1 year at residence	0	1	0
- part-time resident	0	0	1
- medical condition	2	1	1
- eye condition	2	0	0
- high VOCs in residence	0	1	1
Completed some or all vision tests	49	43	12
- color-blind	0	1	0
- Farnsworth results lost	0	1	0
Completed Farnsworth (D15)	49	41	12
Completed Lanthony (D15d)	49	42	12
Children			
Enrolled	71	49	18
- did not visit clinic	8	3	1
- less than 1 year at residence	0	2	0
- part-time resident	0	0	2
- autism	0	0	1
- ADHD/learning disability	3	3	0
- <6 years old	2	1	2
- low attention	1	0	0
- eye condition	0	1	0
- high VOCs in residence	0	0	1
- did not finish (per request)	1	0	0
Completed some or all vision tests	56	39	11
- color-blind	1	0	0
- Lathony not taken (Farnsworth difficult)	4	9	1
Completed Farnsworth (D15)	55	39	11
Completed Lanthony (D15d)	51	30	10
Child-Adult Pairs			
Farnsworth (D15)	48	36	10
Lanthony (D15d)	44	28	9

Appendix 1, Table A–2a. Demographic and Socioeconomic Characteristics – Participants with Farnsworth Results.

	Individual Participants			Child-Adult Pairs		
	Reference Buildings	Onsite Dry Cleaner Buildings		Reference Buildings	Onsite Dry Cleaner Buildings	
		< 100 μg/m^3	> 100 μg/m^3		< 100 μg/m^3	> 100 μg/m^3
Households	n=55	n=44	n=13	n=46	n=34	n=9
Race/ethnicity *						
Minority [a]	25 (45.5%)	10 (22.7%)	9 (69.2%)	17 (37.0%)	9 (26.5%)	5 (55.6%)
Non-Minority [b]	28 (50.9%)	27 (61.4%)	3 (23.1%)	27 (58.7%)	18 (52.9%)	3 (33.3%)
Other [c]	2 (3.6%)	7 (15.9%)	1 (7.7%)	2 (4.4%)	7 (20.6%)	1 (11.1%)
No Response	–	–	–	–	–	–
Annual Income *						
< $30.000	20 (36.4%)	6 (13.6%)	5 (38.5%)	13 (28.3%)	5 (14.7%)	4 (44.4%)
$30,000– $60,000	7 (12.7%)	7 (15.9%)	3 (23.1%)	7 (15.2%)	7 (20.6%)	1 (11.1%)
> $60.000	27 (49.1%)	26 (59.13%)	2 (15.4%)	25 (54.4%)	19 (55.9%)	2 (22.2%)
No Response	1 (1.8%)	5 (11.4%)	3 (27.3%)	1 (2.2%)	3 (8.8%)	2 (22.2%)
Individual Participants						
Adults	n=49	n=41	n=12	n=48	n=36	n=10
Age (yrs ± std. dev.) *	44.3 ± 7.8 [a]	44.4 ± 6.0 [a]	35.0 ± 9.5 [b]	44.1 ± 8.1 [a]	44.8 ± 5.9 [a]	35.4 ± 10.3 [b]
Gender (female)	42 (85.7%)	32 (78.1%)	9 (75.0%)	41 (85.4%)	29 (80.6%)	6 (60.0%)
Currently Employed	34 (69.4%)	27 (65.9%)	8 (66.7%)	33 (68.8%)	25 (69.4%)	7 (70.0%)
Residence Duration (yrs ± std. dev.)	9.7 ± 6.8	10.5 ± 8.0	9.7 ± 7.6	10.1 ± 6.7	11.8 ± 7.8	10.9 ± 7.7
Years of Education (yrs ± std. dev.)	15.6 ± 3.1 [a]	16.0 ± 2.8 [a]	12.3 ± 4.6 [b]	15.5 ± 3.1 [a]	15.8 ± 3.1 [a]	12.0 ± 5.2 [b]
Smoking Category						
Non-Smoker	23 (46.9%)	18 (43.9%)	7 (58.3%)	23 (47.9%)	13 (36.1%)	7 (70.0%)
Former Smoker	16 (32.7%)	18 (43.9%)	2 (16.7%)	15 (31.3%)	18 (50.0%)	1 (10.0%)
Current Smoker	9 (18.4%)	4 (9.8%)	3 (25.0%)	9 (18.8%)	4 (11.1%)	2 (20.0%)
No Response	1 (2.0%)	1 (2.4%)	–	1 (2.1%)	1 (2.8%)	–
Alcohol Use *						
Does not Drink	16 (32.7%)	9 (21.9%)	5 (41.7%)	17 (35.4%)	9 (25.0%)	4 (40.0%)
2 or less drinks/wk	20 (40.8%)	14 (34.2%)	7 (58.3%)	18 (37.5%)	13 (36.1%)	6 (60.0%)
3 or more drink/wk	12 (24.5%)	18 (43.9%)	–	12 (25.0%)	14 (38.9%)	–
No Response	1 (2.0%)	–	–	1 (2.1%)	–	–
Children	n=55	n=39	n=11	n=48	n=36	n=10
Age (yrs ±std)	10.8 ± 2.9	10.4 ± .27	9.5 ± 2.4	10.8 ± 2.9	10.2 ± 2.7	9.5 ± 2.6
Gender (female)	25 (45.5%)	22 (56.4%)	6 (54.6%)	22 (45.8%)	20 (55.6%)	5 (50.0%)
Residence Duration (yrs ± std. dev.)	8.4 ± 3.7	8.5 ± 3.2	7.0 ± 3.2	8.3 ± 3.6	8.6 ± 3.0	7.0 ± 3.4
Years of Education (yrs ± std. dev.)	4.8 ± 2.9	4.6 ± 2.6	3.7 ± 2.4	4.8 ± 3.0	4.4 ± 2.6	3.7 ± 2.5

[a] African-American, Hispanic, or either in combination with another race; [b] non-Hispanic White; [c] excluded from race/ethnicity analyses.
* significant difference detected at α =0.05; means with the same letter are not significantly different.

Appendix 1, Table A–2b. Demographic and Socioeconomic Characteristics – Participants with Lanthony Results.

	Individual Participants			Child-Adult Pairs		
	Reference Buildings	Onsite Dry Cleaner Buildings		Reference Buildings	Onsite Dry Cleaner Buildings	
		< 100 μg/m^3	> 100 μg/m^3		< 100 μg/m^3	> 100 μg/m^3
Households	n=55	n=44	n=13	n=42	n=26	n=8
Race/ethnicity *						
Minority [a]	25 (45.5%)	10 (22.7%)	9 (69.2%)	17 (40.5%)	7 (26.9%)	5 (62.5%)
Non-Minority [b]	28 (50.9%)	27 (61.4%)	3 (23.1%)	23 (54.8%)	15 (5.0%)	3 (37.5%)
Other [c]	2 (5.6%)	7 (15.9%)	1 (7.7%)	2 (4.8%)	6 (23.1%)	–
No Response	–	–	–	–	–	–
Annual Income *						
< $30,000	20 (36.4%)	6 (13.6%)	5 (38.5%)	13 (31.0%)	5 (19.2%)	4 (50.0%)
$30,000–$60,000	7 (12.7%)	7 (15.9%)	3 (23.1%)	7 (16.7%)	6 (23.1%)	1 (12.5%)
> $60,000	27 (49.1%)	26 (59.1%)	2 (15.4%)	21 (50.0%)	14 (53.9%)	1 (12.5%)
No Response	1 (1.9%)	5 (11.4%)	3 (23.1%)	1 (2.4%)	1 (3.9%)	2 (25.0%)
Individual Participants						
Adults	n=49	n=42	n=12	n=44	n=28	n=9
Age (yrs ± std. dev.) *	44.3 ± 7.8 [a]	44.5 ± 5.9 [a]	35.0 ± 9.5 [b]	44.1 ± 8.5 [a]	44.8 ± 6.3 [a]	34.1 ± 10.1 [b]
Gender (female)	42 (85.7%)	33 (78.6%)	9 (75.0%)	37 (84.1%)	23 (82.1%)	6 (66.7%)
Currently Employed	34 (69.4%)	28 (66.7%)	8 (66.7%)	29 (65.9%)	23 (82.1%)	6 (66.7%)
Residence Duration (yrs ± std. dev.)	9.7 ± 6.8	10.7 ± 7.9	9.7 ± 7.6	10.6 ± 6.8	11.2 ± 6.0	10.9 ± 8.2
Years of Education (yrs ± std. dev.) *	15.6 ± 3.1 [a]	16.0 ± 2.8 [a]	12.3 ± 4.6 [b]	15.6 ± 3.1 [a]	15.6 ± 3.3 [a]	11.4 ± 5.2 [b]
Smoking Category						
Non-Smoker	23 (46.9%)	19 (45.2%)	7 (58.3%)	22 (50.0%)	13 (46.4%)	6 (66.7%)
Former Smoker	16 (32.7%)	18 (42.9%)	2 (16.7%)	14 (31.8%)	14 (50.0%)	1 (11.1%)
Current Smoker	9 (18.4%)	4 (9.5%)	3 (25.0%)	7 (15.9%)	1 (3.6%)	2 (22.2%)
No Response	1 (2.0%)	1 (2.4%)	–	1 (2.3%)	–	–
Alcohol Use *						
Does not Drink	16 (32.7%)	9 (21.4%)	5 (41.7%)	17 (38.6%)	7 (25.0%)	4 (44.4%)
2 or less drinks/wk	20 (40.8%)	15 (35.7%)	7 (58.3%)	17 (38.6%)	9 (32.1%)	5 (55.6%)
3 or more drink/wk	12 (24.5%)	18 (42.9%)	–	9 (20.5%)	12 (42.9%)	–
No Response	1 (2.0%)	–	–	1 (2.3%)	–	–
Children	n=51	n=30	n=10	n=44	n=28	n=9
Age (yrs ±std)	11.1 ± 2.8	11.0 ± 2.6	9.7 ± 2.4	11.2 ± 2.8	10.9 ± 2.6	9.8 ± 2.6
Gender (female)	24 (47.1%)	16 (53.3%)	6 (60.0%)	21 (47.7%)	15 (53.6%)	5 (55.6%)
Residence Duration (yrs ± std. dev.)	8.7 ± 3.6	8.9 ± 3.4	7.0 ± 3.4	8.6 ± 3.5	9.1 ± 3.2	7.0 ± 3.6
Years of Education (yrs ± std. dev.)	5.1 ± 2.8	5.2 ± 2.4	4.0 ± 2.3	5.2 ± 2.8	5.1 ± 2.5	4.0 ± 2.4

[a] African-American, Hispanic, or either in combination with another race; [b] non-Hispanic White; [c] excluded from race/ethnicity analyses.
* significant difference detected at α=0.05; Means with the same letter are not significantly different.

Appendix 1, Table A–3a. Perc and VOC Exposures – Participants with Farnsworth Results.

	Adult Participants			Child Participants		
	Reference Buildings	Onsite Dry Cleaner Buildings		Reference Buildings	Onsite Dry Cleaner Buildings	
		< 100 μg/m^3	> 100 μg/m^3		< 100 μg/m^3	> 100 μg/m^3
Perc						
Indoor Air (μg/m^3)	n=49	n=41	n=12	n=55	n=39	n=11
Geometric Mean *	2.9 [c]	11.3 [b]	477.9 [a]	3.2 [z]	12.4 [y]	335.8 [x]
Median	2.3	12.5	375.9	2.4	12.5	337.5
25th and 75th percentile	1.5–4.2	4.3–38.9	268.9–735.3	1.6–4.5	4.3–44.3	215.0–699.5
Alveolar Breath (μg/m^3)						
Taken at home	n=44	n=36	n=12	n=49	n=35	n=9
Geometric Mean *	4.6 [c]	18.8 [b]	141.4 [a]	3.7 [z]	12.2 [y]	159.5 [x]
Median	5.0	17.5	172.3	3.8	14.3	176.5
25th and 75th percentile	2.3–8.5	10.2–30.5	92.6–213.9	1.9–6.1	5.2–25.4	128.6–192.5
Taken at clinic	n=36	n=36	n=11	n=39	n=36	n=10
Geometric Mean *	4.8 [c]	13.3 [b]	70.2 [a]	3.1 [z]	8.2 [y]	50.0 [x]
Median	5.6	12.5	57.3	3.2	8.1	55.3
25th and 75th percentile	2.6–7.9	7.9–24.9	48.3–114.5	2.0–4.9	4.2–14.5	23.0–64.5
Blood (μg/L)	n=39	n=37	n=11	n=32	n=28	n=7
Geometric Mean *	0.05 [c]	0.12 [b]	1.3 [a]	0.04 [z]	0.11 [y]	0.51 [x]
Median	0.05	0.12	1.30	0.02	0.11	0.57
25th and 75th percentile	0.02–0.08	0.08–0.21	0.53–1.90	0.02–0.05	0.07–0.16	0.37–0.89

* significantly difference at α=0.05; means with the same letter are not significantly different.

Appendix 1, Table A–3b. Perc and VOC Exposure – Child-Adult Pairs with Farnsworth Results.

	Adult Participants			Child Participants		
	Reference Buildings	Onsite Dry Cleaner Buildings		Reference Buildings	Onsite Dry Cleaner Buildings	
		< 100 μg/m^3	> 100 μg/m^3		< 100 μg/m^3	> 100 μg/m^3
Perc						
Indoor Air (μg/m^3)	n=48	n=36	n=10	n=48	n=36	n=10
Geometric Mean *	3.0 [c]	11.9 [b]	351.1 [a]	3.0 [z]	11.9 [y]	351.1 [x]
Median	2.5	12.5	344.7	2.5	12.5	344.7
25th and 75th percentile	1.6–4.3	3.8–43.2	215.5–699.5	1.6–4.3	3.8–43.2	215.5–699.5
Alveolar Breath (μg/m^3)						
Taken at home	n=42	n=31	n=10	n=44	n=34	n=9
Geometric Mean *	4.8 [c]	19.1 [b]	129.2 [a]	3.8 [Z]	12.0 [y]	159.5 [x]
Median	5.0	18.8	137.3	3.9	14.0	176.4
25th and 75th percentile	2.4–8.5	10.8–27.8	102.2–183.5	2.1–6.4	5.2–25.4	128.6–192.5
Taken at clinic	n=37	n=33	n=9	n=33	n=34	n=9
Geometric Mean *	4.7 [c]	13.4 [b]	44.8 [a]	3.2 [Z]	8.2 [y]	55.8 [x]
Median	5.5	12.1	54.0	3.2	8.1	58.4
25th and 75th percentile	2.4–7.1	8.7–24.8	48.3–57.3	2.1–4.9	3.8–15.3	33.1–64.5
Blood (μg/L)	n=39	n=33	n=9	n=28	n=25	n=6
Geometric Mean *	0.05 [c]	0.13 [b]	0.73 [a]	0.04 [z]	0.11 [y]	0.50 [x]
Median	0.02	0.12	0.58	0.02	0.11	0.55
25th and 75th percentile	0.02–0.08	0.07–0.27	0.53–1.30	0.02–0.05	0.07–0.16	0.37–0.89

* significantly difference at α=0.05; Means with the same letter are not significantly different.

Appendix 1, Table A–4a. Perc and VOC exposures – Participants with Lanthony Results.

	Adult Participants			Child Participants		
	Reference Buildings	Onsite Dry Cleaner Buildings		Reference Buildings	Onsite Dry Cleaner Buildings	
		< 100 μg/m^3	> 100 μg/m^3		< 100 μg/m^3	> 100 μg/m^3
Perc						
Indoor Air (μg/m^3)	n=49	n=42	n=12	n=51	n=30	n=10
Geometric Mean *	2.9 [c]	11.1 [b]	477.9 [a]	3.1 [z]	12.7 [y]	330.0 [x]
Median	2.3	12.3	375.9	2.3	13.6	329.9
25th and 75th percentile	1.5–4.2	4.3–38.9	268.9–735.3	1.6–4.2	4.3–44.3	215.0–382.3
Alveolar Breath (μg/m^3)						
Taken at home	n=44	n=36	n=12	n=46	n=26	n=8
Geometric Mean *	4.6 [c]	18.8 [b]	141.4 [a]	3.5 [z]	13.8 [y]	157.5 [x]
Median	5.0	17.5	175.3	3.6	17.0	160.2
25th and 75th percentile	2.3–8.5	10.2–30.5	92.6–213.9	1.9–6.1	8.2–26.1	107.0–382.3
Taken at clinic	n=36	n=36	n=11	n=35	n=27	n=9
Geometric Mean *	4.6 [c]	13.3 [b]	70.2 [a]	2.9 [z]	9.1 [y]	43.1 [x]
Median	5.6	12.5	57.3	2.9	8.6	52.1
25th and 75th percentile	2.6–7.9	7.9–24.9	48.3–114.5	2.0–4.4	3.8–16.8	23.0–59.6
Blood (μg/L)	n=39	n=38	n=11	n=29	n=25	n=7
Geometric Mean *	0.05 [c]	0.13 [b]	1.28 [a]	0.04 [z]	0.10 [y]	0.51 [x]
Median	0.05	0.12	1.3	0.02	0.11	0.57
25th and 75th percentile	0.05–0.08	0.08–0.21	0.53–1.9	0.02–0.05	0.07–0.13	0.37–0.89

* significantly difference at α=0.05; means with the same letter are not significantly different.

Appendix 1, Table A–4b. Perc and VOC Exposure – Child-Adult Pairs with Lanthony Results.

	Adult Participants			Child Participants		
	Reference Buildings	Onsite Dry Cleaner Buildings		Reference Buildings	Onsite Dry Cleaner Buildings	
		< 100 μg/m^3	> 100 μg/m^3		< 100 μg/m^3	> 100 μg/m^3
Perc						
Indoor Air (μg/m^3)	n=44	n=28	n=9	n=44	n=28	n=9
Geometric Mean *	2.9 [c]	11.6 [b]	346.1 [a]	2.9 [z]	11.6 [y]	346.1 [x]
Median	2.4	12.3	337.5	2.4	12.3	337.5
25th and 75th percentile	1.6–4.0	3.8–43.2	215.5–669.5	1.6–4.0	3.8–43.2	215.5–669.5
Alveolar Breath (μg/m^3)						
Taken at home	n=38	n=22	n=9	n=41	n=25	n=8
Geometric Mean *	4.4 [c]	21.2 [b]	132.6 [a]	3.7 [z]	13.7 [y]	157.5 [x]
Median	4.9	21.7	165.7	3.6	16.2	160.2
25th and 75th percentile	2.2–6.9	13.2–27.8	108.8–183.5	1.9–6.3	8.2–26.1	107.0–382.3
Taken at clinic	n=32	n=25	n=9	n=29	n=26	n=8
Geometric Mean *	4.3 [c]	14.9 [b]	44.8 [a]	2.8 [z]	9.0 [y]	47.9 [x]
Median	4.2	12.9	54.0	2.9	8.5	55.3
25th and 75th percentile	2.3–7.0	9.3–24.9	48.3–57.3	2.0–4.4	3.8–16.8	28.1–62.1
Blood (μg/L)	n=35	n=27	n=8	n=25	n=23	n=6
Geometric Mean *	0.04 [c]	0.14 [b]	0.93 [a]	0.04 [z]	0.09 [y]	0.50 [x]
Median	0.02	0.13	0.89	0.02	0.11	0.55
25th and 75th percentile	0.02–0.07	0.07–0.29	0.53–1.40	0.02–0.05	0.06–0.13	0.37–0.89

* significantly difference at α=0.05; means with the same letter are not significantly different.

Appendix 1, Table A–5. Correlations for Residents of Reference Buildings – Socioeconomic Factors, Personal Characteristics, Color Vision.

	Farnsworth (D15)			Lanthony (D15d)		
	N	**CCI**	**Major Error**	**N**	**CCI**	**Major Error**
Adults						
Annual Income	48	-0.40 *	-0.14	48	-0.47 *	-0.47 *
Race/Ethnicity	49	0.36 *	0.17	49	0.45 *	0.42 *
Years of School	49	-0.28 **	-0.18	49	-0.34 *	-0.43 *
Years at Residence	49	0.20	0.10	49	0.00	0.22
Age	49	-0.10	-0.19	49	-0.28 **	-0.17
Drinks/week	48	-0.18	-0.18	48	-0.20	-0.10
Cigarettes/day	48	-0.11	-0.14	48	0.10	0.05
Blood lead level	40	-0.09	--	40	-0.08	-0.01
Blood mercury level	40	-0.11	--	40	-0.22	-0.38 *
VOC index	35	0.17	0.17	35	0.07	0.19
Children						
Annual Income	41	-0.05	-0.22	38	-0.24 **	-0.10
Race/Ethnicity	42	0.05	0.23	39	0.32 *	0.15
Years of School	42	-0.41 *	-0.25 **	39	-0.51 *	-0.37 *
Years at Residence	42	-0.28 *	-0.28 *	39	-0.26 **	-0.25 **
Age	42	-0.40 *	-0.27 **	39	-0.46 *	-0.31*
Blood lead level	26	0.14	-0.11	24	0.13	0.08
Blood mercury level	22	-0.42 *	-0.25	20	-0.26	-0.24
VOC index	42	0.14	0.03	39	-0.16	-0.21

* nearly statistically significant ($p < 0.10$).
** statistically significant ($p < 0.05$).

Appendix 1, Table A–6. Spearman Correlation Coefficients between Color Vision Measurements and Perc Exposures for Residents in Reference Buildings or Onsite Dry Cleaner Buildings.

	Farnsworth (D15)			Lanthony (D15d)		
	N	**CCI**	**Major Error**	**N**	**CCI**	**Major Error**
Adults						
Indoor Air	112	-0.27 **	-0.12	113	-0.14	-0.17
Exhaled Breath at Home	102	-0.26 **	0.03	102	-0.01	-0.11
Exhaled Breath at Clinic	91	-0.23 **	0.07	91	-0.09	-0.17
Blood at Clinic	96	-0.14	0.05	97	-0.10	-0.14
Children						
Indoor Air	113	-0.02	-0.13	99	-0.11	-0.08
Exhaled Breath at Home	100	0.02	-0.08	87	-0.16	-0.07
Exhaled Breath at Clinic	93	0.03	-0.05	79	0.01	0.12
Blood at Clinic	70	0.05	0.03	64	-0.21*	-0.29 **

* nearly statistically significant ($p < 0.10$).

** statistically significant ($p < 0.05$).

Appendix 1, Table A–7. Significance of Decreasing Trend (Cochran-Armitage Exact Trend Test) in Percent of Residents of Buildings With or Without a Dry Cleaner (Indoor Air Perc < 100 μg/m^3 or > 100 μg/m^3) Making No Major Errors.

		Percent with Maximum Score							
		Adult Residents				Child Residents			
		Reference Buildings	Onsite Dry Cleaner Buildings		p	Reference Buildings	Onsite Dry Cleaner Buildings		p
			< 100 μg/m^3	> 100 μg/m^3			< 100 μg/m^3	> 100 μg/m^3	
	Farnsworth	97.8 (n=49)	95.1 (n=41)	100.0 (n=12)	0.47	89.1 (n=55)	89.7 (n=39)	90.9 (n=11)	0.57
	Lanthony	77.6 (n=49)	85.7 (n=42)	75.0 (n=12)	0.62	56.9 (n=51)	80.0 (n=30)	50.0 (n=10)	0.75
Stratified by Race/ethnicity									
Non-Minority	**Farnsworth**	100.0 (n=28)	95.8 (n=24)	100.0 (n=3)	0.22	96.3 (n=27)	95.2 (n=21)	100.0 (n=3)	0.53
Minority	**Farnsworth**	94.7 (n=19)	90.0 (n=10)	100.0 (n=8)	0.64	80.8 (n=26)	72.7 (n=11)	85.7 (n=7)	0.52
Non-Minority	**Lanthony**	92.9 (n=28)	92.0 (n=25)	100.0 (n=3)	0.57	65.2 (n=23)	80.0 (n=15)	66.7 (n=3)	0.73
Minority	**Lanthony**	52.6 (n=19)	60.0 (n=10)	62.5 (n=8)	0.70	50.0 (n=26)	77.8 (n=9)	42.9 (n=7)	0.57
Stratified by Income									
Non-low Income	**Farnsworth**	100.0 (n=34)	96.7 (n=30)	100.0 (n=4)	0.23	93.8 (n=32)	93.1 (n=29)	100.0 (n=4)	0.59
Low Income	**Farnsworth**	92.9 (n=14)	83.3 (n=6)	100.0 (n=5)	0.60	81.8 (n=22)	66.7 (n=6)	100.0 (n=5)	0.71
Non-low Income	**Lanthony**	88.2 (n=34)	96.8 (n=31)	75.0 (n=4)	0.61	64.3 (n=28)	86.4 (n=22)	100.0 (n=3)	0.98*
Low Income	**Lanthony**	50.0 (n=14)	50.0 (n=6)	60.0 (n=5)	0.63	45.5 (n=22)	66.7 (n=6)	40.0 (n=5)	0.55

* significant increasing trend (p=0.02).

Appendix 1, Table A–8a. Perc Exposure Risk Factors for At least one Major Error on Color Vision Tests – Adult Residents of Reference or Onsite Dry Cleaner Buildings.

			Unadjusted			Adjusted		
Measure of Perc Exposure	**Indoor Air Perc (log µg/m^3)**		**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		Farnsworth	90	0.388	0.022–1.990	61	--	
		Lanthony	91	0.902	0.447–1.681	62	0.169 **	0.018–0.702
	Breath Perc - Home (log µg/m^3)		**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		Farnsworth	81	0.954	0.130–5.075	53	--	
		Lanthony	81	0.717	0.287–1.647	53	0.120	0.004–1.295
	Breath Perc - Clinic (log µg/m^3)		**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		Farnsworth	74	1.361	0.072–12.790	52	--	
		Lanthony	74	0.837	0.249–2.513	52	0.003 **	<0.001–0.287
	Blood Perc (log ng/mL)		**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		Farnsworth	77	1.288	0.076–7.608	60	--	
		Lanthony	78	1.076	0.385–2.663	61	0.164	0.010–1.085

-- computationally invalid estimate.

** statistically significant **decreased** odds ratios ($p < 0.05$).

Adjusted for: race/ethnicity; income; age; smoking; alcohol use; gender; residence duration; years of school; VOC index; blood lead; and blood mercury.

No covariates in the adjusted model were significant or nearly significant.

Appendix 1, Table A–8b. Perc Exposure Risk Factors for At least one Major Error on the Color Vision Tests – Child Residents of Reference or Onsite Dry Cleaner Buildings.

			Unadjusted			Adjusted		
Measure of Perc Exposure	**Indoor Air Perc (log µg/m^3)**		**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		Farnsworth	98	0.435	0.114–1.167	46	--	
		Lanthony	86	0.693	0.369–1.231	43	0.405 *	0.116–1.157
	Breath Perc - Home (log µg/m^3)		**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		Farnsworth	86	0.442	0.097–1.483	37	--	
		Lanthony	75	0.788	0.361–1.630	35	0.299	0.050–1.327
	Breath Perc Clinic (log µg/m^3)		**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		Farnsworth	78	0.454	0.077–2.042	37	--	
		Lanthony	66	1.542	0.569–4.267	34	--	
	Blood Perc (log ng/mL)		**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**
		Farnsworth	64	0.902	0.133–4.408	46	--	
		Lanthony	58	0.266 *	0.053–1.007	43	0.110 **	0.012–0.975

-- computationally invalid estimate.
* nearly statistically significant **decreased** odds ratios ($p < 0.10$).
** statistically significant **decreased** odds ratios ($p < 0.05$).
Adjusted for: race/ethnicity; income; age; gender; residence duration; VOC index; blood lead; and blood mercury.
No covariates in the adjusted model were significant, with the exception of residence duration, which was nearly significant for the Lanthony (D15d) test in the exhaled breath at home and blood at clinic models.

Appendix 1, Table A–9. Summary of Significance of Child-Adult Differences in CCI (Kruskal-Wallis Test for Matched Pairs).

	Mean Difference			P-value
	Reference Buildings	Onsite Dry Cleaner Buildings		
		< 100 μg/m^3	> 100 μg/m^3	
Farnsworth	0.02 (n=48)	0.00 (n=36)	0.03 (n=10)	0.74
Lanthony	0.04 (n=44)	-0.05 (n=28)	0.30* (n=9)	<0.01

* significant difference detected at α =0.05.

Appendix 1, Table A–10. Color Confusion Indices – Miscellaneous Populations.

New York City Perc Project										
Exposure Group	**Paired Adult Binocular CCI Values**					**Paired Child Binocular CCI Values**				
	Mean	**Percentiles**			**Max Value**	**Mean**	**Percentiles**			**Max Value**
		50th	**90th**	**95th**			**50th**	**90th**	**95th**	
Reference (n=44 pairs) adults 44 yrs old children 11 yrs old	1.11	1.00	1.35	1.42	1.73	1.15	1.10	1.39	1.43	1.73
< 100 µg/m^3 (n=28 pairs) adults 45 yrs old children 11 yrs old	1.14	1.06	1.20	2.04	2.04	1.09	1.00	1.25	1.32	1.71
100 µg/m^3 (n=9 pairs) adults 34 yrs old children 10 yrs old	1.04	1.00	1.25	1.25	1.25	1.34	1.16	1.90	1.90	1.90
Other Reference (Unexposed) Values										
Study	**Adult Monocular CCI Values**					**Child Monocular CCI Values**				
	Mean	**Percentiles**			**Max Value**	**Mean**	**Percentiles**			**Max Value**
		50th	**90th**	**95th**			**50th**	**90th**	**95th**	
Iregren et al. (2002) 18–65 yrs old (n=195)	1.22	1.13	1.54	--	2.35					
	1.23	1.16	1.56	--	2.37					
Lomax et al. (2004) 36–45 yrs old (n=73)	--	1.06	1.19	1.25	--					
	--	1.00	1.18	1.22	--					
NYS DOH (2005) 10 yrs old (n=13)						1.30	1.22	1.74	2.06	2.06
						1.36	1.26	1.75	2.03	2.03

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APPENDIX 2. THE FUNCTIONAL ACUITY CONTRAST TEST (F.A.C.T.) AND PARTICIPANT SCORES

THE FUNCTIONAL ACUITY CONTRAST TEST (F.A.C.T.)

Visual Contrast Sensitivity in this study was determined using the Functional Acuity Contrast Test (F.A.C.T.) distance chart (Stereo Optical Co., Inc., 1993) placed 10 feet from the participant under light conditions specified by the manufacturer (i.e., 68–240 cd/m^2). This chart (37" x 27") consists of five rows of nine different patches filled with sinusoidal gratings (parallel dark and light bars within a circle) oriented at +15°, 0°, or -15°. Spatial frequency (number of bars per patch; referred to as cycles per degree (cpd) of visual arc) is constant within rows but increases from the top to bottom row. Contrast of bars against background decreases within rows from left to right. At different spatial frequencies, different degrees of contrast are required to reach threshold visibility. VCS is reflected in a function which relates the threshold stimulus for spatial vision in terms of spatial frequency and contrast.

For each eye, each participant was asked to indicate the orientation of bars in each patch as the test administrator called out each patch from left to right, row by row, beginning at the top row, left patch. If orientation was misidentified, the participant was instructed to view each succeeding 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. This procedure was repeated for each row in descending order. Scores for each eye were recorded on a graph showing a normal range (90 percent confidence interval) provided by the F.A.C.T. manufacturer and typically used for clinical interpretation of VCS. For each participant, the examining ophthalmologist made a judgement as to whether or not VCS was normal or abnormal based on these graphs. Specific contrast values for each frequency, contrast sensitivity combination provided with the F.A.C.T. were recorded.

Instructions for use of the F.A.C.T. provided by the manufacturer is reproduced here (Attachment 1). This information includes specific procedures for testing VCS using the distance chart which were followed in this study (Attachment 1, pg 4-5), and F.A.C.T. Contrast Sensitivity Values possible for each spatial frequency (Attachment 1, pg. 17). Additional information on the use of the F.A.C.T. and interpretation of scores provided by the manufacturer can be obtained at www.contrastsensitivity.net.

Actual VCS scores achieved by each participant are summarized in Attachment 2.

APPENDIX 2. ATTACHMENT 1.

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FUNCTIONAL ACUITY CONTRAST TEST F.A.C.T™

Instructions for use

For Help Call:

800-344-9500

P/N 70 074

Developed with
Arthur P. Ginsburg, Ph.D.

Licensed under U.S. Patent #4,365,873
Patent Pending by Visumetrics Corporation

Stereo Optical Co., Inc.
3539 North Kenton Avenue
Chicago, IL 60641
312–777–2869
800–344–9500
Fax 312–777–4985

NOTES

CONGRATULATIONS!

YOU HAVE JUST PURCHASED ONE OF THE MOST EFFECTIVE, EVALUATED AND PROVEN SYSTEMS FOR TESTING YOUR PATIENTS' FUNCTIONAL VISION ON THE MARKET TODAY. IF AFTER READING THIS INSTRUCTION MANUAL YOU HAVE ANY OTHER QUESTIONS, PLEASE FEEL FREE TO CALL STEREO OPTICAL COMPANY, INC. AT 800–344–9500.

TABLE OF CONTENTS

FUNCTIONAL ACUITY CONTRAST TEST

INSTRUCTIONS FOR USE

INTRODUCTION

The new Functional Acuity Contrast Test (F.A.C.T.™) is an improvement on the original Contrast Sensitivity Test developed by Arthur P. Ginsburg, Ph.D. in 1983. The F.A.C.T.™ also developed by Arthur P. Ginsburg, Ph.D., a pioneer of contrast sensitivity technology, offers a more sensitive and comprehensive measure of functional vision than does standard Snellen acuity.

Normal Snellen acuity only tests the ability to identify progressively smaller, high contrast letters. Although this may be adequate for quantifying refractive errors; it often fails to detect early vision loss due to a wide variety of eye disease and visual pathway disorders such as cataracts, glaucoma, macular and retinal dysfunction, optic nerve disease, toxic chemicals, etc.

Real-world vision is not always high contrast black and white. Rather, it consists of objects having a wide range of sizes viewed under a variety of visually degrading conditions, such as fog, nighttime, bright sun, etc. Many visual disorders will show more significant vision loss under these conditions.

The F.A.C.T. more effectively evaluates your patient's vision over a range of size and contrast which closely simulates their normal environment.

PRODUCT DESCRIPTION

The F.A.C.T. System includes:

- One Near Chart with Calibrated Holder
  or
  One 37" x 27" Framed Distance Chart
- Light Meter
- Instruction Manual
- Record Forms
- Two Color Pen

Specification of the chart are as follows...

1. The progression of the high quality sine-wave grating size changes in steps equal to one octave (*i.e.*, a factor of two) between rows A, B, C, and D and half octave between rows D and E. The corresponding spatial frequencies are 1.5, 3, 6, 12 and 18 cycles per degree (cpd).

2. The contrast step between each grating patch is 0.15 log units. This means that there is 50% loss or a 100% gain in contrast for any two contrast step increase or decrease, respectively. The contrast range exceeds the normal population range of contrast sensitivity.[14]

3. The gratings are tapered into an average gray background to eliminate ghost images (aliasing) and keep the mean retinal illumination constant.[1]

4. The grating patch size, 1.7 degrees, exceeds the size of the macula (1 to 1.5 degrees).

5. The gratings are tilted +15°, 0° and -15° to keep them within the orientation bandwidth of visual channels.

USE OF THE F.A.C.T. 101 NEAR POINT TEST

USE OF THE CALIBRATED HOLDER

- Place the chart at the 18" test distance position or at the test distance for the patient's bifocal.
- Have the patient place the chin rest against their chin.
- If the patient wears bifocals, have them use the reading portion of their lens.

USE OF THE NEAR POINT ROD ON THE REFRACTOR

- Place the chart in the clips of the Near Point Rod.
- Have the patient look through the refractor wing the patient's near point prescription.

CALIBRATION OF LIGHT FOR THE F.A.C.T. 101

The F.A.C.T. will accurately measure contrast sensitivity under normal office lighting 20–70 foot-Lamberts (68–240 cd/m2) indicated by the green area on the lightmeter. A mark has also been placed on the meter at the 25 foot-Lambert (85 cd/m2) position. The lightmeter is included with the F.A.C.T. to insure test accuracy and reproducibility.

1. Hold the lightmeter 2 inches from the center of the chart.
2. The red needle on the lightmeter should be in the green area.
3. If the needle on the lightmeter is not in the green, adjust the room illumination.
4. If using the Near Point Rod on the Refractor and extra light is needed, use the refractor background lamp to increase the needed illumination.

NOTE: If calibration of the chart is not performed, you cannot accurately use the population norms or the Snellen Equivalent Acuities on the Scoring Chart.

INSTALLATION OF THE F.A.C.T. 201 DISTANCE TEST

MOUNTING OF THE CHART

Select a room that will afford you a testing distance of 10 feet. The wall on which the F.A.C.T. is to be mounted should be glare and shadow free. Well illuminated standard office lighting should be sufficient. Mount the chart on the notched hanger supplied. The bottom of the chart should be approximately four feet from the floor.

CALIBRATION OF LIGHT FOR THE F.A.C.T. 201

The F.A.C.T. will accurately measure Contrast Sensitivity under normal office lighting 20–70 foot-Lamberts (68–240 cd/m^2) indicated by the green area on the lightmeter. A mark has also been placed on the meter at the 25 foot-Lambert (85 cd/m^2) postition. The lightmeter is included with the F.A.C.T. to insure test accuracy and reproducibility.

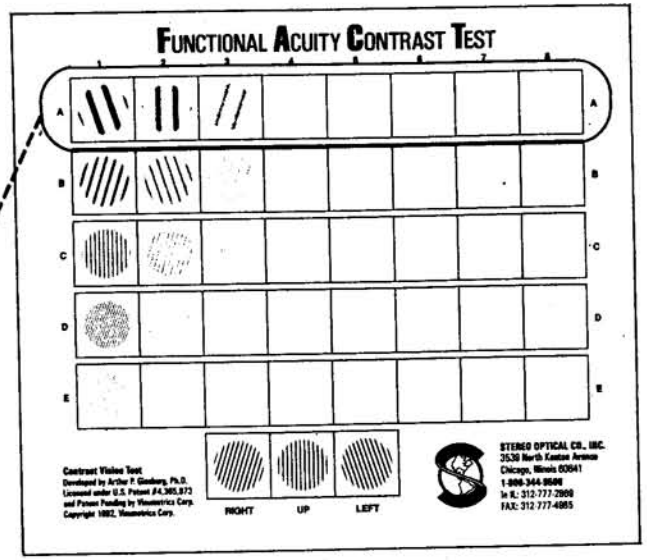
1. Hold the lightmeter 2 inches from each of the four corners of the chart.
2. The red needle on the lightmeter should be in the green area.
3. If the needle on the lightmeter is not in the green, increase the room illumination.

NOTE: If Calibration of the chart is not performed, you cannot accurately use the population norms or the Snellen equivalent acuities on the scoring chart.

F.A.C.T. EXAMINATION PROCEDURE

1. Make sure chart is illuminated properly.
2. Make sure patient is at the proper testing distance. 10 feet (3 meters) Distance or 18" (46 cm) Near.

3. Insure that the patient is wearing their usual optical correction or is properly refracted at the test distance.
4. Show the patient the sample patch making the statement, "Each of the circles contain lines, tell me if the top of the lines point to the left, right or up."
5. Occlude one of the patient's eyes.
6. Point or instruct the patient to look at Row A, proceeding from left to right having them state the last patch they can see by number and stating which way the top of the lines point. For example: The patient response may be, "A" 6 is UP.
7. If the response is correct, encourage the patient to proceed to each subsequent patch to the right until one incorrect response is obtained. (NOTE: The correct responses are indicated on the recording form)
8. If the response is incorrect:
   a. Have the patient look at each subsequent patch to the left until a correct response is obtained.
   b. Then encourage the patient to proceed to the right until one incorrect response is obtained.
9. Mark the last correct patient response in the proper location on the recording form. The vertical column's of numbers marked "A" on the scoring pad corresponds to the "A" horizontal row on the chart. The same is true for columns B, C, D and E on the recording form. (fig. 1)
10. Use the two color pen to distinguish between the right eye and left eye.
11. Repeat steps 6–10 on rows B, C, D and E.
12. To plot the contrast sensitivity curve, connect the marked patient response points.
13. Repeat steps 6–13 for the patient's other eye.



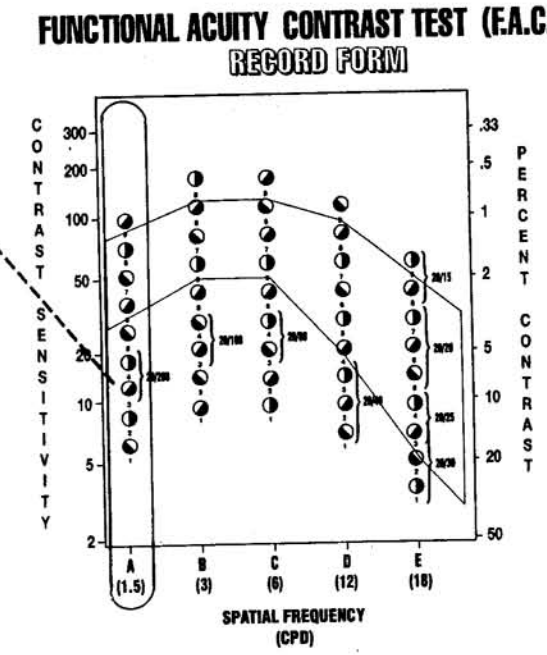


FIGURE 1

F.A.C.T. QUICK TEST

To identify vision loss due to Macular, Retinal or Optic Nerve Defects, testing ROW C may be sufficient. This "Quick Test" provides a quick method of detecting contrast loss.

Individuals whose contrast falls below the normal range are suspect and should be tested using the other frequencies.

RECORDING AND EVALUATION OF RESULTS

1. The last correct response for each row is recorded on the record form.

2. The marked patient response for each contrast sensitivity level are connected with a line.

3. Abnormal contrast sensitivity curves are defined as:

   a. The curve is not within the normal range (gray area) of the record chart. (fig. 2)

   b. The curve of the patient's two eyes differs by more than two contrast values (patches) at any one frequency. (fig. 3)

   c. The curve of the patient's two eyes differs by more than one contrast value (patch) at two or more adjacent frequencies. (fig. 4)

Early losses, neurologic, pathologic or refractive visual problems will have different affects on the contrast sensitivity curve. Losses in the high frequencies usually indicate problems with the macula, which includes refractive problems and macular edema. More severe vision problems may cause degradation of the entire contrast sensitivity curve. (fig. 5)

A curve with normal high frequency contrast sensitivity and abnormal low and/or mid-frequency contrast sensitivity indicates the possibility of a pathologic or neurologic problem.

SNELLEN FUNCTIONAL EQUIVALENTS

The contrast sensitivity curve can be interpreted in Snellen Functional Equivalents. To obtain the Snellen Functional Equivalent value:

1. Look at the contrast sensitivity curve going from left to right.

2. The first bracket the contrast curve intersects is the Snellen Functional equivalent.

In figure 2, the Snellen Functional Equivalent for the right eye is 20/100 and 20/15 for the left.

Normative Values

On average, a healthy visual system is expected to have contrast sensitivity within the normal range shown by the dotted region on the recording form. This should be considered an average performance level. Normative limits which include 90% of the normal population can be used to help minimize the potential for false positives.

This normative range is useful for comparing the shape of a contrast sensitivity curve outside the normative limits.

If the curve is below the normal range for either eye at one or more rows, then the patient should be suspect.

APPLICATIONS

The F.A.C.T. is designed to help identify vision loss from a variety of disorders, many of which are not detected by high or low contrast Snellen Acuity tests.

Many conditions hinder the ability to recognize low contrast objects, while having limited impact on the ability to identify high contrast items.

Visual pathway dysfunction can cause visual loss that is quite different from the visual loss caused by refractive error. Visual pathway dysfunction can reduce the ability to see large objects while sparing the ability to see small objects.[4,5] The visual pathway contains several kinds of contrast sensitive neurons, some responding only to objects of larger size, some to intermediate size and some only to small size objects.

Contrast sensitivity tests address this weakness of Snellen high contrast acuity by varying two parameters...grating size and contrast level. Unlike letters, the visibility of gratings can generalize to the visibility of other objects including letters. The following gives more specific information on its use in many of these conditions.

Contact Lenses

Contrast Sensitivity is useful for helping to ensure proper contact lens fit as well as determining when replacement is necessary. For example, uncorrected residual astigmatism from a soft contact lens can result in decreased contrast sensitivity generally at the higher spatial frequencies when compared to hard lenses. Significant contact lens deposits can result in decreased contrast sensitivity at the middle and higher spatial frequencies when compared to contrast sensitivity obtained when the contact lenses are new.[11,16]

Refractive Disorders

Generally, refractive disorders manifest themselves as a decline in contrast sensitivity first at the smaller grating sizes or higher spatial frequencies for mild refractive disorders. As the degree of refractive disorder increases, contrast sensitivity declines at the middle and then larger grating sizes (middle to lower spatial frequencies).[15,16]

Refractive Surgery

Refractive surgery can generally result in contrast sensitivity curves similar to refractive error if surgery results in undercorrection.[17,18]

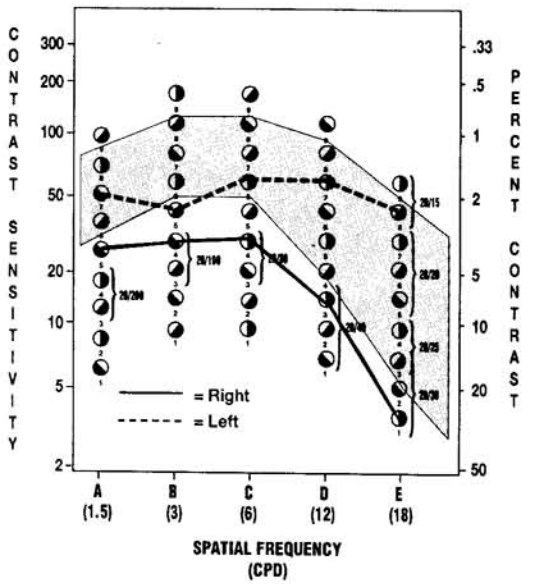


FIGURE 2
Abnormal Curves

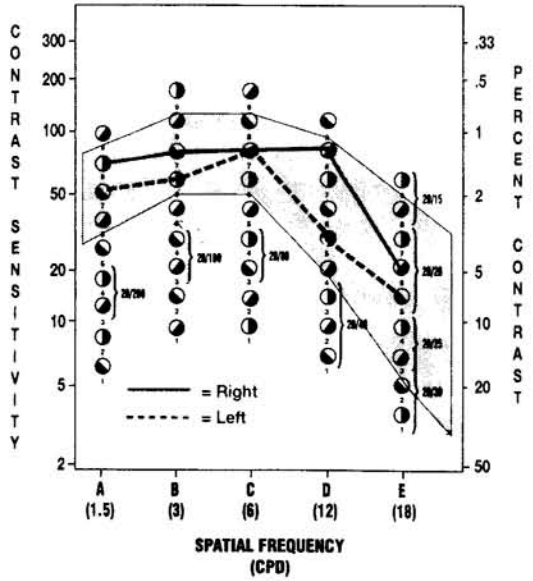


FIGURE 3
Abnormal Curve at D Frequency
for Left Eye

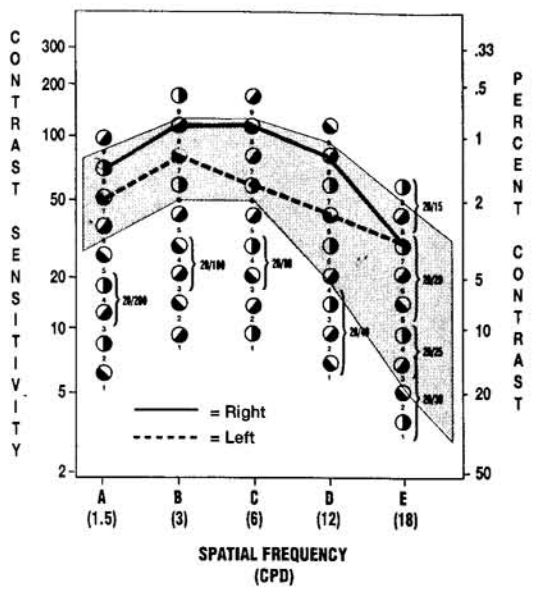


FIGURE 4
Abnormal Curve at the C and D Frequencies
for Left Eye

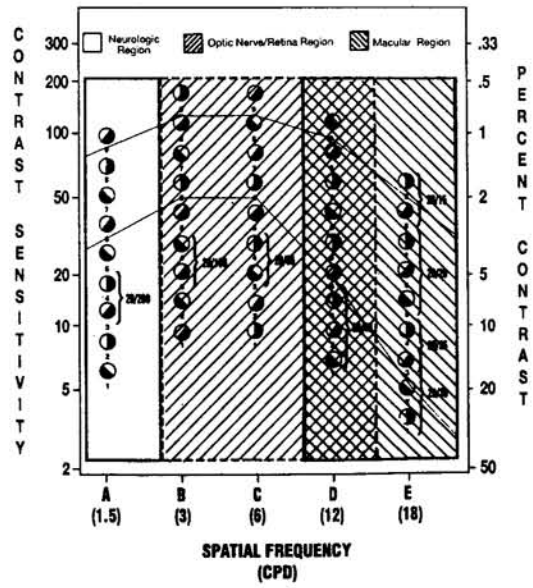


FIGURE 5
Segment of the Contrast Sensitivity Curve Affected
During Early Vision Problems

Cataracts

Early cataracts generally cause contrast sensitivity losses similar to refractive disorders at higher spatial frequencies, rows D and E. Later cataract can reduce contrast sensitivity evenly or unevenly over the lower and middle as well as the higher spatial frequencies (fig. 6).[19-20]

The addition of a glare source will exacerbate the results for patients with cataracts, producing a lower contrast sensitivity at some or all grating sizes.[21,22]

Glaucoma

Although glaucoma can reduce contrast sensitivity for all grating sizes, a number of studies have shown reduced contrast sensitivity mostly at the middle spatial frequencies, especially for row C (fig. 7).[23-25]

Macular Degeneration

Macular degeneration patients as a group appear to exhibit greater contrast sensitivity loss for all grating sizes with increased degeneration.[26]

Diabetic Retinopathy

In diabetic patients, contrast sensitivity loss may occur for all grating sizes.[27]

Optic Neuropathies

A variety of optic neuropathies including afferent pupillary defect, optic neuritis, multiple sclerosis, etc. will effect contrast sensitivity losses over some or all grating sizes. Multiple sclerosis can sometimes effect only the middle sizes.[28]

Amblyopia

Vision loss due to amblyopia can be identified when tests from the amblyopic eye are compared to its fellow eye (as described in the Recording and Evaluation of Test Results section of this manual). Typically, the amblyopic eye has lower contrast sensitivity for all grating sizes than the fellow eye. This has been shown with both anisometropic and strabismic amblyopia, however anisometropic amblyopes appear to have greater losses (fig. 8).[29,30]

Pituitary Adenoma

Pituitary adenoma has been shown to cause contrast sensitivity loss at the middle grating sizes, row C.[31]

Drugs

Certain drugs such as alcohol and Ibuprofen can cause losses in contrast sensitivity.[32,33]

Toxic Chemicals

Exposure to organic solvents of micro electronic workers has been shown to reduce contrast sensitivity for the middle size gratings.[34]

FUNCTIONAL VISION

Normal Variation and Seeing Everyday Objects

Individuals with normal contrast sensitivity, that is without any detectable vision problem or eye disease, can have significant differences in grating contrast sensitivity within the normal range over different grating sizes that can effect their visual capability. Differences in seeing letters, aircraft silhouettes, faces and head-up displays have been related to grating contrast sensitivity.[8,35]

Motor Vehicle Operators

Older drivers, having reduced normal grating contrast sensitivity as compared to younger drivers, have been shown to require to be 24% closer than younger drivers to correctly discriminate road signs even though both groups had better than 20/20 Snellen acuity.[36]

Older drivers have been shown to have significantly higher crash rates correlated to lower grating contrast sensitivity.[7,9]

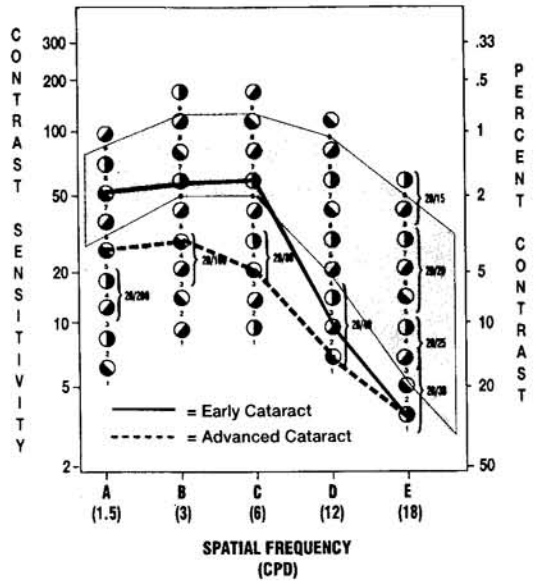


FIGURE 6
Early and Advanced Cataracts

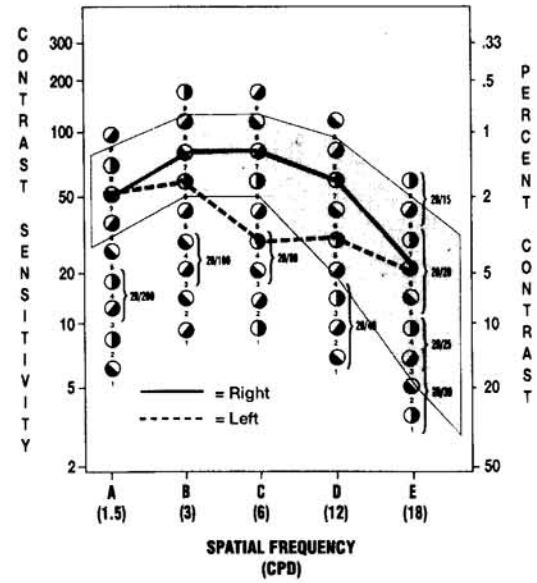


FIGURE 7
Early Glaucoma
Left Eye

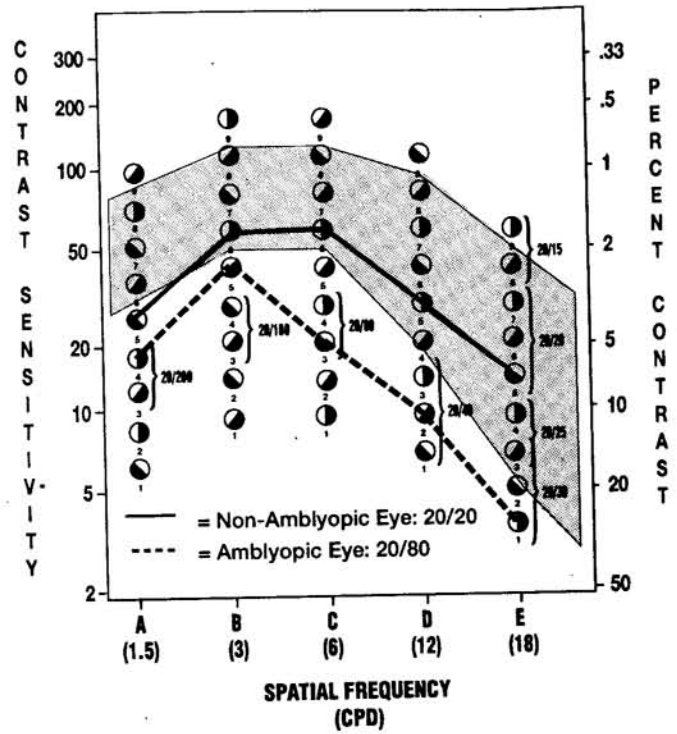


FIGURE 8
Amblyopia

Aircraft Pilots

Pilots have been shown to have significantly longer detection ranges for detecting targets in a flight simulator and field trials that related to individual differences in grating contrast sensitivity.[6,8]

The Canadian Air Force used individual grating contrast sensitivity for pilot selection.[37]

ADVANCED TOPICS

Examination procedure

Methods 1 and 2 below are similar and are used primarily in research. Researchers generally tend to use repeated measures to minimize possible effects of test errors (increase test reliability) and allow statistical analysis. The clinician may want to adopt one of these methods.

Method 1

1. The patient is shown the test rows in a random sequence and tested three times. For example, row sequence C, A, E, D, B, E, C, A, B, D, A, C, E, D, B. Each response is recorded.
2. A final contrast sensitivity score is determined by the lowest contrast patch having at least two of three correct responses.
3. Record the responses on the recording forms.

Method 2

1. The rows are tested in a random sequence two or more times. Each correct response is recorded.
2. Convert each correct patch number into contrast sensitivity from Table 1 and determine the mean score for each row. Standard deviations or other statistics may also be determined.
3. Record mean score for each row on the attached recording form described in Method 1.
4. As with previous methods, scores for each row are connected and compared to the normative curves.

F.A.C.T. CONTRAST SENSITIVITY VALUES

ROW	CYCLES PER DEGREE	COLUMN 1	2	3	4	5	6	7	8	9
A	(1.5)	7	9	13	18	25	36	50	71	100
B	(3)	10	15	20	29	40	57	80	114	160
C	(6)	12	16	23	33	45	64	90	128	180
D	(12)	8	11	15	22	30	43	60	85	120
E	(18)	4	6	8	12	17	23	33	46	65

The numbers (ABOVE) are the contrast values for each patch on the F.A.C.T. chart. To find the contrast value, identify the patch by row and column. For example: the Contrast value for Patch B,4 is 29.

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APPENDIX 2. ATTACHMENT 2.

ATTACHMENT 2. INDIVIDUAL PARTICIPANT VCS SCORES

Each participant's VCS scores can be found in the following tables. Participants have been grouped by whether the participant lived in a reference building or a dry cleaner building, and for those in dry cleaner buildings, also by whether the residence had a level of perc above or below 100 $\mu g/m^3$.

ID is the unique identifier for the participant. The first portion of the identifier is unique for each household. In general, adult-child pairs have been listed in the same line. In cases where there were two children from a household, the adult's score has been listed with the first child.

Reference Buildings												
Adults							Children					
ID	CPD					Eye	ID	CPD				
	1.5	3	6	12	18			1.5	3	6	12	18
55-0001	100	160	180	120	65	L	55-0003	71	160	180	85	65
55-0001	100	160	180	85	65	R	55-0003	71	160	180	60	65
69-0001	50	114	90	30	8	L	69-0002	100	160	180	120	33
69-0001	50	160	90	30	12	R	69-0002	100	160	180	120	65
224-0001	71	80	64	11	12	L	224-0002	100	80	180	43	65
224-0001	71	80	23	8	4	R	224-0002	100	114	128	60	65
414-0004	100	114	180	30	17	L	414-0002	100	114	45	85	65
414-0004	100	160	90	43	17	R	414-0002	100	80	128	30	8
427-0001	100	160	180	85	65	L	427-0002	100	160	180	120	65
427-0001	100	160	180	85	46	R	427-0002	100	160	180	120	65
442-0001	100	114	180	30	12	L	442-0002	100	160	90	60	46
442-0001	100	160	128	30	17	R	442-0002	71	114	90	30	23
484-0003	100	114	90	30	17	L	484-0002	71	160	180	120	65
484-0003	100	114	128	60	33	R	484-0002	71	160	128	60	65
683-0001	100	114	180	30	23	L	683-0002	100	160	180	120	65
683-0001	100	114	90	43	12	R	683-0002	100	160	180	120	65
						L	694-0002	50	114	128	120	33
						R	694-0002	50	80	90	120	46
1086-0002	71	114	128	60	33	L	1086-0003	50	80	128	85	23
1086-0002	71	114	90	15	6	R	1086-0003	50	114	128	85	33
1492-0001	100	160	180	60	33	L	1492-0002	100	114	90	85	17
1492-0001	50	114	180	60	33	R	1492-0002	100	114	180	43	65
1561-0001	100	160	180	43	12	L	1561-0002	100	160	128	120	46
1561-0001	100	114	180	60	4	R	1561-0002	71	114	128	85	65
1596-0001	100	114	128	60	33	L	1596-0002	100	160	180	120	46
1596-0001	71	114	128	60	46	R	1596-0002	71	160	128	120	65
2653-0001	71	160	128	85	65	L	2653-0002	100	160	180	120	65
2653-0001	71	160	180	85	12	R	2653-0002	100	160	128	120	65
4524-0001	100	114	90	30	12	L	4524-0002	100	160	180	120	46
4524-0001	100	114	180	85	33	R	4524-0002	100	114	180	85	46
5015-0002	50	57	64	43	8	L	5015-0003	100	160	180	85	65
5015-0002	71	57	64	30	8	R	5015-0003	100	160	180	85	65
5194-0001	71	114	90	60	33	L	5194-0003	100	160	180	85	33
5194-0001	50	57	90	60	33	R	5194-0003	100	160	180	120	65
5452-0001	100	114	128	60	17	L	5452-0002	71	160	64	15	17
5452-0001	71	114	128	60	23	R	5452-0002	100	160	180	120	12
6401-0001	100	160	64	22	4	L	6401-0002	100	160	180	120	65
6401-0001	71	114	128	60	8	R	6401-0002	100	160	128	120	12
6583-0001	100	114	128	85	65	L						
6583-0001	100	114	180	60	65	R						
						L	6595-0002	100	114	180	120.	
						R	6595-0002	100	160	180	120	65
6598-0001	71	114	128	43	12	L	6598-0002	100	80	64	43	33
6598-0001	71	80	64	15	8	R	6598-0002	100	114	128	60	33

Reference Buildings												
Adults							Children					
ID	CPD					Eye	ID	CPD				
	1.5	3	6	12	18			1.5	3	6	12	18
						L	6598-0003	100	160	128	85	65
						R	6598-0003	71	80	90	43	8
6648-0001	100	160	128	30	17	L	6648-0002	71	114	128	85	46
6648-0001	100	114	180	43	23	R	6648-0002	50	114	180	85	46
7405-0001	71	114	128	60	17	L	7405-0002	71	114	128	85	33
7405-0001	71	114	90	30	12	R	7405-0002	71	57	128	85	33
7766-0001	100	160	180	120	65	L	7766-0002	100	114	180	120	46
7766-0001	100	160	180	60	17	R	7766-0002	100	160	90	120	33
7855-0001	71	160	128	60	46	L	7855-0002	71	80	180	120	33
7855-0001	100	160	128	85	46	R	7855-0002	100	114	180	85	23
7946-0001	100	114	90	120	65	L	7946-0002	100	160	180	120	65
7946-0001	71	160	180	120	46	R	7946-0002	100	160	128	120	65
10068-0001	100	80	90	30	17	L	10068-0002	100	114	180	60	46
10068-0001	100	80	64	30	23	R	10068-0002	100	160	180	120	65
10208-0001	100	114	64	43	17	L	10208-0002	100	80	128	85	65
10208-0001	71	114	128	60	23	R	10208-0002	71	160	128	120	65
10230-0001	100	160	180	85	46	L	10230-0002	100	114	180	85	46
10230-0001	100	160	180	120	65	R	10230-0002	100	160	180	85	46
14795-0001	100	57	128	60	17	L	14795-0002	100	160	180	120	33
14795-0001						R	14795-0002	71	114	180	43	33
14892-0001	100	160	180	60	12	L	14892-0002	71	114	180	120	65
14892-0001	100	160	180	30	17	R	14892-0002	71	160	180	85	65
15037-0001	100	114	90	30	12	L						
15037-0001	100	160	90	22	23	R						
15642-0001	71	160	128	60	33	L	15642-0002	100	160	180	120	65
15642-0001	100	160	90	22	46	R	15642-0002	100	160	180	120	65
15643-0001	100	114	180	85	65	L						
15643-0001	71	114	128	85	46	R						
45456-0001	100	160	180	120	46	L	45456-0002	100	160	180	85	65
45456-0001	100	160	64	120	65	R	45456-0002	100	160	180	85	65
45537-0001	100	160	128	85	46	L	45537-0002	100	160	180	120	65
45537-0001	100	160	128	60	23	R	45537-0002	100	160	90	120	65
45567-0001	71	160	180	120	65	L	45567-0002	100	160	180	43	65
45567-0001	100	160	180	85	33	R	45567-0002	100	160	180	60	46
45568-0001	71	114	180	85	33	L	45568-0002	100	114	180	120	46
45568-0001	100	160	180	60	33	R	45568-0002	100	160	128	120	65
						L	45574-0003	100	114	180	120	65
						R	45574-0003	50	160	90	85	46
45576-0001	71	57	64	30	12	L	45576-0003	100	114	180	60	65
45576-0001	71	57	64	30	17	R	45576-0003	100	114	128	85	46
45577-0001	100	160	180	120	65	L	45577-0002	50	114	128	85	33
45577-0001	100	114	180	120	65	R	45577-0002	36	80	90	60	65
45578-0001	100	160	128	120	65	L	45578-0002	100	80	64	30	65
45578-0001	71	160	128	120	23	R	45578-0002	100	160	180	120	23

Reference Buildings												
Adults							Children					
ID	CPD					Eye	ID	CPD				
	1.5	3	6	12	18			1.5	3	6	12	18
						L	45579-0002	100	114	180	85	33
						R	45579-0002	100	114	180	85	23
						L	45579-0003	100	160	128	120	65
						R	45579-0003	100	160	180	43	65
						L	60912-0002	100	160	180	120	33
						R	60912-0002	100	160	128	120	46
60913-0001	100	114	180	120	65	L	60913-0002	100	160	180	120	65
60913-0001	71	160	180	120	46	R	60913-0002	71	80	180	85	65
60914-0001	100	160	180	85	65	L	60914-0002	100	160	180	120	46
60914-0001	100	160	128	120	65	R	60914-0002	100	160	128	120	46
60915-0001	100	160	180	120	46	L	60915-0003	100	160	180	120	46
60915-0001	100	160	180	85	23	R	60915-0003	100	160	180	120	65
						L	60916-0002	100	160	128	43	33
						R	60916-0002	100	114	128	43	46
61140-0001	100	160	180	60	46	L	61140-0002	100	160	90	85	65
61140-0001	100	114	180	120	33	R	61140-0002	71	160	90	120	65
61176-0001	100	160	180	120	46	L	61176-0002	100	160	180	120	65
61176-0001	100	160	90	60	12	R	61176-0002	100	160	180	120	65
61177-0001	100	160	128	120	46	L	61177-0002	100	80	128	85	33
61177-0001	71	160	128	120	33	R	61177-0002	71	80	128	120	33
						L	61178-0002	100	160	180	120	65
						R	61178-0002	100	160	180	120	46
61180-0001	100	160	90	30	17	L	61180-0002	100	114	180	120	65
61180-0001	100	57	180	30	46	R	61180-0002	100	114	180	120	65
						L	61180-0003	100	160	180	120	65
						R	61180-0003	100	160	180	120	65

Dry Cleaner Buildings < 100 µg/m^3												
	Adults							Children				
ID	CPD					Eye	ID	CPD				
	1.5	3	6	12	18			1.5	3	6	12	18
1338-0001	100	114	180	43	23	L	1338-0002	100	160	180	120	65
1338-0001	100	160	180	43	12	R	1338-0002	100	160	180	120	65
1363-0001	71	160	128	120	46	L	1363-0002	100	160	180	120	65
1363-0001	100	160	90	30	17	R	1363-0002	71	160	90	43	65
1401-0001	100	114	180	85	33	L	1401-0002	100	114	180	120	65
1401-0001	100	160	128	60	8	R	1401-0002	100	160	180	120	65
2208-0001	100	160	180	120	65	L	2208-0002	100	160	180	120	65
2208-0001	100	160	180	120	46	R	2208-0002	100	160	180	120	65
2217-0001	100	114	180	120	46	L	2217-0002	71	160	180	120	65
2217-0001	100	160	128	120	33	R	2217-0002	100	160	180	60	65
2219-0001	100	160	180	120	65	L	2219-0002	100	160	128	60	33
2219-0001	71	160	90	85	65	R	2219-0002	100	160	128	60	12
2359-0001	71	114	180	85	65	L						
2359-0001	71	160	180	85	33	R						
2391-0001	100	160	180	85	33	L						
2391-0001	100	80	128	85	46	R						
3208-0001	100	114	90	30	12	L	3208-0003	71	160	90	85	17
3208-0001	100	114	90	30	12	R	3208-0003	71	80	90	60	33
5038-0001	71	114	90	43	12	L	5038-0002	100	160	180	85	65
5038-0001	50	114	128	60	17	R	5038-0002	100	160	128	120	65
5840-0001	100	114	90	60	17	L	5840-0002	100	160	180	120	65
5840-0001	71	80	64	22	8	R	5840-0002	100	160	180	120	65
6203-0001	100	160	180	60	46	L	6203-0002	100	160	128	120	65
6203-0001	100	114	90	85	46	R	6203-0002	71	114	180	85	65
6236-0001	100	114	180	60	33	L	6236-0002	100	114	180	120	65
6236-0001	71	160	128	60	33	R	6236-0002	100	160	180	85	23
7633-0001	100	160	180	22	12	L	7633-0002	100	160	180	120	65
7633-0001	100	160	128	120	17	R	7633-0002	100	160	180	120	65
8450-0001	100	114	180	43	33	L	8450-0002	100	160	90	120	65
8450-0001	100	114	128	120	17	R	8450-0002	100	160	128	120	65
8457-0001	100	114	128	85	33	L	8457-0002	71	160	180	120	46
8457-0001	100	80	180	85	46	R	8457-0002	100	160	90	60	65
8484-0001	71	160	90	30	12	L	8484-0002	71	160	128	85	46
8484-0001	71	114	180	85	23	R	8484-0002	100	160	180	120	65
8577-0001	25	29	45	22	12	L	8577-0002	100	114	180	85	23
8577-0001	50	40	45	15	6	R	8577-0002	100	160	128	43	33
8776-0001	100	114	180	22	33	L	8776-0002	100	160	128	120	33
8776-0001	71	160	90	120	23	R	8776-0002	100	114	128	120	23
8823-0001	100	114	128	60	23	L	8823-0002	100	160	180	120	65
8823-0001	100	160	180	85	8	R	8823-0002	100	160	180	120	65
8840-0001	100	160	180	120	17	L	8840-0002	71	160	128	120	65
8840-0001	100	114	128	60	33	R	8840-0002	100	160	90	120	65

Dry Cleaner Buildings < 100 µg/m^3												
	Adults							Children				
ID	CPD					Eye	ID	CPD				
	1.5	3	6	12	18			1.5	3	6	12	18
8845-0001	100	114	90	85	33	L	8845-0002	50	114	180	120	65
8845-0001	71	80	180	120	12	R	8845-0002	36	80	90	120	23
8848-0001	100	114	180	60	23	L	8848-0002	36	57	64	43	23
8848-0001	100	114	128	85	33	R	8848-0002	36	57	64	43	23
8868-0001	71	114	90	30	23	L						
8868-0001	71	57	64	11	4	R						
9082-0001	100	114	128	85	65	L	9082-0002	100	160	180	120	65
9082-0001	100	160	128	120	33	R	9082-0002	100	160	180	120	65
9083-0001	100	114	180	30	23	L	9083-0002	100	80	128	120	46
9083-0001	100	160	90	15	4	R	9083-0002	100	160	180	60	33
						L	9117-0002	100	160	128	60	46
						R	9117-0002	100	160	180	85	46
9139-0001	100	114	90	22	4	L	9139-0002	100	160	180	85	65
9139-0001	100	160	180	30	8	R	9139-0002	71	160	180	85	65
10458-0001	100	114	180	85	33	L	10458-0002	50	160	128	60	65
10458-0001	71	114	128	43	17	R	10458-0002	50	160	128	85	33
10535-0001	100	160	180	85	65	L	10535-0002	100	114	90	60	65
10535-0001	100	160	180	85	46	R	10535-0002	100	114	128	85	46
11391-0001	100	160	128	60	33	L	11391-0002	100	114	180	120	65
11391-0001	100	160	180	120	46	R	11391-0002	100	160	180	120	65
12049-0001	71	114	128	60	33	L						
12049-0001	100	114	128	60	33	R						
12050-0001	100	160	180	85	23	L						
12050-0001	71	114	128	30	23	R						
12208-0001	71	114	180	85	65	L	12208-0002	100	160	180	85	46
12208-0001	100	160	128	85	33	R	12208-0002	100	114	128	120	65
12643-0001	71	160	180	85	23	L	12643-0002	50	80	128	60	65
12643-0001	100	160	90	43	17	R	12643-0002	71	160	90	85	46
						L	13805-0002					
						R	13805-0002					
13944-0001	100	160	180	120	46	L	13944-0002	100	114	180	120	46
13944-0001	100	114	180	60	46	R	13944-0002	71	114	128	85	65
15462-0001	100	114	128	120	65	L	15462-0002	100	160	180	60	65
15462-0001	100	160	180	43	33	R	15462-0002	100	160	128	120	65
15465-0001	100	160	180	120	46	L	15465-0002	100	160	180	43	46
15465-0001	100	160	180	120	65	R	15465-0002	100	160	180	120	65
15466-0001	100	160	128	85	65	L	15466-0002	100	160	128	60	46
15466-0001	100	160	180	60	23	R	15466-0002	100	160	90	85	65

Dry Cleaner Buildings >100 µg/m^3												
	Adults							Children				
ID	CPD					Eye	ID	CPD				
	1.5	3	6	12	18			1.5	3	6	12	18
669-0001	100	114	180	43	12	L						
669-0001	100	80	180	60	12	R						
						L	671-0002	100	160	128	120	65
						R	671-0002	100	160	180	85	46
2417-0001	100	114	128	43	17	L	2417-0002	100	160	180	60	46
2417-0001	100	114	128	60	12	R	2417-0002	100	160	180	120	46
8479-0001						L	8479-0002	71	160	128	120	23
8479-0001	71	160	90	30	8	R	8479-0002	71	80	128	30	12
13661-0001	100	80	64	30	12	L	13661-0002	100	160	180	60	46
13661-0001	71	160	90	30	23	R	13661-0002	100	114	180	60	33
13868-0001	100	114	128	120	33	L	13868-0002	100	160	128	60	65
13868-0001	100	114	128	120	46	R	13868-0002	100	160	128	85	46
15433-0001	50	160	90	60	23	L						
15433-0001	36	80	90	30	46	R						
15463-0001	71	160	90	85	46	L	15463-0002	71	160	128	60	65
15463-0001	71	80	64	43	17	R	15463-0002	71	57	128	85	33
15464-0001	100	80	128	85	33	L	15464-0002	100	160	128	120	65
15464-0001	100	160	90	120	65	R	15464-0002	100	160	180	85	46
15468-0001	100	160	90	85	65	L						
15468-0001	100	160	90	85	17	R						
15475-0001	71	80	128	85	33	L	15475-0002	36	57	128	60	23
15475-0001	71	80	128	60	23	R	15475-0002	50	80	128	43	17
						L	15475-0003	71	114	90	85	65
						R	15475-0003	100	160	180	120	33
30126-0001	100	160	180	120	65	L	30126-0002	71	160	180	60	65
30126-0001	100	160	128	85	33	R	30126-0002	71	160	90	120	65
45554-0001	25	57	64	30	17	L	45554-0003	71	114	128	85	46
45554-0001	71	57	45	22	6	R	45554-0003	50	114	90	43	46

APPENDIX 3. EXPOSURE RESPONSE ANALYSES.

The exposure response analyses in this report apply a method developed by Wheeler (2005) to model risk using the SAS procedure NLMIXED. It also uses MACRO programming language to estimate profile likelihood confidence intervals.

The following SAS code was used to fit a model (modified from the original code provided by Wheeler, personal communication).

```
%MACRO BMDLOGIT(DATA,RESULT,BKGD,CONC,ER,CL,DSN);

data _temporary_;
 bkgd=&bkgd;
 bkgd_lg=log10(bkgd);
 CALL SYMPUT("BKGD_LG",bkgd_lg);
run;

data __one;
 set &data;
run;

%LET MODEL = _ALPHA + _BDOSE*(&CONC);

ods listing close;
ods output fitstatistics = fitstatistics
     ParameterEstimates=ParameterEstimates;

/*FIT THE MODEL*/
proc nlmixed data= __one;
 _LINK = &MODEL;
 P = 1/(1+exp(-_LINK));
 p_bkgd =1/(1 + exp(-(_ALPHA + _BDOSE*(&bkgd_lg))));
 BMR = &ER+(1-&ER)*p_bkgd;
 _BMD = (- log(1/BMR - 1) - _ALPHA)/_BDOSE;
  predict p out=pred;
 CALL SYMPUT("BMD",_BMD);
 CALL SYMPUT("P_bkgd",p_bkgd);
 CALL SYMPUT("BMR_ER",BMR);
 MODEL &RESULT ~ BINARY(P);
run;


data fitstatistics;
 set fitstatistics;
 format value best16.;
 informat value best16.;
 if (Descr = "-2 Log Likelihood");
 NegLogLike = value/2;
 keep value NegLogLike;
```

```
run;
data _temp_;
  set fitstatistics;
  call symput("MLIKE",NegLogLike);
  val = cinv(1-2*(1-&CL),1)*0.5;
  call symput("CRITVAL",val);
run;


%LET ERROR = 0;
%LET CRITLIKE = &MLIKE;
%LET I = 1;
%LET BMDL = &BMD;
%LET J = 1;

/*PUT A LOWER BOUND ON THE BMD THIS IS DONE BY SLOWLY SHAVING
 2% OFF THE PRESENT ESTIMATE FOR THE BMD
 AFTER THIS IS FOUND WE FIND THE EXACT VALUE*/

%DO %WHILE (%SYSEVALF(&CRITLIKE - &MLIKE < &CRITVAL) AND &J <
200);

 %LET FIRSTTOKEN = 1;
 %LET LASTBMDL = &BMDL;
 %LET BMDL = %SYSEVALF(0.96*&BMDL);

 data pe; set ParameterEstimates; if(Parameter='_ALPHA')then
delete; run;

 ods listing close;
ods output fitstatistics = fitstatistics
     ParameterEstimates=ParameterEstimates;

 proc nlmixed data= __one;
  parms /data=pe;
  _Z=EXP(_BDOSE*(&BMDL-&bkgd_lg));
  _X=((1-&ER)*_Z - 1)/&ER;
  _ALPHA = - LOG(_X)-_BDOSE*&bkgd_lg;
  _LINK = &MODEL;
  P = 1/(1+exp(-_LINK));
  MODEL &RESULT ~ BINARY(P);
 run;

 ods listing;
 data fitstatistics;
  set fitstatistics;
  format value best16.;
```

```
  informat value best16.;
  if (Descr = "-2 Log Likelihood");
  NegLogLike = value/2;
  keep value NegLogLike;
 run;

 data _temp_;
   set fitstatistics;
   call symput("CRITLIKE",NegLogLike);
 run;
 %let J = %EVAL(&J + 1);

%END;

%LET TOP = &LASTBMDL;
%LET BOTTOM = &BMDL;

DATA _TEMP_;
 X = ABS(&CRITLIKE - &MLIKE-&CRITVAL);
 X = X<0.0001;
 CALL SYMPUT("TEST",X);
RUN;


/*ZOOM IN ON THE BMDL USING A BINOMIAL HALVING SEARCH*/
%LET J = 1;
%DO %WHILE (&TEST = 0 AND &J < 20);

 %LET BMDL = %SYSEVALF((&TOP+&BOTTOM)/2);
 %LET FIRSTTOKEN = 1;
 %PUT &BMDL;

 data pe; set ParameterEstimates; if(Parameter='_ALPHA')then
delete; run;

 ods listing close;
ods output fitstatistics = fitstatistics
     ParameterEstimates=ParameterEstimates;

 proc nlmixed data= __one;
  parms /data=pe;
  _Z=EXP(_BDOSE*(&BMDL-&bkgd_lg));
  _X=((1-&ER)*_Z - 1)/&ER;
  _ALPHA = - LOG(_X)-_BDOSE*&bkgd_lg;
  _LINK = &MODEL;
  P = 1/(1+exp(-_LINK));
  MODEL &RESULT ~ BINARY(P);
```

```
 run;

 ods listing;

 data fitstatistics;
  set fitstatistics;
  format value best16.;
  informat value best16.;
  if (Descr = "-2 Log Likelihood");
  NegLogLike = value/2;
  keep value NegLogLike;
 run;

 data _temp_;
   set fitstatistics;
   call symput("CRITLIKE",NegLogLike);
 run;

 DATA _TEMP2_;
  X = ABS(&CRITLIKE - &MLIKE-&CRITVAL);
  X2 = X < 0.0001;
  CALL SYMPUT("TEST",X2);
  Z = &CRITLIKE - &MLIKE-&CRITVAL;
  Z2 = Z < 0;
  CALL SYMPUT("LOCALTEST",Z2);
  output;
 RUN;

 %IF (&LOCALTEST = 1) %THEN %DO;
  %LET TOP = &BMDL;
 %END;
 %IF (&LOCALTEST =0) %THEN %DO;
  %LET BOTTOM = &BMDL;
 %END;
  %LET J = %EVAL(&J+1);
%END;


data BMDLOGIT&dsn;
 NAME = "LOGISTIC";
 BMD_LG = &BMD;
 BMDL_LG = &BMDL;
 MAXLIKE= 2*&MLIKE;
 BKGD=&bkgd;
 ER=&ER;
 BMD=10**&BMD;
 BMDL=10**&BMDL;
```

```
 P_bkgd=&p_bkgd;
 BMR_ER =&BMR_ER;

RUN;

%MEND;
```

To invoke this macro one needs the name of the dataset (DATA), the name of the health outcome variable (RESULT), the level of perc considered to be 'background' (BKGD), the variable name of the estimated indoor air level of perc for the individual (CONC), the benchmark response or extra risk (ER), the desired confidence level (CL), and the name of the dataset that will contain the results (DSN).

APPENDIX 3. ATTACHMENT.

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Paper 201-30

Benchmark Dose Estimation Using SAS®

Matthew W. Wheeler, National Institute for Occupational Safety and Health

ABSTRACT

Toxicologically-based quantitative risk assessment is concerned with estimating human risks based upon experimental data linking an environmental agent to a known outcome (tumor incidence, acute toxicity, etc.). For dichotomous outcomes dose-response curves are modeled as complex functions of dose which often require specialized software to estimate.

The SAS procedure NLMIXED readily allows for maximum likelihood estimation of binomial response data to any non-linear function. This power gives the SAS system the ability to fit dichotomous response curves that have traditionally been modeled using specialized software. For this paper excess risk is estimated within SAS using NLMIXED and the SAS MACRO programming language. Nine dose-response curves are fit examining the excess risk associated with renal tubular degeneration in ethylene glycol exposed rats. The results are compared with those given using the USEPA Benchmark Dose Software. The results show that these models can be reliably implemented within the SAS system producing very similar results as the USEPA software.

INTRODUCTION

Toxicologically based quantitative risk assessment is concerned with estimating human risks based upon experimental data linking an environmental hazard to a known outcome (tumor incidence, acute toxicity, etc.). Risk, the probability of some adverse response, is often derived from dose-response models which parameterize risk as a function of dose. These models are commonly fit using maximum likelihood (ML) estimation. The complexities of the likelihood equation and corresponding risk estimation have forced investigators to use specialized software outside of SAS to conduct their analyses. This is not only an inconvenience for experienced SAS users, but prevents the modeler from incorporating techniques which are not directly implemented by the third party software. For example, if one wanted to examine the behavior of a given dose-response curve through Monte Carlo simulation this task is overly cumbersome, given current software, as most risk estimation packages do not provide the ability to generate random data sets.

This paper examines SAS as a software package which can be used to model risk. Specifically we demonstrate the ability of NLMIXED to model risk derived from dichotomous data. Doses associated with a specified level of excess risk above control response, so-called benchmark doses, are estimated as well. This is done using the procedure NLMIXED with help from the MACRO programming language. Nine popular models, which are also parameterized in the United

States Environmental Protection Agency (USEPA) Benchmark Dose Software [1], are fit and compared to results from that software package.

MODELING RISK

Toxicologically based risk assessment frequently models the probability of adverse outcome, π, as a function of dose, d. Though this dose-response relationship can be modeled through a wide class of functions, we restrict our discussion to implementing nine popular dose-response curves, which are also fit by the USEPA Benchmark Dose Software [1]. These models are as follows

logistic: $$\pi(d) = \frac{1}{1+\exp\left[-(\alpha+\beta d)\right]} \quad (1)$$

log-logistic : $$\pi(d) = \gamma + \frac{(1-\gamma)}{1+\exp\left[-(\alpha+\beta\ln(d))\right]} \quad (2)$$

gamma: $$\pi(d) = \gamma + (1-\gamma)\frac{1}{\Gamma(\alpha)}\int_0^{\beta d} t^{\alpha-1}e^{-t}dt \quad (3)$$

multistage $$\pi(d) = \gamma + (1-\gamma)\left[1-\exp(-f(\underline{\theta},d,n))\right] \quad (4)$$

probit $$\pi(d) = \Phi(\alpha+\beta d) \quad (5)$$

log-probit $$\pi(d) = \gamma + (1-\gamma)\Phi\left[\alpha+\beta\ln d\right] \quad (6)$$

quantal-linear $$\pi(d) = \gamma + (1-\gamma)\left[1-\exp(-\beta d)\right] \quad (7)$$

quantal-quadratic $$\pi(d) = \gamma + (1-\gamma)\left[1-\exp(-\beta d^2)\right] \quad (8)$$

weibull $$\pi(d) = \gamma + (1-\gamma)\left[1-\exp(-\beta d^{\alpha})\right] \quad (9)$$

where $\Gamma(\alpha)$ = gamma function evaluated at α, $\Phi(x)$ = CDF for N(0,1) and $\pi_i = \gamma$ when d=0 for models (2) and (6). Further $f(\underline{\theta},d,n)$ in model (4) is an n degree polynomial of the dose d having the vector of coefficients $\underline{\theta}$. Models (1)-(9) are fit using maximum likelihood estimation. Further, in models (2),(4) and (6)-(8) the slope terms $(\beta,\underline{\theta})$ are bounded to be non-negative, in models (3) and (9) the power term (α) is bounded below by one, and the background response term (γ) for models (2)-(4) and (6)-(9) is bounded between zero and one.

For any particular dose-response function excess risk is often characterized through the use of the benchmark dose [2]. A Benchmark dose (BMD) is defined as the dose that increases risk over the background response rate by some amount relative to the control response. For dichotomous outcomes this pre-specified level, known as the benchmark response (BMR), is commonly given values of 1 and 10%. Given this value of the BMR and a model representing the dose-response [e.g. models (1)-(9)] excess risk can be found by finding the dose (BMD) which satisfies the following equation

$$BMR = \frac{\pi(BMD) - \pi(0)}{1 - \pi(0)} \tag{10}$$

where $\pi(0)$ is the background response. The above formulation is known as the extra risk, and can be thought of as the probability that an effect is observed among individuals who would not have the adverse response in the absence of exposure to the environmental hazard. Though other definitions of excess risk exist, specifically added risk, and are implemented in the USEPA software, for illustration purposes the extra risk formulation is used in the following discussion. It should be noted that the added risk formulation can also be programmed into NLMIXED as it is very similar to the extra risk formulation.

RENAL TUBULAR DEGENERATION DATA ANALYSIS

Consider a 10 day exposure study where Sprague-Dawley rats were exposed to ethylene glycol (EG) in their drinking water [3], with the number of rats exhibiting renal tubular degeneration measured as the observed response. In this experiment, ten rats were exposed to one of 5 dose groups (0, 0.5, 1.0, 2.0 and 4.0% EG). The observed proportions of rats exhibiting renal tubular degeneration were 2/10, 2/10, 2/10, 6/10, and 9/10 for EG concentrations of 0, 0.5, 1.0, 2.0, and 4.0%. The data are analyzed using models (1-9).

For illustration, consider the Weibull model (9) and the definition for extra risk given in equation (10). The SAS procedure NLMIXED can provide ML estimates for this model's parameters as well as estimates for the BMD. The parameters are estimated directly through the use of the MODEL statement, but because the BMD is specified through model parameters, its ML estimate must be computed through programming statements which algebraically relate the ML estimates for the model parameters to the BMD. In the case of the assumed model NLMIXED programming statements estimate the BMD using the following equation

$$\hat{BMD} = \left[\frac{-\ln(1 - BMR)}{\hat{\beta}}\right]^{1/\hat{\alpha}} \tag{11}$$

which is found by substituting the Weibull model (9) into the extra risk equation (10) and algebraically solving for the *BMD* term. The following NLMIXED code which implements the above, subject to the bounds on the parameters of $\alpha \geq 1$, $\beta \geq 0$ and $0 \leq \gamma \leq 1$.

```
001   data EGdata;
002         input dose obs n;
003         cards;
004   0 2 10
005   0.5 2 10
006   1.0 2 10
007   2.0 6 10
008   4.0 9 10
009   ;
010
011   %LET BMR = 0.1;
012
013   PROC NLMIXED data= EGdata;
014         PARMS _GAMMA = 0.006 _BDOSE = 0.5 _ALPHA = 1;
015         BOUNDS _GAMMA >= 0, _GAMMA <= 1, _ALPHA >= 1, _BDOSE >= 0;
016         P = _GAMMA;
017         IF (DOSE > 0) THEN DO;
018               _LINK = _BDOSE * (DOSE** _ALPHA);
019               P = _GAMMA + (1- _GAMMA)*(1-EXP(- _LINK));
020         END;
021         _X = -LOG(1-&BMR);
022         _BMD = (_X/_BDOSE)**(1/_ALPHA);
023         CALL SYMPUT("BMD", _BMD);
024         MODEL OBS ~ BINOMIAL(N,P);
025   RUN;
```

Though NLMIXED can be used to model non-linear mixed models and has a variety of features to aid in this facility, the above code only utilizes it's maximum likelihood estimation ability, which include the statements PARMS, BOUNDS, and MODEL. These programming statements, which are described in the documentation [4], set up the initial parameter estimates, the bounds on the parameters, and the likelihood equation respectively. The Weibull dose-response curve in the above code is estimated through programming statements found in lines 16-20, where the variable "dose" represents the amount of exposed EG, "obs" represents the number observed rats exhibiting renal tubular degeneration, and n is the number of rats in each dose group. Further lines 21-23 algebraically specify the ML estimate for the benchmark dose, and line 24 specifies the likelihood equation. Though it is possible to output the BMD estimate to a dataset using the PREDICT statement, this is not done in favor of outputting the final value to a MACRO variable labeled BMD, which is referenced as &BMD; this variable is created in line 25.

Though the above code is sufficient to allow NLMIXED's algorithm to converge using the EG data some data sets may require more precise starting values. In this case, a grid search is often sufficient for most problems which require more precise starting values. The above code produces the following estimates which correspond within three significant figures to the output produced by the USEPA Benchmark Dose Software.

TABLE 1.

	NLMIXED		USEPA	
	MLE	Standard Error	MLE	Standard Error
$\hat{\gamma}$	0.1724	0.08877	0.1724	0.08877
$\hat{\alpha}$	2.0275	0.8264	2.0275	0.8263
$\hat{\beta}$	0.1373	0.1382	0.1373	0.1382

CONFIDENCE INTERVALS FOR THE BENCHMARK DOSE

Though NLMIXED can be used to estimate the BMD as well as asymptotic confidence intervals, using the PREDICT statement, it is not advisable to use the confidence intervals provided by this facility of NLMIXED. These intervals are based upon standard large sample asymptotic approximations, which may not be appropriate in small sample situations. Instead Crump and Howe [5] suggest the use of the profile likelihood in computation of the confidence interval for the benchmark dose, as it generally gives better coverage behavior in such conditions.

It is convenient to look at the profile likelihood in terms of a likelihood ratio test, and remember the fact that that the -2 log of the likelihood ratio follows an approximate chi-squared distribution with n degrees of freedom, where n represents the number of parameters fixed under the null hypothesis. A profile likelihood confidence interval, in essence, is a likelihood ratio test where one finds a "null" model that fixes the parameter of interest while allowing the other model parameters to vary such that the -2 log-likelihood of this model is different from the -2 log-likelihood of the original or "full" model by $\chi^2_{(1,1-\alpha)}$. Where $\chi^2_{(1,1-\alpha)}$ represents the $(1-\alpha)^{th}$ quantile of a chi-squared distribution with one degree of freedom. Thus the two distinct values that fix the parameter of interest and reduce the maximum likelihood by $\chi^2_{(1,1-\alpha)}$ represent the 100(1-α)% upper and lower confidence bounds on this parameter. In our context the lower bound of the benchmark dose (BMDL) is found by searching for the BMD that changes the -2 log-likelihood of the full model by $\chi^2_{(1,1-2\alpha)}$, where the 1-2α is chosen because the confidence interval of interest is one sided. Though models (1)-(9) do not explicitly parameterize the BMD, they can be parameterized as a function of the BMD.

It is not possible to directly estimate profile likelihood confidence intervals using NLMIXED; however one can use a combination of the MACRO programming language and the Output Delivery System to estimate the proper 100(1-α)% profile likelihood based confidence interval. This is achieved by fixing a parameter in the model relative to the BMD and maximizing the likelihood relative to the other free parameters in the model. Again for illustration we examine the Weibull model. In this situation we set β equal to a function of the BMD i.e.

$$\beta = \frac{-\ln(1 - BMR)}{BMD^{\alpha}}. \qquad (12)$$

By using equation (12) one can decrease the value of the BMD until the resultant -2 log-likelihood is greater than $\chi^2_{(1,1-2\alpha)}$. This is done using the macro programming language as follows.

```
%macro boundBMD(BMDL,MLIKE,CL);
%let BMR = 0.1;
%let MLIKE = %sysevalf(&mlike/2);
data _temp_;
                val = cinv(1-2*(1-&CL),1)*0.5;
                call symput("CRITVAL",val);
run;
%LET CRITLIKE = &MLIKE;

%DO %WHILE (%SYSEVALF(&CRITLIKE - &MLIKE < &CRITVAL));
       *set up the initial parameters for the new likelihood;
       %LET FIRSTTOKEN = 1;
       %LET LASTBMDL = &BMDL;
       %LET BMDL = %SYSEVALF(0.98*&BMDL);
       %LET BOUNDS = _GAMMA >= 0, _GAMMA <= 1, _ALPHA >= 1, _ALPHA <= 18;
       %LET SMODEL = ;
      data pe; set ParameterEstimates; if(Parameter='_BDOSE')then delete;
run;
       data pe;
              set pe;
       run;
       ods listing close;
       ods output fitstatistics = fitstatistics
                  ParameterEstimates=ParameterEstimates;
       *fit this new "constrained" likelihood;
       proc nlmixed data= one;
              parms /data=pe; ;
              bounds &bounds;

              _X = (-LOG(1-&BMR))**(1/_ALPHA);
              *solve for the BETA parameter BDOSE as a function of the BMD;
              _BDOSE = (_X/&BMDL)**_ALPHA;
              P = _GAMMA;
              IF (DOSE > 0) THEN DO;
                     _LINK = _BDOSE*DOSE**_ALPHA;
                     P = _GAMMA + (1-_GAMMA)*(1-EXP(-_LINK));
              END;
              MODEL OBS ~ BINOMIAL(N,P);
       run;
       ods listing;
       *obtain the Fit statistics to determine if the algorithm has bounded
        the BMDL;
       data fitstatistics;
              set fitstatistics;
              format value best16.;
              informat value best16.;
              if (Descr = "-2 Log Likelihood");
              NegLogLike = value/2;
              keep value NegLogLike;
       run;
       data _temp_;
              set fitstatistics;
              call symput("CRITLIKE",NegLogLike);
       run;
%END;
%put &bmdl;
%mend;
```

To invoke this macro one needs to have the ML estimate of the BMD, the -2 log-likelihood of the unconstrained ML and the desired 100(1-α)% confidence level. These values are represented by the macro variables BMDL, MLIKE, and CL respectively. Further, to link it with the code used for the EG data one would need to specify the parameter estimates of the maximum likelihood in a data set named ParameterEstimates; an example of retrieving this dataset is found within the macro on line 24.

The above macro iteratively lowers the estimate of the BMDL by 2% until -2 log-likelihood is reduced by $\chi^2_{(1,1-2\alpha)}$ as stored in &CRITVAL. Lines 13-22 initialize the variables for the current iteration, 27-40 use NLMIXED to optimize the likelihood with the "β" constrained by the BMD, and lines 42-55 retrieve the necessary statistics from the data sets to determine the stopping criteria. Though this procedure puts a lower bound on the BMD it dose not produce a valid 100(1-α)% confidence level. To find the approximate 100(1-α)% confidence interval one can take the value from the lower bound procedure described above, the ML estimate, along with a root finding algorithm to find this value to any specified level of tolerance. In the context of the profile likelihood one finds the root of the function

$$-2\ln(l(\hat{BMD}_{profile})) + 2\ln(l(\hat{BMD}_{ml})) - \chi^2_{(1,1-\alpha)} \qquad (13)$$

where $l(\hat{BMD}_{ml})$ represents the likelihood function evaluated at the ML and $l(\hat{BMD}_{profile})$ represents the likelihood function evaluated at the current estimate of the BMD lower bound.

The above code has been packaged with a root finding procedure in one macro which estimates dose-response model parameters, the BMD, and BMDL given the BMR with a specified confidence level. These macros have been applied to the EG data using the 9 dose-response and produce the following output.

TABLE 2.

Model	BMD 10%	BMDL 10%	BMD 1%	BMDL 1%
Logistic	0.59	0.40	0.07	0.04
Log-Logistic	1.07	0.39	0.52	0.08
Gamma	1.01	0.28	0.47	0.03
Multi-Stage Quadratic	0.86	0.25	0.27	0.02
Probit	0.56	0.40	0.06	0.04
Log-Probit	1.10	0.42	0.64	0.15
Quantal-Linear	0.29	0.18	0.03	0.02
Quantal-Quadratic	0.86	0.65	0.27	0.20
Weibull	0.88	0.26	0.28	0.03

The estimates of table 2 correspond within three significant figures to the estimates from the USEPA Benchmark Dose Software.

ESTIMATION ABILITY

Consider a hypothetical experiment where four groups of 50 rats are exposed to an environmental agent and mortality, which is recorded at the end of the two year study, is the measured response. In this experiment, the four dose groups represent 0, 25, 50 and 100% of the maximum dose administered, with mortality proportions of 4/50, 11/50, 32/50, and 50/50 corresponding respectively to the dose-groups (e.g. 0, 25, 50 and 100%). If one were to fit the two-stage multistage model (4) using the USEPA Benchmark Dose Software, the software would fail to converge to the ML estimate. However if one were to model risk using the procedures outlined above one would obtain the ML estimates for all parameters as well as the benchmark dose value 0.16 with the 95% lower bound of this estimate being 0.12.

CONCLUSION

The SAS procedure NLMIXED allows for the fitting of many common BMD models. Though NLMIXED alone is not sufficient to find proper confidence intervals the MACRO programming language in combination with NLMIXED can be used effectively to compute profile likelihood based confidence intervals. Further the NLMIXED procedure has been shown to find the maximum likelihood when other models fail to find the optimum. Finally, as SAS is a multipurpose statistical package, it is versatile enough to extend present BMD software capabilities beyond those provided by specialized software.

ACKNOWLEDGEMENTS

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APPENDIX 4. RESPONSE TO COMMENTS ON DRAFT REPORT: EFFECT OF TETRACHLOROETHYLENE (PERC) EXPOSURE ON VISUAL CONTRAST SENSITIVITY (VCS) IN ADULTS AND CHILDREN RESIDING IN BUILDINGS WITH OR WITHOUT A DRY CLEANER (JULY 2007).

DESCRIPTION OF EXTERNAL REVIEW PROCESS

Eight scientists (see Attachment 1) with expertise in human health risk assessment, visual contrast sensitivity (VCS) and color vision, neurotoxicology, ophthalmology, exposure-response assessment, and public health were asked to peer-review an external review draft of "Effect of Tetrachloroethylene (Perc) Exposure on Visual Contrast Sensitivity (VCS) Test Performance in Adults and Children Residing in Buildings With or Without a Dry Cleaner" dated July 2007. Five of the reviewers had previously reviewed the NYS DOH "Tetrachloroethene Ambient Air Criteria Document" (dated February 1996) and/or the "Pumpkin Patch Day Care Center Investigation" Public Comment Draft (dated March 1999). Two scientists were invited to comment because of their expertise in vision, neurotoxicology, and ophthalmology. One scientist with expertise in risk assessment and toxicology and representing the halogenated solvents industry was also invited to comment. The eight scientists were given a written peer-review charge (Attachment 2), and asked to provide written comments by late November 2007.

The draft report was revised after consideration of all comments, results of additional analyses recommended by the peer reviewers, and new relevant scientific articles appearing between July 2007 and July 2009. New analyses and information gathered and considered in response to reviewer comments generally support the conclusions of the original draft report.

Our responses to reviewer comments and responses to Charge Questions are provided below. For each charge, overall summaries of reviewer comments are followed by specific individual comments offered by each reviewer and our specific response.

SUMMARY OF MAJOR CHANGES IN FINAL PERC VISION REPORT

1. The report title was changed from: "Effect of Tetrachloroethylene (perc) Exposure on Visual Contrast Sensitivity (VCS) Test Performance in Adults and Children Residing in Buildings With or Without a Dry Cleaner" to: "Tetrachloroethylene (Perc) Exposure and Visual Contrast Sensitivity (VCS) Test Performance in Adults and Children Residing in Buildings With or Without a Dry Cleaner."

   This title more appropriately reflects uncertainty in concluding that residential perc exposure was a causal factor in the VCS changes observed given the limitations noted in the final report.

2. Where appropriate, more detailed explanations of how effects on VCS might indicate an effect in the central nervous system (CNS) were added. Also, statements are added indicating that the study population was selected to have at least normal VCS because of the exclusion criteria applied, so that it's not surprising that as a group they tended to perform very well (see pp. 2, 19, 25-26 in the final report).

3. Where appropriate, it is noted that multiple statistical analyses on the same exposure and VCS data may have increased the possibility of statistically significant observations occurring by chance (p. 30). However, it is also noted that multiple analyses, e.g., correlation and stratified trend analyses, were warranted to help identify potential factors other than perc exposure, e.g., age, race/ethnicity, income, that may have influenced VCS. Expanded rationale for various analyses are described in an expanded Data Analyses section (pp. 10-12).

   These changes appropriately capture the way in which data were explored given the unexpected ceiling effect, the low number of participants with elevated perc exposures, and the apparent/possible confounding of elevated perc exposures with race/ethnicity and income.

   These changes appropriately respond to limitations in the data and analyses noted by several reviewers.

   These changes better explain the bases for multiple analyses and help justify consideration of both "nearly significant" as well as "significant" statistical results throughout the report.

4. A discussion of sample size calculations is added to the Methods section on pages 4-5; and comparison with actual sample sizes achieved is added to the Results section on page 13-14.

5. Appendices were added:

   Appendix 2. The Functional Acuity Contrast Test (F.A.C.T.) with Attachment 1 (Instructions for Use. Stereo Optical Co., Inc.) and Attachment 2 (Individual Participant F.A.C.T. Results).

Appendix 3. Exposure-Response Analyses. This appendix provides a detailed explanation of the benchmark concentration method used.

Appendix 4. Response to Comments on Draft Report. This appendix includes a summary of all reviewers' comments and our responses. It includes Attachment 1 (Peer Reviewers) and Attachment 2 (Peer Reviewer Comments).

6. Analyses are presented and discussed for "better" performing eyes as well as "worse" performing eyes. Rationale for doing this is added on page 10.

   As noted in the final report, analyses of "worse" eyes highlights the maximum possible differences in VCS detectable in this study, and provides the best indicator of whether perc exposure may be associated with a detectable effect on the CNS. Analyses based on "better" eyes highlight minimum differences in VCS observed in this study.

   Overall, analyses for better performing eyes tended to indicate less or no effect due to perc exposures.

7. Figure 1 illustrating group VCS functions reference and dry cleaner building adults, and reference and dry cleaner children has been replaced by a new figure which better illustrates the proportions of participants achieving each VCS score using bubble plots. An additional figure (Figure 2) has been added which illustrates the numbers of participants achieving each VCS score within each of the 3 categorical exposure groups – reference, < 100 $\mu g/m^3$, and > 100 $\mu g/m^3$. Reference to the new Figure 1 appears in the Methods section on p. 10, and reference to the new Figure 2 appears in the Results section on pp. 15-16.

8. Group differences in VCS scores (as opposed to whether participants scored < max) across exposure categories were analyzed using Kruskall-Wallace ANOVA (based on ranks) followed by post-hoc Bonferroni t-tests. Results of this analysis are summarized in an added table (Table 9) and an added figure (Figure 3). Results are not inconsistent with trend or other analyses, and are discussed on page 16.

9. Logistic regressions were corrected to eliminate adjustment for too many covariates. In the final report adult logistic regressions are adjusted only for age, smoking, and alcohol use; child logistic regressions are adjusted only for age. These are the only factors shown in correlation analyses to be related to VCS scores.

   In general, the corrected regressions indicate odds ratios with considerably smaller confidence intervals, indicating greater confidence.

   Corrected regressions indicate no effect on adult VCS. So, the possibility that perc had an effect on adult VCS has been de-emphasized throughout.

   Corrected regressions still indicate a significant effect of perc exposure on child VCS at 12 cpd.

   Emphasis is placed on the final adjusted regression results.

10. The quantitative exposure-response modeling was de-emphasized given the wide confidence intervals associated with the effect level estimates. And discussion of the indoor air perc levels associated with each of the dry cleaner building exposure categories (< or > 100 $\mu g/m^3$) was added to support consideration of the median perc level in the > 100 $\mu g/m^3$ as a possible LOEL. (see pp 18, 27-28).

11. A separate section entitled Vulnerability of Children was added to the discussion to highlight discussion of whether the data and analyses suggested children might be more vulnerable to perc than adults (pp. 24-25).

12. Additional limitations were added to the discussion. These included:

    the limitation that participants were only tested once and the VCS test has poor test-retest correlation (p. 29);

    the limitation that exposure was hopelessly confounded with race/ethnicity and income and sample sizes were too small to control for this (p. 30);

    the limitation associated with the increased likelihood of observing statistically significant results the more tests that are done (p. 30); and

    limitations associated with the exposure metric (p. 31).

13. A Recommendations section was added suggesting the need for additional research to address limitations associated with VCS testing with the F.A.C.T. as well as to better define indoor air perc exposure effect levels (pp. 31-32).

14. All tables were modified to reflect additional analyses as noted above.

RESPONSES TO REVIEWER COMMENTS

Note: in some cases comments were not offered as an explicit response to a particular charge. These comments are summarized under Charge Question 1, 2, or 3 if they clearly addressed the issues addressed by those questions or under Charge Question 4 if they were less clearly pertinent to Charge Questions 1, 2, or 3.

Charge Question 1. The report attributed a decreased proportion of children achieving the maximum VCS score at 12 cpd, and an increased likelihood (odds ratios) for children to score < maximum VCS score at 12 cpd to increased perc exposure. Is this conclusion supported by the data obtained and analyses performed?

SUMMARY OF REVIEWER RESPONSES

Seven reviewers (1, 2, 4-8) found that the above conclusion was supported by the data and analyses presented in the report. One of these reviewers noted that the conclusion was also consistent with published literature, and another cautioned that the effect was small and could be due to responses of a small number of participants. One reviewer (3) concluded that the above conclusion was not supported by the data and analyses presented in the report largely because the statistical analyses were flawed.

SPECIFIC COMMENTS AND RESPONSES

Reviewer 1

Comment 1:
One key result supporting the conclusion is provided in Table 8. Significant correlations were reported for children with lower VCS scores and scoring less than maximum at 12 cpd, compared to perc concentrations in the indoor air and in alveolar air; increased perc concentrations were associated with lower scores. The comparison of VCS scores and scoring less than maximum to perc concentrations in blood was nearly statistically significant. The fact that the lower VCS score was associated with all measures of exposure at 12 cpd, provides support to the relationship.

Response 1: No change to the report is recommended. However, in response to other comments (e.g., see Comment 8 below) we note that application of multiple statistical tests to the same data increase the chances that a statistically significant result will be observed. Therefore, observation of statistically significant effects across multiple statistical tests does not increase confidence in study findings. We also note that consistency of statistically significant effects of perc on VCS across different measures of perc exposure (indoor air, breath, blood perc level) does not increase confidence in concluding that perc exposure is causative. This is because these measures of exposure are very highly correlated and consistency in perc exposure-response relationships is expected.

However, in both cases a lack of consistent findings would diminish confidence in the overall conclusion that perc exposure was associated with decreased VCS. These concepts have been noted in the Strengths and Limitations section of the final report (p. 30).

Comment 2:
Another key result supporting the conclusion is provided in Table 1. Table 1 considers the influence of increasing perc exposure on the ability of obtaining a maximum score in the VCS test. For children, increasing perc exposure was associated with statistically significant increased odds for scoring less than maximum in the VCS test at 12 cpd. Using the unadjusted data, the relationship was statistically significant for perc in indoor air, perc in exhaled breath at home, and in perc level in blood. When the data were adjusted for race, income, age, gender, resident duration, years of education, volatile organic compound index, blood lead level, and blood mercury level, the relationship remained for perc in indoor air and perc level in blood (although the significance level decreased).

Response 2: No change to the report is required. However, we repeated the logistic regression with control for fewer confounders. Neither race/ethnicity, income, gender, residence duration, years of education, VOC index, nor blood lead or mercury level significantly influenced VCS, and none are included as co-variates in the revised logistic regression. See revised Tables 10a and b, 11a and b. For adults, co-variates included in the logistic regression are age, smoking, and alcohol use; for children, the only co-variate is age. These changes increased sample sizes for adjusted regression analyses and decreased the confidence intervals. Overall conclusions did not change.

Comment 3:
A third key result supporting the conclusion is provided in Table 9a. In this table the percent of children achieving a maximum score is analyzed using the Cochran-Armitage Exact Trend Test. At 12cpd, 37 percent of the children in the reference building achieved a maximum score; in contrast no children in the high perc exposure group achieved a maximum score.

Response 3: No change to the report is required. However, we added statement(s) to the text highlighting the observation that at some spatial frequencies none of the high exposure adults and/or children scored the maximum. See last paragraph, p. 15.

Comment 4:
A fourth key result is the stratification by minority status in Tables 5 and 7. From the tables it is clear that those identified as "minority" were more likely to have had higher exposures to perc and poorer VCS results than "non-minorities."

Response 4: No change to the report is required. However, in response to Comment 53, we noted in the Limitations section (1st paragraph, p. 30) that most high exposures occurred in a small number of minority and/or low income households (n=5-8 adults; n=5-7 children); therefore, an effect of race/ethnicity and/or income on VCS could not be completely separated from an effect of perc exposure on VCS. However, logistic regression analyses indicated an effect of perc independent of race/ethnicity or low income, suggesting that any effect of race/ethnicity or income on the VCS outcome was minor.

Comment 5:
Consequently, these data support the conclusion that a decreased proportion of children achieving the maximum VCS score at 12 cpd, and an increased likelihood (odds ratios) for children to score < maximum VCS score at 12 cpd was associated with increased perc exposure. However, the data have limitations as discussed in the document.

Response 5: No change to the report is required.

Reviewer 2

Comment 6:
The many analyses performed along with the consistency with published literature build a strong weight-of-evidence case for the conclusion that perc exposure in this study population was a contributor to the decreased proportions achieving the maximum. The findings are most robust at 12 cpd, but as discussed similar trends are present in other endpoints. It is difficult to conceive of alternative explanations other than chance. However the consistency with the outcome effects associated with all exposure parameters makes it highly unlikely that the observations are due to chance. It is unlikely that selection biases could account for the findings.

Response 6: No change to the report is required. However, in response to other comments (e.g., Comment 8 below) we have addressed the issue of multiple statistical tests on the same data and using correlated measures of perc exposure as noted in Response 1.

Reviewer 3

Comment 7:
The study was well designed and well conducted.

Response 7: No change to the report is required.

Comment 8:
The analysis of the results involves too many statistical methods and over-interpretation of relatively weak findings has resulted. To quote a colleague "Just like humans, if you torture data hard enough you will eventually hear what you want to hear, whether it is true or not."

Response 8: As noted in Response 1, multiple statistical tests on the same set of data do not increase confidence in findings. However, in some instances (e.g., stratification by race/ethnicity or income) multiple tests are helpful in interpreting results because they help determine what factors, other than or in addition to, perc exposure may have contributed to changes in VCS test performance. Discussion of the rationale for, and limitations of, multiple analyses are added on p. 12 and p. 30 of the final report, respectively.

Comment 9:
It is undesirable to use "nearly statistically significant" relationships as a basis for interpretation when multiple determinations have been made.

Response 9: Discussion of nearly statistically significant as well as statistically significant observations are informative as consideration of both can inform further research based on study findings. To make the text more readable, however, rather than repeatedly indicating whether results are statistically or nearly statistically significant, we have indicated throughout whether the p-value associated with the specific test was < 0.05, or > 0.05 and < 0.10, in accordance with standard practice.

Comment 10:
The conclusion that the results "suggest" an effect is appropriate but there should be an indication that this depends heavily on the validity of the findings at a single spatial frequency (12 cpd) and for worst eye only.

Response 10: Alteration of VCS in only one eye and only at a specific spatial frequency is biologically plausible given that individual eye's optical and central nervous system components that determine VCS function independently (Purves et al. 1997). Change in VCS at a specific spatial frequency is thought to reflect changes to the function of the central nervous system pathways, or channels, that are most sensitive to detecting contrast at that specific spatial frequency. An introductory paragraph has been added to the VCS Test Performance, Vision and CNS section to highlight the value of VCS testing to evaluate CNS function (see p. 25). The remainder of this section presents evidence supporting the notion that an effect at a single spatial frequency is a biologically plausible indicator of an effect on the CNS (see pp 25-26).

Comment 11:
If the core hypothesis is based on Schreiber et al (2002) and NYS DOH (2000) and is "perc reduces VCS at levels found in residences with co-located dry cleaners," these results are not sufficiently robust to prove or disprove the hypothesis.

Response 11: No change to the report is necessary.

Comment 12:
The results do not support a firm conclusion that children are more vulnerable than adults and, as detailed above, some of the logic used to support that conclusion is faulty.

Response 12: As noted in the report, the results "suggest" that children's VCS test performance may be more vulnerable to perc than adults' VCS test performance. A new section entitled Vulnerability of Children has been added to the Discussion to more clearly highlight study findings suggesting that children may be more vulnerable than adults to the effect of perc on VCS (see pp. 24-25).

Comment 13:
Selection of data: The only data presented and analyzed in determining an effect at 12 cpd (children) was that for "worst eye." This despite the opinion (p 10) that "Analyses based on averaged VCS scores would reflect group differences in VCS scores associated with possibly greater functional consequences" than those based on worst eye. That opinion makes sense and thus the results for average of eyes should be shown and given weight in the interpretation. For completeness, the results for "best eye" should also be displayed. Based on Table 10, we assume that no associations were indicated in the omitted results but that is no reason not to consider them, particularly given the "greater functional consequences" of changes in average VCS scores.

Response 13: Additional explanatory information has been added to the report to explain that analyses of the most affected (i.e., worse eye) provides an indication of the maximum possible effect of perc on VCS in this study (see 2nd paragraph, p. 10). Analyses for "better" performing eyes have also been included in the report. "Better" eye analyses provides an

indication of the minimum possible effect of perc on VCS in this study (see p. 10 of final report). Analyses of results averaged for both eyes is not included because individuals' eyes function independently of one another; eyes were tested monocularly; and there is no basis for assuming that VCS scores based on the binocular vision would represent an arithmetic average of the VCS of each eye.

Under the conditions of this study CNS, rather than visual function, was assessed. This is explained in the Section entitled VCS Test Performance, Vision and the CNS (pp. 25-26) and again highlighted in the Strengths and Limitations section (pp. 28-29). These discussions note how both optical (e.g., the pupil, lens) and CNS components (e.g., retina, optic nerve, visual cortex) of the eye contribute to visual function. Explanation has been added explaining how exclusion of those with optical or medical conditions likely to influence VCS controlled for the optical components of vision and allowed assessment of the CNS components of vision.

Comment 14:
Manipulation of results: Data analysis of the primary dependent variable, i.e. contrast sensitivity for each eye, is rendered difficult because of the ceiling effect seen in the VCS scores (maximum possible scored by a number of subjects). These are censored data and there are special statistical techniques that could have been used for analyzing results of this sort. Instead, the authors decided to transform their raw continuous data into counts of subjects with maximum score or with <maximum score. This dichotomous presentation removes the richness of the raw data. We recommend that the results be reanalyzed using an appropriate statistical technique and that the raw data for the scores be made available, perhaps in an appendix.

Response 14: Analyses recommended in Rosner (2006) were applied given the truncated nature of the VCS data obtained. Raw F.A.C.T. data are not continuous. Appendix 2 has been added to the report to explain and illustrate the VCS data obtainable using the F.A.C.T. This appendix also presents the raw data obtained from study participants.

Comment 15:
Some decisions about the data were taken after the information had been acquired. The results for some adults and children were excluded from analysis for various reasons (p 12) - these subjects should have been excluded prior to testing. In particular, results for young (less than 6 years) children, children said to be learning disabled or exhibit ADHD were excluded from analysis. By taking these decisions after collecting data, inadvertent bias may have been introduced. The cut-off for children's age is shown as 9 (p. vi), 5 (p. 4) and 6 (p. 12). It may be necessary to display (even analyze) data for all completed tests to demonstrate the effects of selecting results to omit (in particular an age cut-off).

Response 15: All volunteers for this study were offered a complete eye exam, including VCS and color vision testing, if they wished. Hence, excluding volunteers prior to testing was not an option. After testing and prior to analyses, VCS and color vision results were eliminated if participants met exclusion criteria which had been established *a priori*. For both adults and children this included anyone with eye or medical conditions known to influence vision. For children, analyses were also excluded if they were less than 6 years old or had conditions (such as a learning disability, autism) that might contribute to poor performance on the VCS test. Data for children < 6 years old were excluded when clinicians administering the VCS test observed they were often unable to attend sufficiently during the VCS test to provide

reliable results. Participants were also excluded if their visual acuity (which is different than VCS) was worse than 20/25 and could not be corrected to at least 20/25. This criterion excluded participants with optical characteristics, such as astigmatism, which might interfere with VCS testing. Exclusion of participants based on pre-established exclusion criteria allowed an assessment of the CNS component of the visual system, which was the goal of this study. Without these pre-established exclusion criteria, the influence of perc exposure on VCS test performance would be difficult to separate from the influence of other conditions or poor acuity. The report includes explanations of the rationale for study procedures and exclusion criteria in the Participant Recruitment (p. 4), and Visual Function (p. 8) sections of the Methods section as well as in Table 2 of the final report.

The children's age range on page vi simply refers to the ages of children for which VCS data were obtained. The age range of 5-14 years noted on page 4 was to identify eligible households with children for this study. During recruitment, before testing, it was anticipated that children as young as 5 would be able to perform the VCS test. Subsequent observations in the clinic convinced clinicians administering the test that, for 5 and 6 year old children, the test was too difficult to perform due to inattention, inability to sit still, etc. and VCS test results from these young children were unreliable.

Comment 16:
Display of data: Figure 1 does not allow any close comparison of the results dry cleaner vs. reference. Presented this way it looks as though there is no difference worth discussing between exposed and unexposed. If the recommendation to work with censored data techniques is followed, a new diagrammatic presentation may develop, but the present results could be shown in a full page for adults and another for children with result for reference and dry cleaner side by side on a single graph.

Response 16: Figure 1 in the draft report presented a summary of the quantitative VCS scores at each frequency for each group using box and whisker plots and was intended to demonstrate that a ceiling effect was present. Because of the ceiling effect, differences between groups are not apparent. To provide a better idea of the range of VCS scores, new figures have been included in the final report which illustrate the absolute number of participants and the percentage of total participants achieving each score at each spatial frequency (cf. Figures 1 and 2). Also, raw VCS scores for all participants have been included in Appendix 2.

Comment 17:
Statistical significance: A large number of data analyses have been performed on VCS data (worst eye), whether adjusted or unadjusted, at 5 spatial frequencies, indoor air, breath at home or clinic, children and adults etc. Given that a large number of p values has been derived, it is to be expected that some will show statistical significance by chance alone. That would be true when $p < 0.05$ is the criterion employed for Type 1 errors and any result with a p value close to 0.05 must be considered potentially due to chance alone. The use of "near statistical significance" as the indicator of an effect for p values < 0.1 compounds this likelihood of the result being due to chance alone. All use of near statistical significance should be removed (tables and text) because of its unreliability as an indicator. The interpretation of results with p just below 0.05 should be approached with caution and that caution should be spelled out in the report.

Response 17: Limitations of the outcome variable (e.g., ceiling effect), low incidence of elevated perc levels in dry cleaner buildings, and a higher prevalence of elevated perc in minority and/or low income households were unanticipated observations of this study. Many types of analyses were applied to assess associations of perc exposure with VCS test performance given the characteristics of the data obtained. These analyses were helpful in determining whether race/ethnicity and/or income were confounders of the perc exposure-response relationship, and also in assessing whether children might be more affected than adults by perc exposure. Consideration of nearly statistically significant as well as statistically significant tests are informative when exploring unanticipated observations. Therefore results when $p < 0.05$ and when $0.05 < p < 0.10$ are presented. However, text has been added noting the likelihood of observing one or more statistically significant result when multiple tests are applied to the same data as noted above in Response 1. Also the text has been simplified by indicating p-values (i.e., $p < 0.05$; $0.05 < p < 0.10$) instead of repeatedly using the terms “statistically” or “nearly statistically” significant.

Given the limitations of the findings of this study, we agree that even the results of the logistic regression are viewed as preliminary. Hence, emphasis is placed more on consideration of increased odds for decreased VCS in the context of the 95 percent confidence intervals, and less on whether the increased odds are “nearly statistically” or “statistically” significant. This changed interpretation has been included in the final report when discussing logistic regression results on pp. 22-23 and 24.

Comment 18:
Correlations for reference buildings: On p. 13 it is stated that “a statistically significant correlation between increased residence duration and scoring <max at 12cpd [should this be 18 cpd?] may be spurious, since there is no reason to expect that residence duration of reference building residents would have influenced their VCS test performance.” This fallacy may be classified as “denying the antecedent” – something like “if people are exposed to perc they have vision problems...if they are not exposed they cannot have vision problems.” Another way to look at the results is that there are good reasons for using controls: If similar results are obtained in control and treated groups, the first and simplest interpretation to consider is that they can be explained by the same factor (Ockham’s razor). The same fallacy is committed at the top of p.14. These correlations are as “real” as those relating to perc exposure, and simply dismissing them could be seen as introducing (presumably unintended) bias.

Response 18: The report has been changed throughout so that all statistically significant correlations are appropriately interpreted as noted in this comment. No observations are noted as being "spurious."

Comment 19:
Correlations: Statistically significant ($p<0.05$) correlation between VCS measurements and perc levels in air, breath, or blood have been recorded in Table 8 for adults at 18 cpd and in children at 6 and 12 cpd. There are two points to be made: (i) The statistically significant correlations range from 0.22 to -0.35; this means that between 5 and 12 percent of the difference between control and exposed might be explained by perc – the remaining 95 to 88 percent having to be explained by other independent variables. This is noteworthy information. (ii) Adults showed a statistically significant correlation limited to score <max and perc breath level (at home) for 18 cpd. Children had a statistically significant correlation for 6 cpd between score <max and perc blood level only. At 12 cpd, the statistically significantly correlations for both VCS score and score <max were confined to indoor air level and breath level (at home).

Thus the information shows that there is no common pattern of response between adults and children (correctly noted in the report), that the response (if any) in children is limited to specific comparisons and that there is no consistent support between different spatial frequencies. Perc represents at most 12 percent of the variance found in this analysis.

Response 19: The text of the report was modified to better describe the meaning of Spearman correlation coefficients (see p. 15), and to reflect the observation that most coefficients were very small (close to zero) indicating that VCS scores at most spatial frequencies, when the entire study population was considered, were not correlated with any measure of perc exposure. Perfect correlations would result in correlation coefficients of 1.0 or –1.0. Table 8 was modified to illustrate coefficients between perc exposures and VCS scores only for clarity, and to include correlation coefficients for better performing as well as worse performing eyes. Despite these clarifications, we agree that the correlations provide little evidence that perc exposure influences VCS score. However, these correlations, when considered along with the results of trend analyses and logistic regression, are not inconsistent in suggesting that perc exposure is associated with decreased VCS of children's worse eyes, specifically at 12 cpd. These correlations, however, are not emphasized in the report.

Comment 20:
Exploratory approaches: Tables 9a through 13 provide different cuts/views on the same data. They could be seen as a way of generating hypotheses – any interesting hypothesis would have to be tested in a specific study that follows the scientific method. As it is, these multiple analyses are bound to show relationships that are statistically significant or nearly significant whether there is a true relationship, one that has arisen by chance, or one that has arisen because of an unrecognized confounder. If these treatments are to remain in the report, the nearly statistically significant identifier should be removed and the "hypothesis setting" character should be acknowledged. It is interesting that the authors are willing to reject statistically significant associations between reduced VCS and duration of residence or "improved" color vision (adult and child) and perc exposure as "spurious" but are prepared to accept even "nearly statistically significant" elsewhere.

Response 20: As noted in Response 17, text has been added to the report noting that the unexpected nature of the observations (e.g., VCS ceiling effect, high exposures in minority and/or low income households) led us to perform a variety of different analyses. As noted in Response 1, we acknowledge that multiple analyses on the same data increases the likelihood of observing "significant" or "nearly significant" relationships that may be due to chance or to unrecognized confounders and have added discussion of that to the report as noted in Response 1. Also, references to "spurious" observations have been removed as noted in Response 18.

Comment 21:
Discussion/Interpretation: Nearly statistically significant findings: Please do not use "nearly statistically significant" results to add weight to interpretations anywhere in the Discussion (see 1.4 above).

Response 21: See Response 17.

Comment 22:
Adults: The correct degree of caution is displayed (pp. 19-20) until the last sentence where "a very subtle effect" is suggested. This is probably too speculative given the degree of uncertainty as to whether an effect exists at all.

Response 22: We agree that study results are insufficient to suggest a subtle effect of perc exposure on VCS of some adults. The statement referred to has been removed from the report.

Comment 23:
Children: The interpretation is dominated by a possible effect at 12 cpd. It has to be recognized that the dip at this spatial frequency could have arisen by chance (as the authors claim for an apparent effect of residence time or perc improved color vision). Such a wobble would then show up in any number of data manipulations – so statistical significance in multiple manipulations does not add weight to the interpretation. The opinion that the statistical significance obtained for indoor air, exhaled breath (home only) and blood levels adds weight is incorrect because these measures are not independent (they should be highly correlated).

Response 23: As noted in Response 10 above, alteration of VCS in only one eye and at a specific spatial frequency is biologically plausible given that individual eye's optical and central nervous system components that determine VCS function independently (Purves et al. 1997). Change in VCS at a specific spatial frequency is thought to reflect changes to the function of the central nervous system pathways, or channels, that are most sensitive to detecting contrast at that specific spatial frequency. So, there is reason to conclude that an effect at a single spatial frequency, in this case at 12 cpd, is not a "chance" event, but possibly a real one. Response 10 describes the changes made in the final report to clarify this issue.

The issues of multiple statistical analyses on the same data some of which are correlated (perc exposure measures) are valid ones and have been addressed as noted in Response 1.

Comment 24:
The analysis of child-adult differences is used to suggest a greater vulnerability of children to perc but this hangs on a "nearly statistical significance" at 12 cpd. The evidence is too weak to conclude an increased vulnerability.

Response 24: The results of paired analyses only suggest the possibility that children may be more vulnerable than adults at the specific spatial frequency of 12 cpd. However, the conclusion that children may be more vulnerable than adults is also based on consideration of trend analyses and logistic regression results which also indicate that increased perc exposure is associated with decreased VCS, specifically at 12 cpd, in children but not in adults. To clarify and discuss study findings consistent with the notion that children may be more vulnerable than adults, the Discussion section now includes a section entitled Vulnerability of Children.

Comment 25:
Although the data in Table 6b do not seem to show it, much is made of the lower level of perc in blood in children vs adults from the same household. This is perhaps to be expected: After exposure ceases, children will exhale unmetabolized perc more rapidly and have less perc held in a lipophilic reservoir; the longer the time from exposure to the time of blood and breath being taken at the clinic, the wider the gap between adult and child even if levels when departing home were similar. I do not know what is in Mazor et al, but a back PBPK calculation from measurements at the clinic to blood and breath levels at home could be interesting. Bottom line: greater vulnerability of children is unproven here and speculation about pharmacodynamic differences unwarranted.

Response 25: Additional analyses are needed to evaluate whether children may be more vulnerable than adults based on pharmacokinetic or pharmacodynamic differences. This suggestion has been included in the report in an added Recommendation section.

Comment 26:
Mutual support between indoor air, breath and blood: As discussed above, these parameters are expected to be correlated – do not increase confidence in the result, therefore.

Response 26: Consistency of statistically significant effects of perc on VCS across different correlated measures of perc exposure (indoor air, breath, blood perc level) does not, by itself, increase confidence in concluding that perc exposure is a causative factor in decreasing VCS. However, because the correlations observed in this study between all measures of perc exposure (in indoor air, breath and blood), and the associations between some measures of perc exposure and VCS decreases fits within the context of established literature, overall confidence in study findings is increased. Changes in the final report noted in Response 1 address these issues.

Comment 27:
Vulnerability of children: Just because adults show no definite effect does not mean that the possible effect in children at 12 cpd is real and indicative of vulnerability. The paired adult-child differences analysis does not increase confidence in children's greater sensitivity.

Response 27: Please see Response 24.

Comment 28:
Consistency across different types of statistical treatment: Sorry, does not help if the apparent reduction in VCS performance at 12 cpd is due to chance (or unrecognized confounder), you would still expect statistical significance in many tests.

Response 28: Please see Response 1.

Comment 29:
Maximal scores: Yes, such a high proportion of children achieving maximal scores is a constraint on the interpretation (and we suggest use of a statistical technique for censored data). However, it cannot be said that "these results do not convey the magnitude of alterations in VCS associated with perc exposure." This suggests that you know perc has a larger effect that was hidden – in reality, you just do not know.

Response 29: The phrase noted was not intended to convey that perc had a large effect on VCS, but that the size of the effect of perc on VCS, if any, is unknown. This has been clarified on p. 29 in the final report to read "…….. these results do not convey the possible quantitative magnitude of alterations in VCS associated with perc exposure."

Comment 30:
General conclusions regarding effects: An appropriate amount of caution is indicated but 12 cpd should be indicated as the driver for the "suggested" effect in children.

Response 30: Discussion throughout the final report emphasizes that the most consistent perc exposure-related observation was decreased VCS at 12 cpd among children. This is especially apparent in a revised summary Table 14.

Comment 31:
Vulnerability of children: No conclusion possible.

Response 31: A firm conclusion about the vulnerability of children is not possible, but we believe that the results of the analyses of these data are suggestive. Please see Response 24.

<u>Reviewer 4</u>

Comment 32:
The data, as analyzed, support that children are more likely to score less than the maximum VCS score at 12 cpd. The study carefully controlled for possible confounding health conditions and other exposures that could also affect VCS performance. Furthermore, the conditions for collecting VCS test performance including blinding of examiners adds to the confidence of the

measurements. The analysis of the data was performed carefully and interpretations fit the data collected.

Response 32: No response required.

Reviewer 5

Comment 33:
The conclusion that there is an increased likelihood for children to score < maximum VCS score at 12 cpd is supported by the data obtained and analyses peformed. Tables 1 and 11b provide the clearest illustration of the significant increase in Odds Ratio associated with ambient monitoring or internal level as assayed by exhaled breath.

Response 33: No response required.

Comment 34:
With reference to a decreased proportion of children scoring < maximum VCS score at 12 cpd, I am confused by figure 1d compared to Table 9a. My understanding of Table 9a is that 0 percent of children in homes with > 100 $\mu g/m^3$ scored the maximum value; in Figure 1d, the box plot goes up to the maximum achievable score mark.

Response 34: Figure 1 only illustrates VCS scores for two groups: residents of reference buildings and residents of dry cleaner buildings. Figure 1 is not directly comparable to Table 9a which represents VCS test performance for three exposure categories: residents of reference buildings, residents of dry cleaner buildings where perc < 100 $\mu g/m^3$ and residents of dry cleaner buildings where perc > 100 $\mu g/m^3$. Nevertheless, Figure 1 has been changed to a "bubble plot" in the final report to better illustrate the actual scores achieved by participants. Figure 1 now illustrates both the numbers of participants achieving a particular score and also the percentage of participants achieving each score. Additionally, a new Figure 2, also a "bubble plot," has been added to illustrate the numbers of participants achieving each VCS score in each of the three exposure categories. Both figures include illustrations for worse and better performing eyes, and both allow the reader to relate summaries of data appearing in tables to group VCS functions. Both figures better illustrate the distribution of actual VCS scores.

Comment 35:
Given the significant differences in Odds Ratios, in fact, I expected to see a more notable difference in the VCS functions across spatial frequencies when comparing Figures 1c and 1d. Does this lack of difference on the Contrast sensitivity scale reflect the small magnitude of the measured effect on contrast sensitivity, particularly when compared to the dichotomized results?

Response 35: Comparisons of odds ratios for decreased VCS associated with increased perc exposure with data in Figure 1 are problematic. Figure 1 in the draft report dichotomized participants into two groups (reference or dry cleaner building residents) and simply summarized the scores using box and whisker plots. Logistic regression uses VCS test performance from all participants (reference and dry cleaner building residents) and assesses

the associations between increases in perc exposure and VCS test performance. Comparability of the two ways of handling study data would not be expected.

The box and whisker plots in Figure 1 of the draft report were intended to convey our initial observation that VCS scores exhibited a marked ceiling effect for both children and adults and for both reference and dry cleaner building residents. We agree that differences in VCS between adults and children and between reference and dry cleaner building residents are not well illustrated using a box and whisker figure. As noted in Response 34, Figure 1 has been changed to a "bubble plot" in the final report to better illustrate the actual scores achieved by participants. Figure 1 now illustrates both the numbers of participants achieving a particular score and also the percentage of participants achieving each score. Additionally, a new Figure 2, also a "bubble plot," has been added to illustrate the numbers of participants achieving each VCS score in each of the three exposure categories. Both figures include illustrations for worse and better performing eyes, and both allow the reader to relate summaries of data appearing in tables to group VCS functions. Both figures better illustrate the distribution of actual VCS scores.

We have also revised the adjusted logistic regression analyses to eliminate inappropriate inclusion of multiple correlated co-variates. The resulting odds ratios are much smaller, although still increased in some cases, and are associated with much smaller confidence intervals. Modified discussion in the text on p. 21 notes increased odds ratios for not achieving the maximum scores at some spatial frequencies for children without emphasizing the size of the odds ratio or its statistical significance.

Reviewer 6:

Comment 36:
I consider this conclusion to be well supported by the data that you obtained and by the analyses that you performed. It is important to bear in mind that it is inherently very difficult to discern an association between an environmental exposure and a neurobehavioral effect. Detection of an association is especially difficult when the environmental exposure is transient. Perc is a highly volatile compound and is therefore rapidly dissipated in air. It also has a relatively short residence time in the human bloodstream. It is therefore inherently very difficult to discern associations between perc exposure and neurobehavioral outcomes. This difficulty is somewhat ameliorated in the present situation in that the existence of a dry cleaning establishment in a residential building creates a somewhat stable exposure scenario. But nonetheless, the difficulty of discerning associations with volatile organic compounds should not be underestimated, and it needs to be borne in mind that this inherent difficulty in exposure assessment inevitably biases towards the null the ability of investigators to detect associations.

Therefore, in light of this difficulty in ascertaining associations, I consider it highly credible that an association was indeed observed in this study and that the associated effect was in the hypothesized direction, namely that increasing levels of exposure were associated with diminishing levels of performance.

Response 36: No response required.

Reviewer 7:

Comment 37:
I am not a specialist in the statistical techniques used, but it is my impression that the analysis was competently done and the results properly described. It seems clear that the changes in VCS associated with perc exposure in the range of indoor exposure in buildings with co-located dry cleaners are small and subtle, with the biggest changes in response in children at 12 cpd. The text, tables, and figures present the data and the results of the statistical analysis.

Response 37: No response required.

Comment 38:
My impression from reading through the draft report is that the test results provide evidence for an association between perc exposure, especially as measured from blood and breath samples, and VCR response in children and adults. A causal relationship between the perc exposure and the VCS changes seems plausible, particularly in view of other data from previous studies at higher levels of perc exposure. Central nervous system (CNS) effects are well established in the scientific literature for perc and a variety of other chlorinated solvents, some of which have been used as anesthetics.

Response 38: No response required.

Comment 39:
The decrement in VCS from perc exposure seems to be a small effect that shows up with the application of sophisticated statistical tests. The sample sizes from the number of subjects are not large (65 households in the buildings with dry cleaners; only about 10 adults and children from the high-exposure buildings and about 40 from low exposure buildings gave valid VCS test results: see Tables 3 and 4). The results from only a few of these subjects may be responsible for statistical significance.

Response 39: The small number of participants in the highest exposure group is a limitation of this study. This is noted in the Limitations section on p. 30.

Comment 40:
I am not a specialist in the statistical techniques used, but it is my impression that the statistical analysis was competently done and the results properly described. The report is well organized and well written. There are few typos or other editorial problems needing fixing. (One is the sentence on page 26, lines 9-10, which appears to be missing a word, such as “this,” following the second comma.)

Response 40: No response required.

Reviewer 8:

Comment 41:
The data are at least suggestive, and are certainly disturbing.

Response 41: No response required.

Charge Question 2: Are limitations and strengths of the study adequately described and appropriately considered?

SUMMARY OF REVIEWERS COMMENTS

Four reviewers noted that strengths of the study were adequately described (1, 3, 6, 8); three reviewers had no comment regarding strengths (2, 4, 7); and one reviewer (5) noted that the specificity of an effect at 12 cpd may not be a strength, as noted in the report.

One reviewer noted that the limitations had been adequately described (6), and another had no comment (7). Other reviewers noted limitations not adequately discussed in the report were: uncertainty associated with interpreting the meaningfulness of VCS test results in general and of an effect at only one of several cpds tested specifically (1); reduced power associated with the need to address confounders (2); reliance on inappropriate statistical analyses (3); reliance on VCS test results from only "worst" performing eyes (3, 8); possible bias in results due to exclusion of some participants after testing (3); uncertainty in whether the observed effect may be due to acute and/or chronic perc exposures (4, 5); possible unreliability of a single VCS test result (4); inability to completely control for minority status in analyses since race/ethnicity and exposure are confounded (4); uncertainty associated with the indoor air perc levels measured (8); limitations associated with the VCS ceiling effect observed (8); and, the need to replicate the observation (8). These comments are addressed below.

SPECIFIC COMMENTS AND RESPONSES

Reviewer 1:

Comment 42:
One limitation mentioned was that since a high proportion of the participants scored as well as possible on the VCS test, the variable had to be compared from a categorical perspective. Although this is a limitation of the study, it also indicates the strength of the result. That is, the outcome variable was fairly insensitive, thus obtaining a result supports the conclusion of an actual effect. Further, using nonparametric statistics are generally not as powerful and therefore less likely to obtain a significant effect.

Response 42: Given the nature of the outcome variable the actual size of an effect of perc on VCS, if any, is unknown. Largely for this reason we believe the nature of the outcome variable is a study limitation. This is noted in the final report on p. 29. The outcome measure can be viewed as being insensitive because it does not reflect variability in actual VCS scores. This is reflected by the large percentages of those tested who scored as high as possible. Although we know these individuals scored well on this test, this test does not allow us to know how much higher than the maximum score on the F.A.C.T. they may have achieved. This consequent lack of information may have made differences in VCS more difficult to detect. Thus, although dichotomization of the VCS measure may be viewed as a limitation of the study, the observation that perc significantly affects this limited measure for children's worse eye at 12 cpd may be an indication of the strength of a reponse to perc. That is, even though the outcome measure was insensitive to quantitative changes in VCS in response to

perc exposure, the effects on dichotomized responses were still strong enough to suggest perc related effect. These concepts have been noted in the Discussion of the final report on p. 21.

The dependent variable in this study very clearly did not meet assumptions for parametric analyses. When the assumptions required for parametric analyses, such as normal distribution of the dependent variable, are not met then it is not necessarily true that non-parametric tests applied to the same data are less powerful (Tomkins 2006). Therefore, it cannot be concluded that the non-parametric analyses applied in this study were less powerful than parametric analyses and therefore less likely to detect a significant effect.

c.f., Tomkins C. C. (2006) An introduction to non-parametric statistics for health scientists. Univ. Alberta Hlth. Sci. J. 3(1):20-26

Comment 43:
Another limitation mentioned in the study is meaningfulness of the result. Particularly, since one is measuring the number of scores of maximum in the test, the question is raised as to whether the result, while significant statistically, is important biologically. This issue is the basis of the second question below. A related limitation is the meaning of a specific result in a test that is conducted at a range of frequencies. Due to the fairly limited use of this type of test method in evaluating dose-response relationships, possibly a little more information on the method and its use would be helpful, at least in the appendix.

Response 43: Appendix 2 describing the F.A.C.T. and summarizing raw data scores for study participants has been added to the final report.

Comment 44:
The strengths of the study are fairly well detailed in the report. The strengths include the multiple exposure measures, the precision of the result at 12 cpd, the presence of the result increasing with dose, the presence of the result even after adjusting for a large number of possible confounding variables, the consistency of findings using several different statistical analyses, the rigorous selection criteria for including participants, the presence of matched controls, the presence of the effect being stronger in children than adults and the use of an objective criterion, VCS results. However, the strengths of the study can be further identified by the nature of the association between exposure to perc and VCS results.

Response 44: The strengths of the study have been adequately described in the final report. It is not clear what is meant by “strengths of the study can be further identified by the nature of the association between exposure to perc and VCS results.”

Comment 45:
Methodological issues that could be considered in the review of the study include: 1) the sample size of the study, which affects the power to detect an effect; 2) the extent to which the analysis or design takes into account potential confounders, or other risk factors; 3) selection bias, or whether the study groups were comparable; and 4) the potential for bias in ascertaining exposure. Each of these factors appears to be addressed in the present study. The sample size is fairly large. Potential confounders were considered and were taken into account in the analysis. The comparability of the groups appears to have been addressed. Finally, exposure bias was addressed using three exposure measures.

Response 45: No response required.

Comment 46:
Several factors can be considered to evaluate the association between perc exposure and VCS score that underline the strength of the study: strength of association, consistency, temporality, biological plausibility, dose-response and specificity. A strong association between a factor and a disease (historically considered to be a relative risk or odds ratio ≥ 2; and statistically significant) makes alternative explanations for the disease less likely. In this case, the odds ratios are greater than 2, providing support for the association. If several studies find an association between a factor and a disease, then the factor is more likely to be causal. In this case, the neurological tests, such as the VCS response have been measured in a number of populations and circumstances, and found to be an effect of perc, and supporting causality of the relationship. In this study it appears easy to associate the exposure with the response in terms of temporality. A causal interpretation cannot conflict with what is known about the biology of the response. In this case, the neurotoxic properties of perc are well accepted, and have been shown in humans as well as laboratory animals. Further, a reasonable hypothesis is that perc is affecting dopaminergic pathways in the frontal cortex of the brain which is causing the effect. Further, this study demonstrates the presence of a dose-response, as exhibited by the various trend tests used to evaluate the data. Finally, specificity is generally interpreted to mean that a single cause is associated with a single effect. In this case, the importance of other causes is not well understood. However, substantial effort was made in the study to eliminate the influence of other factors in the analysis. Thus, the conclusions are well supported by the data obtained and the analyses performed.

Response 46: No response required.

<u>Reviewer 2:</u>

Comment 47:
This was a carefully constructed and rigorously implemented complex study. It provides a rich data set that was exhaustively investigated and analyzed. It is by far the most comprehensive study to date of VCS and perc exposure with multiple exposure measures. Despite the effort the complexity of potential confounders quickly reduced the statistical power of the study. Thus, while the statistical "p value" criteria are important, the sample sizes resulted in reduced power and the weight-of-evidence and consistency of the observations is important in interpreting the results.

Response 47: A discussion of the limitations associated with the small number of participants in the highest exposure group has been added to the text on p. 30. Also, as noted in Response 1, consistency of statistically significant results across different analyses, or based on correlated measures of exposure may not explicitly increase confidence in findings. However, inconsistencies across statistical analyses and exposure measures would tend to decrease confidence in those inconsistent significant results

Comment 48:
It might be useful if there were some mention of the target sample size included in the grant application.

Response 48: Text describing the calculation of appropriate sample sizes for this study has been added to the Results section, pp. 4-5, of the final report.

Comment 49:
It would also be helpful to have some discussion of the types of diseases and conditions that have been associated with VCS findings.

Report 49: This information is noted on p. 8 in the Methods section.

Reviewer 3:

Comment 50:
Comments on the strengths and limitations, as reported, are given above. With the exceptions noted, the strengths and limitations have been correctly identified.

Response 50: No response required.

Reviewer 4:

Comment 51:
The authors acknowledge that the perc measurements reflect current levels and therefore in the present study, they cannot determine whether the effects observed are due to the combination of chronic and acute effects or simply acute effects. This issue speaks to the public health relevance. If the results observed are transitory resulting from acute exposure, then they are of relatively less concern than if the effects are permanent. A clear statement indicating that the present study cannot address this issue should be added to the last paragraph in the limitations section.

Response 51: Text indicating that the present study cannot address whether chronic, acute, or chronic plus acute exposures has been emphasized in the final report on p. 31.

Comment 52:
However, this can only be considered a preliminary finding for several reasons. VCS was administered only once for each eye. Although not routinely done in all studies, the reliability of the findings would have been improved by having participants perform this test twice per eye as recommended for research in the F.A.C.T. manual (Stereo Optical Co., 1993). The possible unreliability of measurement particularly with children should be acknowledged in the limitations section.

Response 52: Text addressing the possible unreliability of analyses based on single VCS measurements has been added to the report on p. 29.

Comment 53:
Also, it appears that minority status and exposure are confounded in the study. There simply were not enough children in the non-minority, > 100 $\mu g/m^3$ group to be confident that the effect is not somehow related to minority status. Furthermore, a large percentage of children in the

reference homes also did not perform at the maximum for 12 cpd and minority status is correlated with lower VCS performance. Thus, one cannot fully rule out the effects of ethnicity on test performance. This also needs to be acknowledged clearly in the limitations.

Response 53: Text discussing the inability to separate out a possible effect of race/ethnicity or income on VCS from a possible effect of perc due to the small number of non-minority and higher income participants in the highest exposures category has been added to the report on p. 30.

Reviewer 5:

Comment 54:
I have one reservation about the description of the strengths of the study; it is not clear to me that the specificity of the effect at 12 cpd is a strength, since there is, at this time, no strong mechanistic link that would lead one to expect an association with this particular spatial frequency.

Response 54: The specificity of an effect at 12 cpd is probably not best considered a strength. Evidence for an effect at 12 cpd is more an observation that is consistent with other observations of the effect of volatile organic compounds on VCS at middle frequencies. It therefore suggests that an effect of perc at 12 cpd is plausible. This is discussed in the Discussion section of the final report entitled VCS Test Performance, Vision and the CNS, pp. 25-26.

Comment 55:
PERC is rapidly cleared from the body, as can be observed in a comparison of the exhaled PERC levels from taken in the residence and at the clinic. If the change in VCS function is a result of compound on board, then the measurements taken at the clinic may, in fact, underestimate the functional deficit and reduce both the magnitude of the effect and the likelihood of detection of the effect. I note that in Table 6A, the level of PERC exhaled by children dropped 2/3 in the comparison of residence to clinic, where for adults it dropped by only 1/2, perhaps due to the more rapid ventilation rate of children.

Response 55: Using indoor air perc levels at home and VCS measurements at the clinic for exposure-response analyses might underestimate the effect of perc on VCS, especially if it is an acute effect, if there is one. However, based on comparison of clinic breath perc levels for matched adults and children summarized in Table 6b, the apparent rate of perc elimination between home and clinic for adults and children is similar. Among these matched pairs, levels of perc in breath decreased by about 2/3 for both adults and children. Therefore, when considered matched pairs of adults and children, exposures measured at the clinic do not appear to differ between adults and children.

Reviewer 6:

Comment 56:
I consider the limitations and strengths of the study to be adequately described and appropriately considered.

Response 56: No response required.

Reviewer 8:

Comment 57:
One issue not discussed is how variable perc levels might be (air, breath, blood) through the day. Is it possible, for example, that levels were measured during business hours, when the cleaners were active but no one (especially school age kids) was at home? Trends reported in results might thereby be either confounded or maybe even strengthened.

Response 57: As noted in the Methods section of the report, indoor air perc levels were measured over a 24-hour period beginning on Monday, Tuesday, or Wednesday afternoons and ending the following afternoon. The resulting air levels reflect a time weighted average of perc in air over the entire 24-hour period. Sampling on these days was done to measure perc levels during the week, when dry cleaners were most likely operating. It is likely that these 24-hour TWA measurements will vary over time for any one household depending upon a variety of factors such as operating conditions of the dry cleaner, ventilation of the home, etc. Individual exposures will also vary depending upon the time spent at home, etc. Also, relating single indoor air perc levels at home to these factors as well as single VCS measurements at the clinic in exposure-response analyses has some uncertainty. Additional discussion of these issues has been added to the report on p. 31.

Comment 58:
It would be ideal for the study to be repeated, perhaps by another research team. I have concerns about the ceiling effect and the possibility that spurious changes in the probability of scoring the maximal level in a few cases might be responsible for the principal conclusion. On the other hand, the consistency of findings from different analyses is fairly convincing.

Response 58: Ideally, additional research should be conducted to further evaluate the preliminary findings in this report. It should be recognized though that the likelihood of conducting another very similar study is diminished due to federal changes in the regulation of co-located dry cleaners. Recommendations for additional research are included in the final report.

Charge Question 3: VCS of both adults and children was in the upper range of what is considered normal for the VCS test administered. Nevertheless, significant associations between increased perc in indoor air, breath, and blood of children and decreased performance on the VCS test were observed. Should the decreased VCS test performance observed be considered an adverse effect?

SUMMARY OF REVIEWER COMMENTS

Two reviewers concluded that the observed decreased VCS test performance should be considered adverse (2, 6); three reviewers were uncertain as to whether the observed VCS decrease was adverse (1, 5, 8); and three reviewers concluded that the effect was not adverse (3, 4, 7), although one of these noted that the results may be cause for concern for those with pre-existing impaired VCS were exposed to levels of perc > 1000 $\mu g/m^3$ repeatedly (7).

SPECIFIC COMMENTS AND RESPONSES

Reviewer 1:

Comment 59:
This question needs to be addressed from several perspectives. Looking at the effect from an individual perspective, one could argue that the effect is in the normal range, and that the measure is subclinical. While this may be true, one still must consider that exposure to fugitive emissions of perc from drycleaners within the same building is resulting in measurable levels in expired breath as well as blood, and in a visual change. One striking result is that none of the children in the high exposure group achieved a maximum score at 12cpd. Thus, the high exposure group should be considered the lowest observed adverse effect level (or lowest observed effect level). The choice of using VCS is in part due to the simplicity of performing the test, the lack of invasiveness of the test, and background information indicating that perc can affect the visual system. Thus, while VCS is measure of the effect of perc, it is also an indicator of possible effects of perc throughout the body that may not be measurable.

Response 59: Discussion of the relationship between alterations in VCS test performance and other possible change, i.e., in the CNS, is presented in a section entitled VCS Test Performance, Vision and CNS on pp. 25-26 of the final report. Consideration and discussion of median group indoor air perc levels as lowest or no observed effect levels has been added to the report in the context of the exposure-response analyses on pp. 27-28.

Comment 60:
The visual contrast sensitivity test was chosen as a clinical/subclinical indicator of neurotoxicity. The positive results indicate the possibility of some neurotoxicological injury. While the extent of any injury would likely be minor, based on the sensitivity of the test, it is detectable. However, as stated in the report, reduced contrast sensitivity can also indicate an effect on, or damage to, the centrally mediated visual pathways in the brain. As indicated in the report, VCS is an important characteristic of vision. Everyday activities, including learning for children, can be adversely impacted if an individual's ability to detect contrast is impaired.

Response 60: These issues are noted in the section entitled VCS Test Performance, Vision and CNS on pp. 25-26 of the final report.

Reviewer 2:

Comment 61:
VCS is an important visual function. Reduction in VCS can lead to adverse consequences and thus decreases should be considered adverse. It is likely that the changes detected represent early changes in the continuum leading to clinically abnormal VCS. Only prospective observation will be able to determine the impact of the changes documented.

Response 61: Discussion of this issue has been added to the text in a Recommendations section of the final report beginning on p. 31.

Comment 62:
The high proportion of individuals scoring at the maximum can partially be explained by the strict exclusion criteria as well as the efforts to correct the visual acuity of all participants before testing. Thus selection criteria and testing conditions were truly maximized for high performance among those tested. Given the selection criteria it is not surprising that none of the individuals tested had VCS endpoints in the "clinically abnormal" range.

Response 62: Reference to participant exclusion criteria as a contributor to the observation that no results in the "clinically abnormal" range were obtained has been added to the Discussion on pp. 20-21.

Reviewer 3:

Comment 63:
If the possible reduction in VCS performance is real then it is technically "adverse." However, is it of concern? Starting from the question "if there is an effect, is it of functional significance?" The answer is clearly "no" for the experimental subjects. There is no indication that those naturally at the lower end of the range of normal are pushed into an abnormal classification. The other important factor is that, as indicated in the report, the average performance for both eyes has more functional significance than the worst eye alone. We assume since results are not presented for the average that no perc-related effects were evident (also based on Table 10). We recommend that the results for the average and best eye be included in the report. If the "effect" is truly apparent in one eye only, that will need some explanation – one interpretation being that the worst eye result is "spurious," to use a term from the report.

Response 63: As noted in Response 13, analyses of results averaged for both eyes is not included because individuals' eyes function independently of one another, and eyes were tested monocularly. Therefore each eye is associated with its unique VCS function. Further, while it is true that functional vision is the result of centrally mediated integration of images from both eyes, there is no apparent justification for assuming VCS scores obtained binocularly reflect the arithmetic average of VCS scores obtained monocularly. However, analyses for "better" performing eyes have been included in the report. As noted on p. 10 of the final report, "better" eye analyses provide an indication of the minimum possible effect of perc on VCS; whereas analyses of the most affected (i.e., worse) eye provide an indication of the maximum possible effect of perc on VCS.

To better distinguish for the reader the difference between possible effects of perc exposure on functional vision and on CNS function, additional discussion has been added to better explain how both optical (e.g., the pupil, lens) and CNS components (e.g., retina, optic nerve, visual cortex) of the eye contribute to VCS in the section entitled VCS Test Performance, Vision on CNS on pp. 25-26. Additional text also notes that exclusion of those with optical or medical conditions likely to influence VCS helped to control for the optical components of vision and allowed assessment of the CNS components of vision.

Also, discussion is included in the Strengths and Limitations section noting that because of the exclusion criteria and the well-controlled clinical testing, participants could be expected to perform well on the VCS test. Using appropriate statistical techniques to control for other

possible contributing factors, decreases in VCS could be associated with perc exposures, recognizing limitations noted in the Limitations section of the report.

Reviewer 4:

Comment 64:
At this stage of investigation, it would be an overstatement to consider the effect observed, adverse. I would describe the effect as subclinical and in need of replication where confounding factors can be more controlled.

Response 64: Recommendations for additional research have been added to the report on p. 31.

Comment 65:
The authors acknowledge that the perc measurements reflect current levels and therefore in the present study, they cannot determine whether the effects observed are due to the combination of chronic and acute effects or simply acute effects. This issue speaks to the public health relevance. If the results observed are transitory resulting from acute exposure, then they are of relatively less concern than if the effects are permanent. A clear statement indicating that the present study cannot address this issue should be added to the last paragraph in the limitations section.

Response 65: Limitations of the present study having to do with interpretation of whether observed effects may be associated with chronic, acute, or chronic and acute exposures are noted on p. 31.

Reviewer 5:

Comment 66:
Decreased VCS performance associated with ambient and internal measures of exposure to PERC should be taken as an indication of a perturbation of the central nervous system by a xenobiotic compound. Subtle differences in VCS itself, as described here, are unlikely to have functional consequences for individuals.

Response 66: Interpretation of study findings with respect to vision and the CNS is discussed on pp. 25-26 of the final report.

Reviewer 6:

Comment 67:
In my opinion, as a pediatrician who has spent several decades studying the adverse effects of chemicals on developing nervous system of children, I consider the observed effect to be an adverse effect. Putting it the other way around, I can conceive of no possible scenario in which the observed effect could be considered beneficial to the children who are exposed to perc in these apartments. In addition to being a recognized carcinogen, perc is a chemical with known neurotoxic properties. Acute, high-dose, occupational exposure to perc is capable of producing acute neurobehavioral intoxication. It is therefore physiologically plausible that perc should cause neurobehavioral effects at lower levels of exposure. Also in view of what we know of the

enhanced susceptibility of children to toxic chemicals in the environment, it is not surprising to find an especially strong effect in children.

Response 67: No changes to the report were made in response to this comment.

Comment 68:
An additional aspect of this finding has to do with the fact that the range of test results that is considered normal is a broad range. It is quite possible to have reductions in function in persons who are exposed to a neurotoxic chemical and for the resultant diminished function to still be within the broad range of normal. The effect is still real. The impact of the effect is still negative. This is the essence of subclinical toxicity.

Response 68: No changes to the report were made in response to this comment.

Reviewer 7:

Comment 69:
I find nothing in this report that persuades me that the measured effects should be considered "adverse" in the context of regulatory decision making. But I think these findings are cause for concern that there *could* be adverse effects such as significant deterioration in some subjects who already have impaired visual contrast sensitivity or color vision, if these subjects are repeatedly exposed in their residences to very high levels, for example, >1000 $\mu g/m^3$. This report does not describe any situations in which such high indoor perc exposure and exposed individuals with significantly impaired visual contrast sensitivity or color vision have been identified. In my judgment, further investigation is warranted, by encouraging ophthalmologists to be aware that perc exposure from dry cleaners co-located in buildings with residences could adversely affect some aspects of vision, especially in young children (less than 9 years old) and older persons (over 45) who have weaknesses in their vision. (Such subjects were not included in the tests described in the draft report.) Hence, I regard it as an excellent idea to submit the research described in this report for publication in a journal read by ophthalmologists.

Response 69: No changes to the report were made in response to this comment.

Comment 70:
The responses in 9-11 year old children and 35-45 year old adults were generally at the upper end of the normal range for VCS. The statistical analysis is on the changes in the number of subjects below the maximum level, as opposed to at the maximum level, for various spatial frequencies measured in cycles per degree (cpd). Given the variation in adults and in children in VCS over the range of cpd (for example, as displayed in Figure 1, page 38), this measurement in number at the maximum versus below the maximum seems like an unusual way to assess significance for a health effect, and perhaps it is a very sensitive measure for statistical significance. None of the subjects tested seemed to show an effect that indicated a serious decrement in ability to observe contrast. Rather, a small and "subtle" (draft report, pages 20, 23) effect shows up in the comparison of maximum VCS, versus below maximum, as statistically significant.

Response 70: No response needed.

Reviewer 8:

Comment 71:
The answer is totally unknown. It is disturbing to contemplate an organic solvent being responsible for any measured variation (no matter how contrived or obscure) in the physiology of people living nearby (especially children), and VCS is a neurologic function. The abnormality may not be isolated. But the physiologic significance of the findings is tenuous, at best. Ophthalmologists do not even measure contrast sensitivity at all clinically.

Response 71: No response needed.

What is the public health significance of these findings for the general population?

SUMMARY OF REVIEWER COMMENTS

Four reviewers noted that the findings had public health significance (1, 2, 5, 6). One reviewer noted that the public health significance of the findings was imposition of an additional burden on subpopulations of minority or low income children already at a disadvantage (1). Two reviewers noted that the results justify elimination of dry cleaners, and hence perc exposures, from residential buildings (2, 6). Another noted that perturbation of the CNS indicated by the results obtained should be considered a sentinel effect justifying further action (5). Two reviewers (4, 7) noted that the public health significance depended upon whether the effect was irreversible (4) or the exposure was chronically high (7). One reviewer indicated that the results did not have much public health significance (8), and another indicated that the results were actually encouraging for the general population (3).

SPECIFIC COMMENTS AND RESPONSES

Reviewer 1:

Comment 72:
From a population perspective, one should be concerned that subpopulations of children are being affected in this manner. Further, based on the study, the children most affected are those of low income and minority racial or ethnic description. Children learning to read may find it more difficult if contrast sensitivity is impaired due to the inability to see printed material under conditions of low contrast. These same children are likely to face other challenges in achieving their learning potential. Thus, the imposition of an additional burden, no matter how seemingly slight should be taken seriously. In a study of VCS deficits in Bohemian children, it was reported that children attending schools for the learning disabled scored significantly lower on VCS, particularly in the mid- to high spatial frequencies while visual acuity was normal (Hudnell et al. 1996). Thus, there could be a link between learning ability and VCS. Clear establishment of the adverse nature of the outcome would be quite burdensome in terms of resources and time. Further, as indicated recently by the National Academy of Sciences report (NRC 2007), "dividing effects into 'adverse' and 'nonadverse' ignores the scientific reality that adverse effects may be manifest along a continuum." Instead one should determine "appropriate effects to evaluate," and an "understanding of the underlying biochemical mechanism for an effect of interest."

Response 72: Study findings suggest that minority and/or low income children may be most at risk for altered VCS as a result of perc exposure. Assessment of this is hindered because minority and low income residents are over represented in the high exposure groups. However, neither correlations between race/ethnicity or income and VCS, nor trend analyses of perc-exposure related decreases in VCS indicated either race/ethnicity or income influenced VCS. It is therefore not possible to conclude that minority or low income children represent a susceptible subpopulation for the effect on VCS observed in this study.

Additional discussion has been added to the report to explain how both optical (e.g., the pupil, lens) and CNS components (e.g., retina, optic nerve, visual cortex) of the eye contribute to visual function (see pp. 25-26). Also, the desirability of better defining a clinically meaningful change in VCS, of better understanding whether and how changes in VCS reflect changes to CNS, and conversely, whether and how changes in CNS reflect changes to VCS is emphasized in a Recommendations section in the final report.

Comment 73:
Seen is this light VCS is clearly an effect of interest. A possible mode of action is that perc results in a depletion of dopamine in the prefrontal cortex that results in the poorer VCS results. Perc has been demonstrated to cause neurological effects in humans and laboratory animals along a continuum. At 700 mg/m^3, exposed subjects reported neurological symptoms and had poor equilibrium (Stewart et al. 1970). At 350 mg/m^3, exposed subjects had effects on the visual system, motor/cognitive function and motor function (Altmann et al. 1990). At 83 mg/m^3, workers exposed to perc had poorer performance on tests of perceptual speed (Seeber 1989). At concentrations ranging from 7 to 470 mg/m^3, workers exhibited reduced reaction time, reduced vigilance and increased stress (Ferroni et al. 1992). At concentrations of 2.2 mg/m^3, day care workers exhibited a reduced mean VCS (Schreiber et al. 2002). At concentrations of 0.778 mg/m^3 apartment residents exhibited a reduced group mean VCS (Schreiber et al. 2002). In the current study, children exposed to average concentrations of 0.012 and 0.351 mg/m^3, exhibit a significant trend of lower VCS scores. In animals, perc exposure of pregnant rats to 700 mg/m^3 has been shown to deplete dopamine levels in the brain of the offspring (Nelson et al. 1980). Exposure of gerbils to 420 mg/m^3 of perc resulted in a lower mean DNA concentration per wet weight of the frontal cerebral cortex (Karlsson et al. 1987). The role of dopamine levels in VCS function has some support from the literature. Dopamine is the major catecholamine of the retina. Children with phenylketonuria (PKU) have been reported impaired across a range of spatial frequencies when VCS was tested (Diamond and Herzberg, 1996). Impairment was highest at 12 cpd. The authors indicate that lower dopamine levels in the prefrontal cortex and lower dopamine levels in the neurons of retina, if affected, could result in reduced VCS. Further, they concluded that moderately elevated levels of phenylalanine versus tyrosine may reduce the levels of tyrosine reaching the eye and brain, due to transporter competition, affecting the firing of dopamine neurons in the retina. In other studies, patients with diseases affecting brain dopamine levels had increased VCS after receiving dopaminergic drugs (Gorrlob and Srangler-Zuschrorr, 1990). Consequently, it is reasonable to assume that perc may be affecting dopaminergic pathways in the frontal cortex in children exposed to emissions in their apartment buildings, and that this affects VCS. If this is the case, it unclear if other neurological pathways are also being affected or if this effect may impede normal brain and behavioral development in children.

Response 73: No response needed.

Reviewer 2:

Comment 74:
This strong, carefully conducted study supports the need to separate housing from small industry activities such as dry cleaning establishments. This study suggests that VCS impacts are a sensitive pre-clinical endpoint, and although the differences seen were subtle and of a pre-clinical nature, are likely to occur under current dry cleaning establishment operations in New York, and also in any community where dry cleaning is co-located with residential housing. Preventive public health action is justified.

Response 74: No response required.

Reviewer 3:

Comment 75:
In terms of concern for the general population – the results are encouraging. The outcome indicates that, even in co-located premises where the level is below the NYS Deaprtment of Health guideline of 100 $\mu g/m^3$, no functionally significant effect would be expected and that is true even in situations where the guideline is exceeded by several fold. Clearly exposures such as those in reference residences are of no concern.

Response 75: No response required.

Reviewer 4:

Comment 76:
The authors acknowledge that the perc measurements reflect current levels and therefore in the present study, they cannot determine whether the effects observed are due to the combination of chronic and acute effects or simply acute effects. This issue speaks to the public health relevance. If the results observed are transitory resulting from acute exposure, then they are of relatively less concern than if the effects are permanent.

Response 76: No response required.

Comment 77:
The associations with biologic measures of exposure (breath and blood) lend support to the conclusions, but the public health significance does not appear to be significant unless individuals are exposed chronically to concentrations (i.e., > 100 $\mu g/m^3$) that are more likely to be experienced near work sites where perc is used daily. Furthermore, as indicated above we don't know if the effect observed is permanent or transitory.

Response 77: No response required.

Comment 78:
It would also be useful to indicate from a clinical perspective what the current findings in children imply regarding visual function. Is there any clinical benchmark for the implications of such a loss of VCS? The beginning of the discussion section offers background about the importance of VCS function but the losses discussed do not apply to the current findings. It would be more useful to provide a context, if possible, for the losses observed in the present study. This is an issue that another reviewer with specific clinical expertise may be able to address more fully.

Response 78: There is much discussion in the scientific literature about the testing, value, and interpretation of VCS. An ophthalmologist was included on the review panel and noted that the observed VCS effect would not be considered clinically significant. Discussion of the clinical interpretation of VCS changes is included in the section entitled VCS Test Performance, Vision and CNS on pp. 25–26 in the discussion of the final report, and the desirability of conducting more research in this area is noted in a Recommendations section added to the final report.

Reviewer 5:

Comment 79:
PERC is a VOC and a solvent; long-term exposures to compounds of this class have been associated with deficits in central nervous system function. A perturbation of the central nervous system, particularly in children, should be considered a sentinel effect.

Response 79: Interpretation of the observed changes in VCS as an indicator of a possible CNS effect is discussed on pp. 25–26 of the final report.

Reviewer 6:

Comment 80:
The principal public health significance of these findings in my view is that dry cleaning establishments should simply not be permitted to exist in residential buildings. This is an inherently hazardous practice that defies common sense. At least in New York City where many thousand of children live in such buildings, the effects on public health across the city are potentially very large.

Response 80: Other findings of the NYC Perc Project (McDermott et al. 2005) have been instrumental in development of new federal regulations restricting the use of perc in residential buildings (US EPA 2006). The findings of this report underscore the desirability of doing that and this is noted in the revised report.

Reviewer 7:

Comment 81:
I can only give a lay opinion, not an opinion based on knowledge and experience on assessment of risks of vision impairment. The changes associated with perc exposure seem small relative to the normal range of variation with groups of children and adult subjects shown in Figure 1, p. 38 (now pp. 30–31). I believe the public health significance of the VCS changes should depend on

whether these changes are at least in part irreversible, and how any irreversible changes compare, for example, to changes from advancing age. Very little background is presented in this report on how age, tobacco smoke or use of tobacco products, consumptions of alcoholic beverages, or exposure to other substances known to cause CNS effects show up as changes in CVS.

Response 81: Uncertainties associated with knowing whether decreased VCS might be permanent or reversible are discussed in the Limitations section of the report. Given the noted ceiling effect for the VCS outcome, it is not possible to derive quantitative distributions for VCS in the study population. Full quantitative distributions of VCS scores are needed to compare the magnitude of possible effect of perc observed in this study to the magnitude of changes in VCS that have been reported with increased age or other exposures such as tobacco and alcohol. Nevertheless, in this study, the possible influence of age, smoking, and alcohol use on VCS were controlled for in the adjusted logistic regressions.

Reviewer 8:

Comment 82:
It is properly emphasized in the report that the performance of exposed subjects was above average, and only a few individuals with less than maximal scores were responsible for the group's significantly poorer performance.

Response 82: No response required.

Charge Question 4: We used the perc exposure-VCS response relationship at 12 cpd in children to estimate indoor air perc levels associated with specified levels of extra risk for decreased VCS. Does the exposure-response analysis provide reasonable potency estimates of effect? Is there a level of extra risk for decreased VCS that is meaningful given the nature of the outcome variable and high background rates of scoring less than the maximum? If so, please explain what level(s) of extra risk is (are) meaningful, and why.

SUMMARY

Two reviewers did not respond to any component of this charge question (6, 8). Two reviewers commented that the exposure-response analyses provided reasonable estimates of potency (1, 2), and two reviewers commented that the exposure-response analyses were not useful (3, 7). One of these reviewers (7) added that there was already ample evidence for public health risk at indoor air perc levels around 100 $\mu g/m^3$, and the results in this report are not sufficient to depart from reliance on 100 $\mu g/m^3$ as a level of potentially significant risk. Another reviewer commented that establishing the relationship between ambient and internal levels of perc might better inform levels of indoor air perc that could be related to the VCS effect (5).

Two reviewers addressed the level of risk that is meaningful (1, 4). One reviewer noted that 50 percent extra risk above the risk at the median background level would be preferred, given the variability in response indicated by the wide confidence intervals around the odds ratios estimated in the regression models, and the observation that the BMCL at this value is within the range of what might be considered a NOEL, the median of about 12 μg/m3 for the low exposure group (1). One reviewer commented that it would be important not to imply, as reflected in the

lower bound of the benchmark concentrations, that indoor air perc levels in reference buildings (i.e., 3 $\mu g/m^3$) might result in increased risk (4). This reviewer also noted that factors likely influencing VCS such as race/ethnicity and possibly age should be considered when interpreting extra risk.

SPECIFIC COMMENTS AND RESPONSES

Reviewer 1:

Comment 83:
The report used the perc exposure-VCS response relationship at 12 cpd in children to estimate indoor air perc levels associated with specified levels of extra risk for decreased VCS. The choice of children and VCS response at 12 cpd is most appropriate since this effect is the strongest and most consistent effect reported in the study. Further, this effect clearly demonstrates a dose-response. Table 12 provides estimates of perc effect levels in children using an unadjusted model. The effect is extra risk, and extra risk levels from 10 to 50 percent are calculated in the table.

Response 83: No response required.

Comment 84:
It appears that the dose-response analysis provides a reasonable estimate of potency. The identification of three distinct exposure groups aids in developing an exposure response relationship. The use of a BMCL in the analysis is appropriate. It takes into account the variability in the experiment and provides a reasonable lower bound. It is worth noting that the result between the BMC and BMCL is very close at all levels of extra risk. Regarding the choice of background scenarios, it would appear that defining background as the median exposure is most appropriate. The report clearly demonstrates that the median background is statistically different from the low exposure residences. Choice of the 90^{th} percentile would have to be preceded by a demonstration that the value is statistically different from the low dose group. The use of extra risk is a reasonable choice. However, the level of extra risk should be chosen carefully. I suggest the following considerations along this line. One issue to get a better understanding of is the response at the low exposure level. Does the lower exposure group (less than 100 $\mu g/m^3$) exhibit an increased response? I am not able to discern that from the data. Clearly there is a trend. And clearly the high exposure group exhibits a significant effect (although clear documentation of this would be helpful). In simpler terms, does the low exposure group appear to be a no observed adverse effect level or lowest observed adverse effect level? Generally, your benchmark should approximate a NOAEL. If the low dose group is clearly a LOAEL, then the benchmark should be below it. Perhaps such a decision could be made by assuming a parametric distribution and using a comparison test, e.g., t-test. The second consideration is the variability in the mean response. A rule of thumb for evaluating a continuous variable is to look at the standard deviation from the mean and see if that provides useful guidance. Granted, the data are evaluated non-parametrically, but a parametric evaluation could be informative. Looking at the confidence interval around the OR suggests to me a considerable variability. For this reason I would choose the 50 percent extra risk, from among the choices provided.

Response 84: The median, rather than the 90th percentile, perc level is the most appropriate indicator of background, and this is noted in the report. Also, discussion of possible effect levels for decreased VCS based on study results in the final report is expanded to include consideration of perc levels of the > 100 μg/m^3 group along with proportions of participants scoring > max in trend tests, significant group differences in VCS scores based on ANOVA followed by post-hoc t-tests, and visual inspection of the exposure-response curve illustrating the benchmark concentration analyses has been added. These considerations led us to conclude that perc levels associated with the > 100 μg/m^3 group may reflect a LOEL. The final report notes that both trend and benchmark concentration analyses suggest a LOEL for decreased VCS at 12 cpd in children at about 90-100 μg/m^3.

Reviewer 2:

Comment 85:
The multiple analyses performed are extremely useful in characterizing the exposure-response. The methodologies applied and especially the use of benchmark dose estimating is quite revealing. The range of potency estimates derived is reasonable.

Response 85: No response required.

Comment 86:
The discussion and calculation of extra risk is a useful exercise. It is difficult to determine how meaningful the findings and differences observed are. Unfortunately there is no available information on whether the changes seen are reversible if the individual is removed from the exposure or at what point the decreases become irreversible. It is also unknown whether the individuals with less than maximum response would have been at the maximum except for the exposure. This is the difficulty of a cross-sectional study. What is now needed is some longitudinal tracking to assess how predictive the decreases are for subsequent more rapid declines.

Response 86: The report includes considerable discussion of uncertainties associated with the VCS outcome measure. This includes discussion of the meaningfulness of the derived measure of achieving < max score; and, of uncertainty regarding whether the effect observed might be irreversible or not, or predictive of greater effect in the future. The final report includes a recommendation section which includes the suggestion that additional research is desirable.

Reviewer 3:

Comment 87:
As discussed in the detailed comments above, the benchmark dose modeling is probably invalid. Hypothetically, even if there is an effect, it is not of functional significance over the range of exposures studies – even if there were a 50 percent probability of moving the worst eye from max score to <max score (to high normal probably) it would not be of concern, particularly if the best eye is unaffected.

Response 87: The report notes that the changes in VCS observed are unlikely to be reflected in a functional decrease in the ability of participants to see contrast. Further, the report notes that the decreases in VCS observed, although apparently very minor, may be an "indicator" for a CNS effect. So, the exposure-response analyses is not intended to determine an effect level for altered vision, but rather an effect level for a possible alteration in the CNS. This is discussed on pp. 25-26 of the final report.

Comment 88:
The results here and from Schreiber et al (2002) and NY DOH (2000) do not allow robust comparisons of potency or derivation of dose response relationships.

Response 88: The exposure response analyses presented in the report are intended to provide a possible range of residential perc indoor air effect levels that can inform further research and consideration of these data in establishing or modifying perc air guidelines.

Comment 89:
Benchmark dose calculations: We need more information about the model and what was plugged into it but it seems clear that the outcome depends on how valid quantitation is at 12 cpd. Thus the foundation appears to be weak. The BMCL is a specific regulatory tool – to display the appropriateness of the modeling (in the statistical sense only), both lower and upper 95 percent CLs should be displayed. Has the BMCL for 10 percent probability been correctly identified? It looks as though it should be way below background. The 95 percent CLs appear to be very wide which would be expected given the limitations of the data being used to derive a dose response relationship. All told, this application of benchmark dose calculation for predictions seems highly insecure and should not be used for any practical purpose – better to omit altogether.

Response 89: Appendix 3 which fully describes the exposure – response model has been added to the final report. Also, both upper and lower 95 percent confidence levels have been included in the table summarizing benchmark concentration estimates. Additionally, it is noted in the report on p. 27 that these analyses are best viewed as exploratory given uncertainties associated with the nature of the outcome variable and the wide confidence intervals associated with the benchmark concentration estimates. Nevertheless, we believe the analyses are helpful in providing a range of indoor air perc levels that might be considered minimum effect levels that can help frame additional research, and be useful in establishing or revising perc indoor air guidelines when considered along with other relevant data.

Comment 90:
Exposure response: Schreiber et al (2002) is not a reliable basis for quantitative comparisons and should be regarded only as having set the hypothesis for the current study. As indicated above, the benchmark dose calculations seem flawed. There is really no basis for exposure response comparisons. The big questions remain: Is there an effect and, if so, is it adverse (clinically significant)?

Response 90: Indoor air perc levels associated with VCS effects by other investigators are provided and discussed to allow readers to consider the current results in the context of previous observations. Such comparisons are qualitative only and are useful even though uncertainty regarding the meaningfulness of the decreased VCS test performance remains.

Comment 91:
Dose response: You just have to admit that dose response determinations or comparisons are not possible with these results.

Response 91: Given that the effect observed, as discussed in the report, may reflect an effect on the CNS, it is reasonable to explore what information this study may provide that would support judgements about a possible range of effect levels.

Comment 92:
Benchmark dose: No conclusions possible.

Response 92: The benchmark concentration analyses are best viewed as exploratory given uncertainties associated with the nature of the outcome variable and the wide confidence intervals associated with the benchmark concentration estimates. Nevertheless, we believe the analyses are helpful in providing a range of indoor air perc levels that might be considered minimum effect levels that can help frame additional research, and be useful in establishing or revising perc indoor air guidelines.

Reviewer 4:

Comment 93:
Factors that need to be considered when interpreting extra risk for lowered VCS include the confounding effects of ethnicity/race and possibly age (most highly exposed were somewhat younger). Although these covariates were adjusted for in regression models and results continued to approach significance, confidence intervals became quite large making these estimates less reliable.

Response 93: Logistic regressions have been redone to eliminate inclusion of covariates that do not independently influence VCS test performance. Also, analyses of correlations between race/ethnicity or income and VCS indicated that neither race/ethnicity nor income influenced VCS for reasons noted in the report on p. 12. Hence, only age, smoking, and alcohol use are included in the adjusted adult model, and only age is included in the adjusted child model. Ninety-five percent confidence intervals for the odds for scoring < max are markedly reduced from those obtained when other confounders were inappropriately included in the draft report. Nevertheless, we recognize that given the disproportionate representation of minority and low income participants with the highest exposures and the very small number of participants with high exposures, especially non-minority and non-low-income, it is not possible to completely eliminate either race/ethnicity or income as a possible confounder in this study.

Comment 94:
In addition, increased risk estimates incorporate concentrations documented in the reference buildings. It would be important not to imply at this stage that the lower bound of the benchmark concentration (i.e., 3 $\mu g/m^3$) would result in increased risk.

Response 94: Discussion of the benchmark exposure-response analysis in the final report now emphasizes extra risks of 40 percent or 50 percent above the median background level of 2.25 $\mu g/m^3$ on p. 27. Estimated indoor air perc levels associated with these extra risks as well as

the lower confidence limits on these estimates are all above the 25^{th} – 75^{th} range observed in reference buildings.

Comment 95:
Also, the study used categories of exposure and of performance in spite of the fact that continuous measures for both the independent and dependent variables were available. This is not the best or most accepted method for analyzing results according to journals providing guidelines for acceptable statistical analyses (e.g., Psychosomatic Medicine).

Response 95: Although categories of indoor air perc levels were used in trend analyses, measures of exposure (indoor air, breath, blood perc levels) used in regression analyses were continuous. And, although VCS measurements may reflect a continuous biological variable, the data were highly truncated (i.e., there was a ceiling) so that parametric analyses assuming the nature of the distribution was known or that the distribution is normal were not warranted. Instead, methods appropriate for these types of truncated data were applied. Appendix 2 in the final report more fully describes the nature of VCS as assessed using the F.A.C.T. in this study.

Reviewer 5:

Comment 96:
It would be helpful to see an analysis that establishes the relationship between the ambient and internal levels of PERC. Quantifying this relationship would allow you to understand whether ambient levels can be used as acceptable surrogates for internal dosimetry.

Response 96: Correlations between indoor air perc level and measures of internal perc exposure have been reported by us and by others (e.g., Schreiber et al. 2002; Storm et al. 2006). This has been noted in the report on p. 3. More detailed analyses of interrelationships between indoor and biological levels observed in this study are underway.

Comment 97:
Given that the internal PERC levels dropped steeply in breath measures taken in the residence and in the clinic, understanding the relationship between ambient and internal dose may allow you to better identify the ambient level associated with a decrement in performance. In other words, calculate the ambient to internal function based on the measures taken in the residence, then use this function to consider what ambient level would be equivalent to that at the time of testing in the clinic (ostensibly a low-PERC location).

Response 97: As noted above, there are uncertainties associated with knowing whether the subtle effect on VCS observed was due to acute (i.e., current) and/or chronic (i.e., past or cumulative) exposures to elevated indoor air perc. The suggested analyses, although of potential interest, would be of most value assuming the observed effect is thought to be due to current or acute exposures only. Since the current study cannot really resolve this issue, the suggested analyses are beyond the scope of the final report.

Comment 98:
Calculating the ambient to internal dose function would also open the way for further meta-analysis, that is, combination of these results with results reported elsewhere. In addition, one of the growing challenges for the Agency and others in public health will be to be able to reconstruct exposures from biomonitoring data. By including internal and external measures of exposure in your report, you will help in that broader effort as well as in your focused effort.

Response 98: The biomonitoring data gathered in this study are being used to explore the pharmacokinetic relationships among breath, blood, and indoor air levels for both adults and children as noted above.

Comment 99:
It is unfortunate that the "ceiling" effect necessitated more elaborate statistical analyses than might otherwise have been necessary. Should future testing situations arise, then other rapid tests of VCS might be considered.

Response 99: We agree that alternative VCS tests should be considered for future research. This is noted in a recommendation section added to the report.

Reviewer 7:

Comment 100:
While there is an indication of a dose response, especially when previous data on VCS and perc exposure are considered, the new data presented in this report show only a small, subtle, and barely statistically significant effect using unusual statistical procedures. A wide range of individual exposures is found in the two groups with elevated exposure from dry cleaners. I am therefore not persuaded that the benchmark concentration (BMC) and 95 percent lower confidence limit (BMCL) calculations are useful. I think the appropriate inference is that the new test data show that perc VCS effects are measurable via the statistical tests used, at levels *of the order* of 100 $\mu g/m^3$. Therefore, New York may want to encourage increased vigilance, with warnings of possible vision effects communicated to exposed adults, parents of exposed children, and the ophthalmologists who treat them. I am of the opinion that, *based on possible cancer risk*, indoor perc exposures at levels above 100 $\mu g/m^3$ from dry cleaners venting into nearby apartment living space ought to be avoided. The previously established NY State guidelines for limiting perc exposure in residential areas co-located in buildings with dry cleaners, described on pages 1-2 of the draft report, seem to me to remain reasonable and appropriate. I do not yet regard VCS changes described in this draft report effects as adding much to a potentially significant (but highly uncertain) health risk from such levels of indoor perc exposure.

Response 100: The small, subtle nature of the effect observed as well as uncertainties associated with the exposure-response analyses are discussed in the report. The findings of this report and reviewers comments on this report are being considered along with other relevant information in a review of the NYS DOH 100 $\mu g/m^3$ guideline for perc.

Reviewer 8:

Comment 101:
This is essentially a statistical question and I am not competent to answer.

Response 101: No response required.

Charge Question 4: Please offer any other comments on this report you feel are of interest and/or of importance that are not addressed in the above questions.

SUMMARY

Reviewers 1 and 2, suggested more detailed information be provided about the F.A.C.T. VCS test, and participants VCS scores. Reviewer 1 also suggested statistical analyses of differences in VCS test performance between the two dry cleaner building exposure categories be performed to help identify whether the perc level in the < 100 $\mu g/m^3$ group was an effect level or not. Reviewer 4 suggested children living in buildings where perc levels were > 100 $\mu g/m^3$ be protected immediately. Reviewer 5 suggested considering the amount of time spent in residences/day to better characterize exposure. Reviewer 7 suggested the results be published in the peer-reviewed literature, and that reviews be solicited from experts in statistical techniques for analysis of data at, or below, a maximum level when many subjects have responses at the maximum level.

SPECIFIC COMMENTS AND RESPONSES

Reviewer 1:

Comment 102:
The New York State Department of Health (NYSDOH) is to be commended for their public health approach to conducting such an innovative and informative study.

Overall the report is fairly well written, clearly describes the details of the study, and provides the substantive calculations and analyses in the appendices.

It would be helpful if the tables indicated what statistical test was used in the evaluation. This is not always the case.

Response 102: Statistical tests have been added to tables.

Comment 103:
On page 7, it would be helpful to indicate, in parens or a footnote if needed, the range of scores that are achievable from the VCS test. Also there should be an explanation of how the scoring was averaged. For example, if the testee achieved the maximum score the value of "x" was used in the calculation.

Response 103: Appendix 2 which includes detailed descriptions of the F.A.C.T. VCS and also individual participant scores has been added to the final report.

Comment 104:

On page 9, it would be helpful if the document explicitly stated which variables were considered categorical and tested using chi-square. Also the document should explicitly state which variables were analyzed using the Spearman correlation coefficients.

Response 104: The methods section of the final report details the nature of variables used in all analyses.

Comment 105:
On page 13, Table 6 should be more clearly explained. Particularly, what is the VCS score versus the score less than max?

Response 105: The VCS score and VCS score < max are explained in the Methods section. Also, in the final report Table 6 which summarizes correlations between VCS test performance and measures of perc exposure only includes the VCS score.

Comment 106:
It would be helpful to run statistical tests on the VCS response for the two exposure groups to see if the children's response is significant statistically. They should be run parametrically as well as non-parametrically. It seems clear that there is a biologic response at the high exposure group. If the results are not statistically significant, there should be discussion of the identification of a biologic response at the exposure level(s).

Response 106: The outcome variable does not meet the required assumption for parametric analyses of normality (cf., Tomkins 2006). Therefore parametric analyses have not been included in the final report.

Reviewer 2:

Comment 107:
It would be useful to have a brief discussion of how the VCS test has been used and the robustness of the "normal" values and distributions provided by the company. The criterion for selection of who was used to generate these normal values is probably less strict than the criteria for inclusion in this study. The test scale of response range that does not provide a full range of scores makes analysis difficult. The line of analysis chosen was the best available.

Response 107: More details on the F.A.C.T. VCS test used in this study are presented in Appendix 2 of the final report; and, discussion of the influence of exclusion criteria on VCS test results are noted on pp. 20-21 of the final report. Details of the population used to generate the "normal" values for the F.A.C.T. are not available.

Reviewer 3:

Comment 108:
I must compliment NY State DoH on the design of this study which was exemplary with great attention to detail. Conduct of the experiment, as far as one can judge, appears to have been handled well also. In some ways the quality of the study deserved results that were easier to interpret and it is the handling of results and their interpretation that leads to concerns.

Response 108: No response required.

Reviewer 4:

Comment 109:
In spite of any caveats including the need to replicate the current findings, the consistency of results for VCS performance at 12 cpd among children exposed at the highest concentration suggests that this is a finding that should be followed up on from a public health perspective. That is, as a precaution children living in buildings where air exposures > 100 $\mu g/m^3$ are documented need to be protected until we understand more fully the implications of the present findings.

Response 109: During the conduct of this study, whenever a level of perc greater than 100 $\mu g/m^3$ was observed, the NYC DOHMH was notified so that action could be taken. This is noted in the report. Also, as a result of this study, NYS DOH is reviewing the residential air guideline of 100 $\mu g/m^3$ along with other relevant information to assess whether it is adequately protective.

Comment 110:
A small edit – Figure 2 needs to have the units of measurements indicated for the air concentrations given on the x axis.

Response 110: Figure 2 is now Figure 3 in the final report and has been modified to include air concentration units.

Reviewer 5:

Comment 111:
The NYS Department of Health took on the difficult task of assessing the effects of environmental exposure to tetrachloroethylene (PERC) in residents of buildings that contained both residences and dry-cleaning businesses. This is an important issue, since exposure to PERC has previously been associated with neurobehavioral and visual effects in occupational and some residential studies. Comprehensive evaluation of the effects on children is a particularly pressing need because of the potential for increased vulnerability of the developing nervous system.

The study (and the report) is impressive, particularly with the care taken to make measurements of exposure. It is rare in environmental epidemiology outside of industrial hygiene to get measures of ambient and internal (i.e., inside the body) levels of the compound of concern.

Response 111: No response required.

Comment 112:
Given the rapid clearance of PERC from the body, an additional factor that one might want to consider is the amount of time spent in the residence/day, since this would have an impact on the chronic level of exposure to the PERC.

Response 112: The amount of time spent in the residence each day was not collected from participants. Although the suggested analyses might be informative about exposures and possibly the perc exposure-response relationship, they would not address whether the effect obtained was a consequence of acute and/or chronic exposures. Nor would it address uncertainties associated with the outcome variable itself.

Comment 113:
The color vision testing was done well. The study is to be applauded for using the paired saturate and desaturate color arrangement tests and testing subjects under clinically controlled conditions.

Response 113: No response required.

Comment 114:
One question about the visual evaluation: Was contrast sensitivity tested using best corrected vision? In other words, when an individual went to the Ophthalmology clinic to be tested, if the evaluation showed that optical correction was necessary, was that optical correction then used during the VCS test?

Response 114: Yes, contrast sensitivity testing was done using best corrected vision, as long as it was better than 20/25. This is noted in the Methods section of the report.

Reviewer 7:

Comment 115:
There is no indication in the report that the reduction in VCS at any spatial frequency effect is cumulative with lengthy repeated exposure over time. No results were reported that indicate whether the change in VCS goes away after perc exposure is discontinued and perc levels in breath and blood go to low levels. (By low levels I mean the levels that might be expected with ambient outdoor levels of perc or levels in a building with no dry cleaner. The test results relate to levels of perc in buildings with a dry cleaner and a measured perc level of < 100 $\mu g/m^3$, or the higher measured levels (>100 $\mu g/m^3$) in buildings with a dry cleaner.

Response 115: These limitations are noted in the report.

Comment 116:
In my judgment these test data should be published in the peer-reviewed professional literature. I do not think the review I am submitting, or reviews from other other non-specialists in these vision effects submit at this time, substitute for peer review from specialists in toxicological effects on the nervous system and on vision in particular. I would also think reviews should be solicited from experts in statistical techniques for analysis of data at, or below, a maximum level, for tests in which many subjects have responses at the maximum level.

Response 116: The eight reviewers of this report represented a diversity of expertise in ophthalmology, neurotoxicity, epidemiology, statistics, risk assessment, and exposure-response. We plan to submit these data to an appropriate scientific, peer-reviewed journal.

APPENDIX 4. ATTACHMENT 1.

EFFECT OF TETRACHLOROETHYLENE (PERC) EXPOSURE ON VISUAL CONTRAST SENSITIVITY (VCS) TEST PERFORMANCE IN ADULTS AND CHILDREN RESIDING IN BUILDINGS WITH OR WITHOUT A DRY CLEANER

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APPENDIX 4. ATTACHMENT 2.

EFFECT OF TETRACHLOROETHYLENE (PERC) EXPOSURE ON VISUAL CONTRAST SENSITIVITY (VCS) TEST PERFORMANCE IN ADULTS AND CHILDREN RESIDING IN BUILDINGS WITH OR WITHOUT A DRY CLEANER

REVIEW PANEL CHARGE

An external scientific review panel is being asked to review findings summarized in the report "Effect of Tetrachloroethylene (Perc) Exposure on Visual Contrast Sensitivity (VCS) Test Performance in Adults and Children Residing in Buildings With or Without a Dry Cleaner." The New York State Department of Health has evaluated relationships among tetrachloroethylene (perc) exposure (indoor air, breath and blood perc levels) and visual function (visual contrast sensitivity (VCS) and color vision) in child and adult residents of buildings with or without a co-located dry cleaner using perc. This report indicates that decreased VCS of adult and child residents was associated with perc exposure. Evidence for an effect of perc on children's VCS is stronger than for an effect of perc on adult's VCS. Further, among children, decreased VCS at the specific spatial frequency of 12 cycles per degree (12 cpd) was most clearly associated with increased perc exposures compared to VCS at other spatial frequencies. Hence, children's perc exposure – VCS response relationship at 12 cpd was evaluated to estimate a perc effect level for decreased VCS.

We are asking the panel for written comments on the following issues.

1. We attributed a decreased proportion of children achieving the maximum VCS score at 12 cpd, and an increased likelihood (odds ratios) for children to score < maximum VCS score at 12 cpd to increased perc exposure. Is this conclusion supported by the data obtained and analyses performed? Are limitations and strengths of the study adequately described and appropriately considered?

2. VCS of both adults and children was in the upper range of what is considered normal for the VCS test administered. Nevertheless, significant associations between increased perc in indoor air, breath, and blood of children and decreased performance on the VCS test were observed. Should the decreased VCS test performance observed be considered an adverse effect? What is the public health significance of these findings for the general population?

3. We used the perc exposure-VCS response relationship at 12 cpd in children to estimate indoor air perc levels associated with specified levels of extra risk for decreased VCS. Does the exposure-response analysis provide reasonable potency estimates of effect? Is there a level of extra risk for decreased VCS that is meaningful given the nature of the outcome variable and high background rates of scoring less than the maximum? If so, please explain what level(s) of extra risk is(are) meaningful, and why.

4. Please offer any other comments on this report you feel are of interest and/or importance that are not addressed in the above questions.

PREPARER'S OF REPORT AND ACKNOWLEDGEMENTS

This investigation was managed and reported by Jan E. Storm, Ph.D. (Bureau of Toxic Substance Assessment (BTSA), NYS DOH). Kimberly A. Mazor (BTSA, NYS DOH) conducted statistical analyses. Lenore J. Gensburg, Valerie B. Haley, and Shao Lin (Bureau of Environmental & Occupational Epidemiology, NYS DOH) provided statistical advice. Daniel A. Luttinger (BTSA, NYS DOH) provided critical review and offered important guidance. All ophthalmologic examinations and VCS and color vision tests were conducted at the Mt. Sinai School of Medicine Department of Ophthalmology Research Clinic under the direction of Janet Searle, M.D. and Scott Brodie, M.D. Indoor air and breath analyses were conducted at the NYS DOH Wadsworth Laboratories under the direction of Kenneth M. Aldous, and blood analyses were conducted at the Centers for Disease Control and Prevention under the direction of Ben Blount, Ph.D.

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Finally, the participation of all the parents, children, and families who volunteered their time and effort in the NYC Perc Project is gratefully acknowledged.

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