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Neurotoxicity of Tetrachloroethylene (Perchloroethylene)

Discussion Paper

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PREFACE

This discussion paper was developed by the U.S. Environmental Protection Agency (EPA) to serve as background material for a workshop discussion with experts regarding neurotoxicity of tetrachloroethylene. Subsequent to these discussions, a revised review of neurotoxicity will be incorporated into a comprehensive health assessment document (toxicological review document) that will be peer reviewed and released for public comment. This work was undertaken by staff in the National Center for Environmental Assessment (NCEA) for EPA's Office of Air Quality Planning and Standards.

Tetrachloroethylene is a widely used solvent. It is produced commercially mainly for use in dry cleaning, textile processing, and metal cleaning operations. It has the following end-use pattern: 55% as a chemical intermediate, 25% for metal cleaning and vapor degreasing, 15% for dry cleaning and textile processing, and 5% for other unspecified uses (ATSDR, 1997). Although dry cleaning facilities are a significant source of atmospheric emissions of tetrachloroethylene, their use of tetrachloroethylene has declined by more than 60% over the last 10 years due to the introduction of equipment with vapor recovery (U.S. EPA, 2003). Tetrachloroethylene is also released into groundwater where it can persist for years because of the limited contact between groundwater and air. When people are exposed, it is readily absorbed by all exposure routes and is widely distributed throughout the body. Tetrachloroethylene is listed as a hazardous air pollutant under the Clean Air Act, a toxic pollutant under the Clean Water Act, a contaminant under the Safe Drinking Water Act, a hazardous waste under the Resource Conservation and Recovery Act, and a hazardous substance under the Comprehensive Environmental Response, Compensation, and Liability Act (Superfund). It is a toxic chemical with reporting requirements under the Emergency Planning and Community Right-to-Know Act, and under the Toxic Substances Control Act. In addition, certain releases must be reported to the Toxics Release Inventory. Because of this wide use and the need for regulatory decisions under various environmental statutes, EPA is soliciting expert advice on the significance of the available information on the neurotoxicity of tetrachloroethylene.

The relevant literature was reviewed through June 2003.

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1. HUMAN STUDIES

The nervous system is a major target organ in humans exposed to tetrachloroethylene by inhalation, and a range of effects on neurologic function are well documented for both acute and chronic exposure. Section 1.1.1 of this paper contains a description of three reports of controlled inhalation exposures. The studies by Stewart et al. (1977) and Hake and Stewart (1977) were funded primarily by the National Institutes of Occupational Safety and Health (NIOSH). These studies are considered to be protective of human subjects, as U.S. Environmental Protection Agency (EPA) and other federal agencies subscribe fully to principles such as those articulated in EPA's Protection of Human Subjects Rule ("the Common Rule"), 40 CFR Part 26. A description of the studies by Altmann et al. (1990, 1992) is also included because the Agency for Toxic Substances and Disease Registry used these studies to develop an acute minimal risk level (MRL) (ATSDR, 1977). EPA considers these studies to be "third party studies." No information is provided in the published papers regarding the procedures the study investigators adopted for informed consent or protection of human subjects, and staff of the National Center for Environmental Assessment (NCEA) have contacted study investigators requesting this information.

Acute controlled inhalation exposures of 100 ppm tetrachloroethylene and higher have induced symptoms consistent with depression of the central nervous system (CNS), including dizziness and drowsiness (ATSDR, 1997). Changes in electroencephalograms (EEGs) have been noted with controlled inhalation exposures at 100 ppm (Stewart et al., 1977). Acute exposure to lower levels of tetrachloroethylene has induced alterations in neurobehavioral function. For example, Altmann et al. (1990, 1992) reported increases in the latency of visually evoked potentials (VEPs) among volunteers with inhalation exposure to 50 ppm for 4 hours per day for 4 days as compared with latency among subjects exposed to 10 ppm (the control group in this study). The observations by these investigators indicate that visual system dysfunction such as delayed neuronal processing time and altered contrast perception is related to tetrachloroethylene exposure.

A number of epidemiologic studies of the prevalence or cross-sectional design are available for subchronic or chronic exposure to tetrachloroethylene. The subchronic and chronic epidemiologic studies are discussed in Section 1.1.2 of this paper. These studies (Lauwerys et al., 1983; Seeber, 1989; Cai et al., 1991; Nakatsuka et al., 1992; Ferroni et al., 1992; Cavalleri et al., 1994; Gobba et al., 1998; Spinatonda et al., 1997; Echeverria, et al., 1995) examined a number of neurobehavioral or neurotoxic outcomes among workers in dry cleaning operations. Two other studies, Altmann et al. (1995) and a pilot study by Schreiber et al. (2002), examined residents or day care workers exposed to tetrachloroethylene through living or working in close proximity to a dry cleaning establishment. Exposure concentrations to tetrachloroethylene in these two studies (mean and median concentrations) are approximately an order of magnitude lower than the time-weighted-average concentrations of the dry cleaner studies.

Together, these epidemiologic studies (Seeber, 1989; Ferroni et al., 1992; Cavalleri et al., 1994; Gobba et al., 1998; Spinatonda et al., 1997; Echeverria, et al., 1995; Altmann et al., 1995; Schreiber et al., 2002) provide some evidence that chronic exposure to tetrachloroethylene affects visual spatial function. Findings from the dry cleaner studies further indicate that tasks requiring the processing of visual information (color vision, reaction time, coding speed, visual memory, visual contrast perception) are particularly vulnerable to alterations from exposure to tetrachloroethylene. Altmann et al. (1995) and Schreiber et al. (2002) observed effects on visual function among residents living in close proximity to a dry cleaning business, and Schreiber et al. (2002) also reported this effect in nine day care workers exposed to tetrachloroethylene from a nearby dry cleaning establishment.

Color vision is another domain assessed in tetrachloroethylene exposed populations. Acquired dyschromatopsia (loss of color vision) is a well-known adverse effect of exposure to solvents (Geller and Hudnell, 1997), and studies suggest that blue-yellow dyschromatopsia is associated with lower-level solvent exposure (Muttray et al., 1997). Moreover, dyschromatopsia is considered an important sign of neurotoxicity (Lucchini et al., 2000). Color vision testing has been reported for four populations of dry cleaners (Nakatsuka et al., 1992; Cavalleri et al., 1994; Gobba et al., 1998; Valic et al., 1997) and among workers exposed to mixtures of solvents that historically contained 10% tetrachloroethylene (Muttray et al., 1997).

Three studies (Seeber, 1989; Ferroni et al., 1992; Altmann et al., 1995) assessed fine motor control, and all found no effect.

1.1. REVIEW OF INDIVIDUAL STUDIES

The following subsections present detailed descriptions of the human studies on tetrachloroethylene exposure. As part of this review, NCEA staff have critically read each of these studies and have also relied heavily upon study descriptions contained in the New York State ambient air criteria document (NYS DOH, 1997). For some studies, more detailed information of study procedures was provided in correspondence between the principal investigator and staff of the New York State Department of Health; this correspondence is cited below.

1.1.1. Acute Controlled Exposure Studies

1.1.1.1. *Stewart, R.O., E.D. Baretta, H.C. Dodd and T.R. Torkelson. 1970. Experimental human exposure to tetrachloroethylene. Arch. Environ. Health. 20:225–229.*

Sixteen healthy adults were exposed to single and repeated exposures of 100 ppm for a period of 7 hours, with five subjects repeatedly exposed for 5 days. During or after exposure, study investigators recorded subjective symptoms, administered a number of neurological tests to exposed subjects, collected blood and urine samples to assess affects on clinical parameters, and collected alveolar breath samples. Additionally, visual acuity and depth perception were measured in exposed subjects. Although not stated in the published report, it is assumed from the design of this study that investigators were not blinded when administering the neurological tests. Additionally, the paper does not discuss whether informed consent was obtained, nor does it describe the procedures used by study investigators.

All subjects reported the ability to detect odor, and this perception decreased over the course of daily and weekly exposure. Of the subjects exposed to a single 7-hour exposure, eye and nose irritation was reported by 60% of the subjects, a slight frontal headache by 25%, slight light-headedness by 25%, feeling slightly sleepy by 40%, and difficulty in speaking by 25%. Some of these complaints were made during the first 2 hours. Of five healthy men exposed to 100 ppm for 7 hours per day on 5 consecutive days, one reported a mild frontal headache during each exposure (this subject also had chronic sinusitis, but this condition did not preclude his participation in the study) and two consistently reported mild eye and throat irritation. Other symptoms were not reported, and individual responses during exposures to 0 ppm were not assessed.

Three tests of equilibrium (a modified Romberg test[1], where an individual stands on one foot with eyes closed and arms at side; a heel-to-toe test; and a finger-to-nose test) were performed every 60 minutes during each day of exposure. After 6 hours, neurobehavioral tests of motor function (the Crawford manual dexterity and Flanagan coordination tests), cognitive function (arithmetic test), and motor/cognitive function (inspection test) were also performed. Three of the subjects had increased difficulty in maintaining their equilibrium when tested within the first 3 hours of exposure (i.e., performance on the Romberg test was impaired). The three subjects were able to perform the test normally when given a second chance. Performance on the other tests was not impaired. An additional subject, exposed during the third day of testing, showed a slight deterioration in his Romberg test and complained of slight dizziness and slight impairment of his intellectual faculties after 1 hour of exposure. This subject was known to study investigators as being susceptible to the CNS–depressant effects of solvents. No

[1] The Romberg test measures CNS depression.

improvement in his Romberg test occurred during the next hour, and he was removed from the test chamber. This subject performed the test normally when retested 30 minutes later.

Overall, these investigators concluded that there were CNS effects in some subjects exposed to 100 ppm, as supported by the findings of light-headedness and abnormal modified Romberg tests. Additionally, these investigators discussed the possibility of a range of individual susceptibility to tetrachloroethylene.

1.1.1.2. *Hake C.L., and R.D. Stewart. 1977. Human exposure to tetrachloroethylene: inhalation and skin contact. Environ. Health Perspect. 21:231-238.*

This review article summarizes a number of previous studies carried out by these authors, including four controlled exposure studies primarily funded by the NIOSH. Hake and Stewart identified these studies as Study A, Study B, Study C, and Study D.

Study A was designed to examine the effect of exercising on tetrachloroethylene blood concentration. Neurological tests were not administered to the one study subject.

As part of a 5-week study, three or four healthy men (Study B) and four healthy women (Study C) were exposed 1, 3, or 7.5 hours per day, 5 days per week, to 0, 20, 100, or 150 ppm tetrachloroethylene. The published paper does not contain a description of the schedule or the total duration of exposure to individual exposure concentrations. These investigators assessed neurological, physiological, and/or behavioral responses as well as subjective symptoms among exposed subjects.

Reports of symptoms (e.g., headache) varied among individuals, but, overall, complaints during exposure were similar to those during exposure to 0 ppm tetrachloroethylene. All subjects were able to detect the odor of tetrachloroethylene at every level of exposure; the odor became less noticeable or disappeared as an exposure progressed on both a daily and weekly basis.

The evaluation of EEG recording made during exposure suggested altered patterns indicative of cortical depression in both male and female subjects exposed to 100 ppm tetrachloroethylene for 7.5 hours. Recordings of visual evoked responses and equilibrium tests were normal in men and women.

The performance of men on neurobehavioral tests of cognitive function (arithmetic), motor function (alertness), motor/cognitive function (inspection), and time estimation were not statistically significantly affected by any exposure. The performance of men on a second test of motor function (Flanagan coordination) was statistically significantly decreased ($p \leq 0.05$) when compared with the response at 0 ppm on at least 1 day during the weeks of 100 ppm and 150 ppm tetrachloroethylene exposure. The performance on physiological tests (tests not identified in published paper) of female subjects exposed to 100 ppm for 5 days was not affected.

Stewart et al. (1977) discuss the conclusions of Study B and Study C, concluding that (1) there was considerable interindividual variation in response to tetrachloroethylene vapors, (2) EEG analysis indicated preliminary signs of narcosis in most subjects exposed to 100 ppm for 7.5 hours, (3) impairment of coordination may occur in subjects exposed to 155 ppm for 7.5 hours, and (4) the effects were likely attributable to tetrachloroethylene and not a metabolite.

Study D was a complex study with 12 healthy adults (6 men and 6 women) of interactions on behavioral and neurological function associated with inhaled tetrachloroethylene and oral doses of alcohol or diazepam, a tranquilizer. A full description of this study was provided to NIOSH (Stewart et al., 1977). Individuals were typically exposed for 5.5 hours to 0 ppm on Monday or Tuesday, 100 ppm on Wednesday and Friday, and 25 ppm on Thursday during each of the 11 weeks of exposure and were given a placebo capsule, alcohol, Valium, or nothing during each period. Numerous neurological tests were performed throughout each exposure, and the authors took great efforts to ensure that all testing was done in a double-blind mode.

Exposure to 25 or 100 ppm tetrachloroethylene for 5.5 hours did not increase the overall prevalence of reported symptoms (e.g., headache) or alter the subjects' mood. Exposure-related increases in the strength and persistence of the tetrachloroethylene odor were perceived by the subjects. Exposure did not significantly reduce performance on two equilibrium tests (Romberg and heel-to-toe) and two neurobehavioral tests of motor function (Michigan eye-hand coordination test and rotary persuit test). At 100 ppm, there was a statistically significant decrease ($p<0.05$) in scores on a third test of motor function (Flanagan coordination test) on some days of exposure. Statistical analyses performed by the investigators revealed no effect of tetrachloroethylene exposure alone on EEGs and no interactive effects between tetrachloroethylene and either alcohol or Valium.

The study authors (Hake and Stewart, 1997; Stewart et al., 1977) concluded that performance on the three neurobehavioral tests of motor function was not consistently affected by exposure to 100 ppm tetrachloroethylene, although exposure did have a significant but inconsistent detrimental effect on the performance of the Flanagan coordination test.

1.1.1.3. ***Altmann, L., A. Bottgor and H. Wiegand. 1990. Neurophysiological and psychophysical measurements reveal effects of acute low-level organic solvent exposure in humans. Int. Arch. Occup. Environ. 3:493–499. Altmann, L., H. Wiegand, A. Bottger, F. Eistwmelor and G. Winneke. 1992. Neurobehavioral and neurophysiological outcomes of acute repeated perchloroethylene exposure. Appl. Psych. 41:269–279.***

These studies, conducted in Germany, reports intentional inhalation exposure of human subjects to tetrachloroethylene for the purpose of measuring potentially adverse health outcomes. The publication provides no information about ethical principles expoused by the U. S. Government for exposure to human subjects. Therefore, the principal author has been contacted and information has been requested regarding procedures that were used to select the subjects and inform them about the nature of the exposure, institutional procedures that were taken to review the design of the study, and ethical standards and guidelines that the institution was operating under at the time of the study. To date, no response has been received. Although the report is not of crucial importance in the evaluation of chronic neurotoxic effects of tetrachloroethylene, the human subjects issue associated with the report is still of interest.

Altmann et al. (1990, 1992) used neurophysiological and neurobehavioral techniques to evaluate the neurological effects of tetrachloroethylene on healthy adults exposed to 10 ppm or 50 ppm for 4 hours on 4 consecutive days. All subjects denied prior occupational exposure to solvents and drug use at the time of the study. Visual acuity of all subjects was normal or corrected to normal. The study was a single-blind study (subjects were not told their level of exposure) and subjects were randomly assigned to either group. Sixteen subjects were exposed to 10 ppm and 12 subjects were exposed to 50 ppm, but neurophysiological measurements were made on only 22 subjects (12 at the low level and 10 at the high level). There was no unexposed control group.

Three neurophysiological measurements were taken on the day before exposure started and on each of the four exposure days: (1) VEPs in response to black and white checkerboard patterns were measured; the VEPs of some subjects (exact number not reported) were also measured on the day after exposure ceased; (2) a visual contrast sensitivity (VCS) test (a test of the central spatial vision that determines the minimum contrast necessary for an individual to see patterns of various sizes) was given to five subjects (three from the low-exposure group and two from the high-exposure group); (3) recordings of brainstem auditory-evoked potentials (BAEPs) (neurophysiological measurements of the electrical signals generated by the hearing system in response to auditory stimuli) were made to evaluate the peripheral hearing loss of the subjects. All measurements were started 2 hours after a subject entered the chamber and were completed within 1 hour.

A German version of the Neurobehavioral Evaluation System was used to assess motor, motor/cognitive, and cognitive function of subjects. The battery included nine tests (finger tapping, eye-hand coordination, simple reaction time, continuous performance, symbol digit, visual retention, pattern recognition, digit span, and paired associates). A vocabulary test and a test of emotional state (moods) were also given. Each subject was assessed with a complete battery of tests during the pre-exposure baseline assessment and at the end of the study. Subsets of the battery covering motor function and mood were given repeatedly at the beginning and end of each 4-hour exposure period.

Tetrachloroethylene was not detected in blood samples collected before the start of the first exposure period. The detection limit was less than 0.0005 mg/L. Mean tetrachloroethylene blood levels increased slightly over the 4-day period. Among subjects exposed to 10 ppm, mean blood levels were 0.33, 0.36, 0.4, and 0.38 mg/L at the end of days 1, 2, 3, and 4 of exposure, respectively. Among subjects exposed to 50 ppm, mean blood levels were 1.1, 1.2, 1.4, and 1.5 mg/L at the end of days 1, 2, 3, and 4 of exposure, respectively.

On the first day of testing, faint solvent odor was reported by 33% and 29% of the subjects exposed to 10 ppm and 50 ppm, respectively. On the fourth day, these incidences changed to 17% and 36%, respectively. The VEP patterns of subjects during the third hour of exposure to 50 ppm on days 1, 2, 3, and 4 of exposure were significantly different ($p<0.05$) from those measured on the control day, and the differences became progressively greater on successive exposure days. One set of VEP patterns on the day after the end of the exposure period appeared different from the control day values (statistical significance was not reported). VEP patterns in subjects during exposure to 10 ppm were different from their patterns on the control day, but the differences were not statistically significant ($p>0.05$). There were significant differences ($p<0.05$) between the VEP patterns of subjects exposed to 10 ppm and those exposed to 50 ppm.

Data on contrast sensitivity indicated greater effects at 50 ppm than at 10 ppm; effects were most pronounced on the last day of exposure. However, statistical analysis was not reported, and the data are limited by the small number of subjects. There were no indications of peripheral hearing loss at either exposure level.

Neurobehavioral test results were reported for only those tests given repeatedly on 4 consecutive days (finger tapping, eye-hand coordination test, simple reaction time, continuous performance, and moods). There were significant post-exposure performance deficits ($p\leq0.05$) among subjects exposed to 50 ppm when compared with the group exposed to 10 ppm in tests of motor/cognitive function (continuous performance test for vigilance) and motor function (eye-hand coordination), and a near-significant difference ($p=0.09$) on a test of motor function (simple reaction time). In all cases, the degree of improvement shown by the subjects exposed to 50 ppm was less than that shown by the subjects exposed to 10 ppm. There were no exposure-related effects on the finger-tapping or moods test.

The study authors concluded that visual function in healthy, young adult males is mildly affected by tetrachloroethylene exposures to 50 ppm, maintained for 4 hours on each of 4 days (Altmann et al., 1990), and they stated that the impaired performance on tests of motor/cognitive and motor function suggests that 50 ppm cannot be considered a NOAEL for neurobehavioral endpoints indicative of CNS depression (Altmann et al., 1992).

1.1.2. Chronic Exposure Studies

1.1.2.1. *Lauwerys, R., J. Herbrand, J.P. Buchet, A. Bernard and J. Gaussin. 1983. Health surveillance of workers exposed to tetrachloroethylene in dry-cleaning shops. Int. Arch. Occup. Environ. Health. 52:69–77.*

Lauwerys et al. (1983) studied 26 workers (24 women and 2 men) occupationally exposed to tetrachloroethylene in six dry cleaning shops in Belgium for a mean of 6.4 years. The controls (31 women and 2 men) were workers in a chocolate factory (20) or an occupational health service (13) who did not report occupational exposure to organic solvents. Several characteristics of the two groups were similar (sex ratio, mean age [32.9 vs. 34.5 years], and level of education). However, 13 of the 26 dry cleaning workers—but only 9 of the 33 controls—were smokers. Neurobehavioral tests of motor function (simple and choice reaction time), sensory function (critical flicker fusion), and cognitive function (sustained attention test) were given twice to each worker, once before work and once after work. Both groups were tested in the middle of the work week. Individuals also were questioned about chronic symptoms related to nervous system disturbances. Blood samples for tetrachloroethylene measurements and liver function tests were collected before work. Urine samples for kidney function tests were collected after work.

The mean tetrachloroethylene air concentration (8-hour TWA) was 21 ppm and the range of TWA values was 9 to 38 ppm, using results from active sampling of personal air. The mean tetrachloroethylene blood level (30 minutes after the end of work) was 1.2 mg/L (range of means from the shops was 0.6 to 2.4 mg/L). There was no significant connection between air concentrations and blood levels.

Seventeen of 22 symptoms related to nervous system disturbances were more prevalent among the workers than among unexposed controls. However, none of the differences were statistically significant, and there was no relationship with duration of exposure. Two symptoms particularly affected were memory loss (7/26 vs. 3/33) and difficulty falling asleep (11/26 vs. 6/33). None of the mean scores of the dry cleaning workers on the four neurobehavioral tests were significantly lower ($p<0.05$) than those of the control group. The prevalence of abnormal scores (those beyond the 5th or 95th percentile of the control group) did not vary significantly between the two groups.

1.1.2.2. *Seeber, A. 1989. Neurobehavioral toxicity of long-term exposure to tetrachloroethylene. Neurotoxicol. Teratol. 11:579–583.*[2]

Seeber et al. (1989) evaluated the neurobehavioral effects of tetrachloroethylene on 101 German dry cleaning workers (machine operators, ironers, touch-up workers, counter attendants, and other employees) who were employed in coin-operated or while-you-wait shops, which were all affiliated with one organization. The workers were separated into a low-exposure group (50 women, 7 men) or a high-exposure group (39 women, 5 men). A third group of 84 sales personnel (64 women, 20 men) from several department stores and receptionists from large hotels served as unexposed controls. Predominant characteristics of both groups included primarily standing work, contact with customers, and moderate physical exercise, all against the background of somewhat matching skills. The mean ages of the low-exposure, high-exposure, and control groups were 38.2, 38.4, and 31.8 years, respectively.

Details on air monitoring methods were sparsely reported, but mean tetrachloroethylene concentrations (8-hour TWA) for the low- and high-exposure groups were 12 (± 8) ppm and 53 (± 17) ppm, respectively, using results from active sampling of room air and passive sampling of personal air. The mean duration of occupational exposure for the low- and high-exposure groups was 11.8 and 10.6 years, respectively.

A number of tests of neuropsychological functioning were administered, including standardized tests of symptoms and personality; tests of sensorimotor function, including finger tapping and aiming; and the Mira and Santa Ana dexterity tests, which are published standardized tests. Threshold of perceptual speed was assessed by recognition of stimuli flashed briefly on a screen; whether this procedure used a standardized instrument is unclear, but it is assumed that it did not. Choice reaction time was also determined using “nine light and tone stimuli.” It is not clear whether the auditory and visual stimuli occurred together or whether some trials consisted of an auditory stimulus and other visual tests. Details of the timing of the stimulus presentation were not provided. One of the response variables, “delayed reactions,” was not defined. The typical dependent variable measured in this task—response reaction time—apparently was not measured. Subtests of the Wechsler Intelligence Test (digit span, digit symbol, and cancellations) were used, as was recognition of words, faces, and digits. The instrument used and the scoring of the last three tests are not described. Intelligence was assessed using the logical thinking subtest of the German Performance Test System.

Each subject was examined during a 1.5-day stay at a clinic located at a large institute for occupational medicine. Each subject came to the clinic in the evening hours, stayed overnight,

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[2] Dr. Seeber provided additional information on this study in written correspondence to the New York State Department of Health dated January 19 and May 20, 1996. This information appears in NYS DOH (1997).

and started the examination and testing process the next morning. The clinic examined numerous people daily, and the dry cleaners and the control group were a small part of the daily routine of the clinic staff. Neurobehavioral tests were given by two specialized clinic staff, who did not question the subjects about exposure status. However, clinic psychologists (six at the time of the study) did inquire about the exposure and living conditions of the subjects. Because the dry cleaner groups and the control group differed in gender ratios, age, and scores on the intelligence test, stratified analysis was used to statistically control the influence of these confounding factors on test scores. The groups also differed in alcohol consumption, so a separate analysis was used to examine the role of alcohol on effects associated with tetrachloroethylene.

Performance of both the low-exposure and high-exposure groups differed significantly (p<0.01) from that of the unexposed control group on the threshold of perceptual speed and "delayed responses" on a choice reaction time task, both of which are measures of information processing speed (p=0.08 and 0.03 for low and high exposure, respectively). Both exposed groups also had worse scores (p<0.01) on two tests of attention (digit reproduction and digit symbol) and on visual scanning (cancellations). The low-exposure group also showed significantly higher scores than the control group on questionnaires on neurological signs (p<0.01) and emotional liability (p<0.05). Scores of the high-exposure group for these measures appeared higher than those for the control group; however, the scores were not statistically significantly different. There were no differences between groups on the other tests. Controlling for group differences in alcohol consumption did not alter any test results.

1.1.2.3. ***Cai, S.X., M.Y. Huang, Z. Chen, Y.T. Liu, C. Jin, T. Watanabe, H. Nakatsuka, K. Seiji, O. Inoue and M. Ikeda. 1991. Subjective symptom increase among dry-cleaning workers exposed to tetrachloroethylene vapor. Ind. Health. 29:111–121.***

Cai et al. (1991) evaluated the CNS effects of tetrachloroethylene exposure among 56 dry cleaning workers (27 women and 29 men) from three shops in China. The control group (37 women and 32 men) was of similar mean age (34 years vs. 35 years for dry cleaning workers), but the male dry cleaning workers were 4 years younger than the male controls and the women were 4.9 years older than the female controls. The controls were recruited from the same factories as the dry cleaning workers but from workshops without known solvent exposures. The geometric mean tetrachloroethylene air concentration (8-hour TWA) was 20 ppm and the range of TWA values was 4 to 97 ppm, using results from passive sampling of personal air. The mean duration of occupational (tetrachloroethylene) exposure was 3 years.

The prevalence of symptoms of tetrachloroethylene exposure was significantly higher among the dry cleaning workers (men, women, and men and women combined) (p<0.001), than among the unexposed controls. Five symptoms (dizziness, drunken feeling, floating sensation, a heavy feeling in the head, and facial flushes) in men and women (combined) were significantly more prevalent among the dry cleaning workers than among the controls ($p<0.001$). Nasal irritation and unusual smell were also reported significantly more often by the dry cleaning workers than by controls ($p<0.05$). Similar findings were reported when the workers were asked about the symptoms they had noticed during the 3 months before the study. The investigators found exposure-related increases in the prevalence of subjective symptoms among dry cleaning workers exposed to 21 ppm (8-hour TWA).

1.1.2.4. ***Nakatsuka, H., T. Watanabe, Y. Takeuchi, N. Hisanaga, E. Shibata, H. Suzuki, M.Y. Huang, Z. Chen, Q.S. Qu and M. Ikeda. 1992. Absence of blue-yellow color vision loss among workers exposed to toluene or tetrachloroethylene, mostly at levels below occupational exposure limits. Int. Arch. Occup. Environ. Health. 64:113–117.***

Nakatsuka et al. (1992) evaluated the effects of tetrachloroethylene exposure on the color vision of 64 dry cleaning workers (34 women and 30 men) in China. The workers were from the same shops studied by Cai et al. (1991). Control workers (72 women and 48 men) were recruited from the clerical sections of dry cleaning shops and from other factories (paint production plants or plants producing tetrachloroethylene from trichloroethylene). The mean ages of the dry cleaning workers (34 years for men, 35 years for women) were lower than those of the controls (34 years for men, 33 years for women). Lanthony's new color test was carried out by ophthalmologists or occupational health doctors in charge of the factories under one of two lighting conditions (natural sunlight or a daylight fluorescent light).

The geometric mean air concentrations of tetrachloroethylene (averaging time not reported) were 16 and 11 ppm for the men and women, respectively, using results from passive sampling of personal air. The overall geometric mean was 13 ppm.

There was no significant difference in the performance of the dry cleaning workers and unexposed controls on Lanthony's new color test. The percentages of men and women dry cleaning workers who correctly separated colored caps from monochromatic caps were not significantly different from the percentages in the corresponding control group. The study authors noted concluded that they found no distinct case of color vision loss among the dry cleaning workers.

The test used to evaluate study subjects, Lanthony's new color test, is not considered as sensitive as the Lanthony's D-15 desaturated panel test (Geller and Hudnell, 1997). Additionally, the investigators did not match exposed subjects and their controls on a number of important covariates, nor did they present results in a quantitative manner (use of the CCI) (Gobba, 2000).

1.1.2.5. ***Ferroni, C., L. Selis, A. Mutti, D. Folli, E. Bergamaschi and I. Franchini. 1992. Neurobehavioral and neuroendocrine effects of occupational exposure to perchloroethylene. Neurotoxicol. 13: 243–247.***[3]

Ferroni et al. (1992) evaluated neuroendocrine and neurobehavioral effects of tetrachloroethylene exposure among 60 female dry cleaners and 30 unexposed controls who were comparable in age (mean ages 39.7 and 37.6 years, respectively) and vocabulary level. Each dry cleaning shop in a small town outside of Parma, Italy, was visited. The workers were invited to participate in the study, which was part of a preventive health program implemented by the local health office and professional associations of small businesses. There were no refusals. Controls were selected from the workers at a hospital who cleaned clothes using a water-based process. Their jobs were essentially the same as those of the dry cleaners, but they were not exposed to any organic solvents. Both groups filled out a questionnaire on their characteristics and health; medication, including oral contraceptives; life style; and current and past jobs. Both groups met the following criteria: no history of metabolic disorders, no history of psychiatric disorders, and low level of daily alcohol intake. The two groups were similar in height, weight, body mass index, smoking habits, and use of medication, but alcohol intake was about 5% higher (p<0.03) in the control group than in the dry cleaner group.

Workers and controls were given five neurobehavioral tests (part of the Swedish Performance Evaluation System, "adapted" Italian version: finger tapping with both dominant hand and nondominant hand, simple reaction time, digit symbol test, shape comparison-vigilance, and shape comparison-response to stress). All subjects were examined in the morning before their work shift in the same room by the same examiners (NYS DOH, 1997). The tests were part of a computer-based battery, and the same machines and software were used to administer the tests and score the results. The same sequence of tests and protocols were used for all subjects. Although the examiners were not blind to the status of the subjects (dry cleaner or control), the examiners and the dry cleaners were blind to the worker's exposure level (NYS DOH, 1997). Serum prolactin levels were measured in all subjects; all samples were taken just before the neurobehavioral tests. Samples from dry cleaners and controls were alternated and analyzed in the same experimental runs. For women, only those samples obtained during the proliferative phase of the menstrual cycle were used for comparison between groups (41 dry cleaners and 23 controls).

Workplace air samples were randomly collected throughout the work week during summer and winter to account for variability related to either the work cycle or seasonal

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[3] Dr. Mutti provided details on the selection process of exposed and control subjects and also clarified reported results to Dr. Ken Bodgen, New York State Department of Health, in written correspondence dated July 29 and September 5, 1995 (see NYS DOH, 1997).

environmental fluctuations. The median tetrachloroethylene air concentration (4-hour TWA) was 15 ppm and the range of TWA values was 1 to 67 ppm. The subjects' range of tetrachloroethylene blood levels was 0.012 to 0.864 mg/L (median = 0.145 mg/L) (incorrectly expressed in Ferroni et al. [1992] as 12,864 and 145 mg/L [NYS DOH, 1997]). The mean duration of occupational exposure was 10 years.

The dry cleaners showed significantly reduced performance when compared with the unexposed, matched controls in three tests (simple reaction time, $p<0.0001$; vigilance, $p<0.005$; and stress, $p<0.005$), as reported in a single sentence in the results section in Ferroni et al. (1992). Performance on the finger-tapping test (both hands) and digit symbol test was not affected (NYS DOH, 1997). Additionally, the mean serum level of prolactin was significantly higher in the workers than in the matched controls ($p<0.001$). None of the three measures of exposure (duration of exposure and air or blood concentration of tetrachloroethylene) was significantly associated with decreased test scores or increased serum prolactin levels among the dry cleaners.

The study authors concluded that tetrachloroethylene exposure in dry cleaning shops may impair performance and affect pituitary function but that the cross-sectional design prevents distinguishing acute effects from chronic effects. They also noted, however, that the most likely bias of cross-sectional studies is a spontaneous selection of the sample (i.e., workers who believe exposure is making them sick or workers who actually become sick may quit work prematurely and not be included in the study). This is known as selection bias and would lead to an underestimate of the actual or underlying risk

1.1.2.6. *Cavalleri, A., F. Gobba, M. Paltrinieri, G. Fantuzzi, E. Righi and C.L. Aggazzoti. 1994. Perchloroethylene exposure can induce colour vision loss. Neuroscience Lett. 179:162–166.*[4] *Gobba, F., E. Righi, G. Fantuzzi, G. Predieri, L. Cavazzuti and G. Aggozzotti. 1998. Two-year evaluation of perchlorothylene-induced color-vision loss. Arch. Environ. Health 53:196–198.*

In a study on the effects of tetrachloroethylene exposure on the color vision of dry cleaners, Cavalleri et al. (1994) compiled a list of all the dry cleaning shops in the municipality of Modena, Italy, (110 shops employing 189 workers) and randomly selected 60 dry cleaners from 28 premises for recruitment into the study (Aggazzotti et al., 1994). Only full-time workers (n = 52) were asked to participate, and 2 declined. All 50 workers provided, via questionnaires, information on work history, health status, occupational and hobby use of solvents, drinking and smoking habits, and drug use. Thirty-five of the 50 dry cleaners (33 women, 2 men) met the

[4] Dr. Cavalleri provided additional information on this study in written correspondence to the New York State Department of Health dated October 8, 1996 (see NYS DOH, 1997).

inclusion criteria; others were excluded for hypertension, smoking more than 30 cigarettes a day, alcohol consumption exceeding 50 g of alcohol per day, oculo-visual pathology, or working less than 1 year. Another worker was excluded because a matched control could not be found.

The controls were factory workers who were not occupationally exposed to solvents or other neurotoxic chemicals; they were selected and recruited into the study using the same methods that were used for dry cleaners. The controls (n = 35) were from factories in the Modena area and met the same inclusion criteria as the dry cleaners and were matched to dry cleaners by gender, age (±3 years), alcohol consumption (±10 g/day), and cigarette use (±5 cigarettes per day). The mean age of both groups (35 years) and the percentages of each group that were smokers (43%) or alcohol drinkers (71%) were the same.

All subjects appeared healthy and met minimal status of visual acuity. None of the subjects reported hobby exposure to solvents or other substances toxic to the eye. There were no known systematic differences between exposed and control groups or between machine operators and ironers.

Color vision was assessed using Lanthony's D-15 desaturated panel test, in which subjects are asked to put a series of small round "caps" in order by color. The types of errors made can distinguish specific types of color vision deficiency; for example, red-green color blindness (common in males) or blue-yellow color blindness, which is produced by solvent exposure (Mergler and Blain, 1987; Mergler et al., 1987, 1988a, b, 1991; Campagna et al., 1995, 1996). Test scores are based on the ability of each subject to recombine a set of 15 caps colored with desaturated colors according to a definite chromatic sequence, with each mistake increasing the score above a perfect score of 1.00. A formula (the CCI) is used to calculate total errors. This test assesses specific visual neurotransmitters and circuits from the retinal ganglion cells in the eye to higher visual areas.

Exposed and control subjects were tested in a random order (NYS DOH, 1997). All subjects were tested at the same time of day (in the morning, before work) under the same lighting conditions by the same investigator. With respect to exposed subjects, the investigator was unaware of both the exposure levels and the job (operator or ironer) of each dry cleaner.

For all dry cleaners, the mean tetrachloroethylene air concentration (8-hour TWA) was 6 ppm and the range of TWA values was 0.4–31 ppm, using results from passive sampling of personal air. For operators (N = 22), the mean air concentration 8-hour TWA was 7 ppm and the range of TWA values was 0.4–31 ppm. For ironers (N = 13), mean air concentration (8-hour TWA) was 5 ppm and the range of TWA values was 0.5–11 ppm. The mean duration of occupational exposure was 8.8 years. Tetrachloroethylene concentrations were also measured in alveolar air for a subset of these dry cleaners, with a high correlation observed between tetrachloroethylene concentration in alveolar air and the 8-hour TWA levels in ambient air (r = 0.8, $p<0.001$) (Aggazzotti et al., 1994).

Only 3 dry cleaning workers, as opposed to 13 controls, had scored a perfect test score ($p<0.01$). Mistakes were made mainly in the blue-yellow range. Overall, the workers showed poorer performance on the test as compared to controls, as they had a significantly higher mean CCI ($p=0.03$). The effect was statistically significant among operators but not among ironers. The observation for ironers may reflect a lower statistical power in this group due to fewer subjects (13 ironers vs. 22 operators). There also was a statistically significant positive correlation ($p<0.01$) between TWA air concentrations and the CCI (r = 0.52), which remained after multivariate analysis considered previous tetrachloroethylene exposure duration, age, number of cigarettes per day, and calculated daily intake of alcohol as covariates. The effect on color vision may not be rapidly reversible; preliminary data showed that some workers did not improve their scores when retested after 4 weeks of vacation (NYS DOH, 1997). Moreover, the finding among some of these workers by poorer performance on this test in the follow-up study by Gobba et al. (1998), described below, suggests that color vision impairment is a chronic effect. The CCI values were not associated with two other measures of tetrachloroethylene exposure (mean duration and an integrated index of exposure, yearly TWA level). The study authors suggested that this may reflect the difficulty in controlling for the interactive effects of age and exposure and accurately evaluating exposure.

Gobba et al. (1998) reexamined color vision after a period of 2 years in 33 of the 35 dry cleaners and ironers examined by Cavalleri et al. (1994). Two subjects had retired during the 2-year period between examinations. These investigators used the Lanthony D-15 test, the test used by Cavalleri et al. (1994), to assess color vision, and performance was compared to a subject's score from the initial survey (self-control). Tetrachloroethylene concentration in the occupational setting was determined in the breathing zone using personal passive samplers. Monitoring was carried out during the afternoon shift, as Cavalleri et al. (1994) did not show any differences between morning and afternoon samples. Gobba et al. (1998) found tetrachloroethylene concentration had increased during the 2-year period for 19 subjects (geometric mean, from 1.67 ppm at the first survey to 4.35 ppm at the second survey), identified as Group A, and had decreased for 14 subjects (geometric mean, from 2.95 ppm to 0.66 ppm), identified as Group B. For the 33 workers overall, tetrachloroethylene concentration did not change over the 2-year period (geometric mean, from 2.4 ppm to 1.94 ppm at the second survey, $p>0.05$).

Color vision had deteriorated between the two surveys for the entire group, a reflection of the color vision loss among Group A subjects, whose exposure had increased in the second survey. As found in the first survey, perception of the blue-yellow range of color was affected the most, with few subjects presenting a red-green deficit. Color vision performance for the entire group was related significantly to age (r = 0.45) and tetrachloroethylene concentration (r = 0.39). The mean CCI score for Group A subjects was statistically significantly different between the two surveys, and analysis of variance methods that controlled for an effect of age further supported the finding of color vision deterioration among these subjects. For Group B, subjects who experienced lower exposure concentrations by the second survey, the CCI score did not change from that of the initial survey. Additionally, analysis of variance did not show any differences between the first and second surveys.

Overall, the findings of Cavalleri et al. (1994) and Gobba et al. (1998) are in agreement with previous studies on other solvents (Geller and Hudnell, 1997; Mergler et al., 1996; Mergler and Blain, 1987), the blue-yellow range of color vision was primarily affected in the dry cleaners, with only a few workers showing an effect on red-green perception. This suggests a retinal location for the effects (Pokorny and Smith, 1986) or, alternatively, post-receptor processing deficits, perhaps the result of a distal axonopathy of the optic nerve (Mergler, 1995; Spencer and Schaumburg, 1978).

1.1.2.7. *Echeverria, D., R.F. White and C. Sampaio. 1995. A behavioral evaluation of PCE exposure in patients and dry cleaners: a possible relationship between clinical and preclinical effects. J. Occup. Environ. Med. 37:667–680.*

Echeverria et al. (1995) assessed neurobehavioral effects and mood disturbances in four patients diagnosed with tetrachloroethylene encephalopathy. Subject 1 was exposed chronically over a 1-year period when the interior woodwork of her home was mistakenly treated with tetrachloroethylene. The three other cases were occupationally exposed. Subject 2 was exposed during two separate periods: first, for 3 years in a dry cleaning establishment, and second, for 7 years cleaning parts. Subject 3 was exposed for 16 years as a dry cleaning worker. Subject 4 was also exposed as a dry cleaning worker, but her duration of employment was not reported. Subjects 2, 3, and 4 were working with tetrachloroethylene when first tested. Air monitoring data were not available; however, occupational health physicians diagnosed each case with tetrachloroethylene encephalopathy on the basis of symptoms, neurophysiological assessment, and their own examinations.

A large battery of standard neurobehavioral tests was given to each subject. For most tests, impairment was inferred clinically when a subject's score was greater than one standard error of measurement below expectation, which is less restrictive than the criterion (more than two standard deviations below mean) commonly used in neurobehavioral testing to separate normal from abnormal scores (Lezak, 1995). Test results for the four subjects most consistently indicated complaints of fatigue and confusion, accompanied by cognitive deficits on tests assessing memory, motor, visuospatial, and executive function. Repeated testing of subjects 3 and 4 indicated post-exposure improvement on neurobehavioral tests of all the affected functional domains, although performance on some of the more difficult tests in each domain remained impaired. These results suggest an association between CNS effects and tetrachloroethylene exposure, but a conclusion of a causal relationship is precluded by the lack of data on the duration and severity of the tetrachloroethylene exposure.

The investigators also assessed the performance of 65 dry cleaning workers on neurobehavioral tests designed to detect the same impairments noted in the clinical cases. The testing was conducted in 1986. The owners of 125 shops in Detroit, Michigan, were contacted, and 23 agreed to allow their workers to participate in the study. Within each shop, operators were matched on education and age (± 5 years) with a lower-exposure subject.

The subjects (35 men and 30 women) were grouped into three categories of chronic tetrachloroethylene exposure (low, moderate, and high), based on type of shop (wet-transfer or dry-to-dry), job title (counter clerk, presser, or operator), and years of employment. All the operators were placed in the high-exposure category. There was no unexposed control group. Dry cleaning workers placed in the chronic exposure categories of low, moderate, and high had been employed at their main job for 2.1, 3.9, and 14.6 years, respectively. Their mean age was 40.9, 40.6, and 43 years, respectively. The three groups were also characterized by estimates of current exposure (low, medium, and high), which corresponded to mean tetrachloroethylene air concentrations (8-hour TWA) of 11, 23, and 41 ppm, respectively, for counter clerks, pressers, and operators in the more common wet-transfer shops (17 of 23 shops). Estimated air concentrations for counter clerks, pressers, and operators in the dry-to-dry shops were 0.5, 10, and 11 ppm, respectively. The estimates were based on a relationship between breath and air concentrations derived from a larger independent study (Solet et al., 1990). The study authors noted that the estimates were comparable to those found in other surveys of dry cleaning facilities in the United States.

All subjects were tested in groups of two in the afternoon after work on the first or second day of their work week. The tests were conducted in a minivan. Each subject provided a breath sample and completed a medical, symptom, work history, and hobby questionnaire. The subjects were administered six neurobehavioral tests, a test of verbal skills, and questionnaires on emotional states (moods) and CNS symptoms. The neurobehavioral test battery consisted of one test of motor/cognitive function (symbol digit) and five tests of cognitive function (digit span, trailmaking A and B, visual reproduction, pattern memory, and pattern recognition), including three tests of an individual’s ability to process and remember visuospatial stimuli (the latter three tests).

Multivariate analysis was used to evaluate the relationship between a chronic index of lifetime exposure and performance on neurobehavioral tests, after adjusting for the confounding variables of current exposure, a 3-year index of exposure, age, education, verbal skill, alcohol consumption, hours of sleep, fatigue, mood, symptoms, medication, and secondary exposures to neurotoxicants. After adjustment for factors affecting performance, the scores of the dry cleaning workers with high chronic exposure were statistically significantly lower ($p<0.01$) than those of the workers with low chronic exposure in three tests of visual function: visual reproduction, pattern memory, and pattern recognition. Adjusted scores were reduced from 6 to 15%; the two most sensitive tests were those that measured short-term memory of visual designs. These impairments of visually mediated function were consistent with the impairment of visuospatial functions observed in the four patients previously studied by Echeverria et al., who were diagnosed with tetrachloroethylene encephalopathy. Other effects seen in the patients (mood changes and decreased cognitive function in nonvisual tests) were not found in the dry cleaning workers with high lifetime exposures. Among complaints by the dry cleaning workers, only the number of complaints of dizziness from standing up rapidly and "solvent-induced dizziness" over the previous 3 months was significantly elevated ($p\leq0.04$) in the high-exposure group.

The study authors concluded that effects on visuospatial function were consistently found in subjects employed as operators for an average at 14.6 years and exposed to an estimated tetrachloroethylene 8-hour TWA air concentration of 41 ppm, suggesting a vulnerability of visually mediated functions with tetrachloroethylene exposure. This conclusion was based on the impaired performance of the high-exposure group when compared with a group of dry cleaning workers with low lifetime exposure, including 16/22 workers who were probably clerks in wet-transfer shops where the mean current exposure level was 12 ppm. This exposure level is substantially above background ambient levels, and whether the performance of the low-exposure group was impaired when compared with that of a group without occupational exposure (i.e., an unexposed control group) is not known. The lack of an unexposed control group limits the ability of the study to characterize fully the magnitude of the effects on visuospatial ability and to detect exposure-related symptoms or effects on tests of nonvisual cognitive ability. It also limits the extrapolation of the results to other populations exposed to tetrachloroethylene.

1.1.2.8. ***Altmann, L., H.F. Neuhann, U. Kramer, J. Witten and E. Jermann. 1995. Neurobehavioral and neurophysiological outcomes of chronic low-level tetrachloroethylene exposure measured in neighborhoods of dry cleaning shops. Environ. Res. 69:83–89.***

Altmann et al. (1995) used neurophysiological and neurobehavioral techniques to assess the effects of long-term exposures to tetrachloroethylene. A total of 19 tetrachloroethylene-exposed subjects (residents of Mulheim, Germany) were chosen from a population of 92 subjects living in neighborhoods close to dry cleaning facilities. Three criteria were used to select subjects: (1) a tetrachloroethylene blood level above 0.002 mg/L, (2) a period of living above or next to a dry cleaning facility for at least 1 year, and (3) no occupational exposure to organic solvents. The mean age of the exposed subjects was 39.2 years (range, 27–58 years) and the mean duration of living near a dry cleaning facility was 10.6 years (range, 1–30 years). The daily activity pattern of the exposed subjects was not reported.

A total of 30 controls were selected from volunteers; their mean age was 37.2 years (range, 24–63 years). One or two controls, matched for age (± 1 years, but 3 years in one case and 6 years in another case) and gender, were chosen for each exposed subject. The control subjects were recruited mainly from the staff of a public health office or an institute for environmental hygiene, and none reported a history of solvent exposure. Voluntary consent was obtained from all subjects prior to the initiation of testing.

All subjects were given medical examinations. Five exposed (26%) and seven control subjects (23%) were excluded for various medical reasons, including impaired vision, diseases with potential neuropathy, hypertension, and joint impairment. The reasons for exclusion were similar in both groups. All subjects met standards for visual acuity and vibration perception. The final exposed group was composed of 5 men and 9 women and the control group was composed of 9 men and 14 women. The two groups did not differ with regard to consumption of alcoholic beverages, regular medication, smoking, or body mass index, but they did differ in degree of education.

VEPs in response to black-and-white checkerboard patterns were recorded for all individuals. Vibration perception using a tuning fork—a crude measure of peripheral neuropathy—was assessed at the ankle. Five tests included in the Neurobehavioral Evaluation System developed in the United States and adapted for testing on a German population were used: finger-tapping speed with the index finger of both the dominant and the nondominant hand; hand-eye coordination using a joy stick to follow a sine wave on a computer screen; a continuous performance test for assessment of vigilance, which requires a response to a specific stimulus appearing on the computer screen and failure to respond to other stimuli; simple reaction time, which requires the fastest possible response to a simple visual stimulus (measured twice); and visual memory on the Benton visual retention test, which requires a match of a previously displayed stimulus out of several choices after a short delay interval. All of these tests are commonly used to assess occupationally exposed adults, and the software for testing and analysis is available for purchase. All testing was completed in a single 3-hour session; testing times were selected randomly for both exposed or control subjects.

Blood samples were taken once in the examination room immediately before testing (all subjects) and, if possible, once when the exposed subjects were at home. The mean blood level for exposed subjects, based on samples collected in the examination room, was 0.0178 mg/L (standard deviation, 0.469 mg/L). For seven of the nine exposed subjects, blood concentrations in samples collected at home were higher than those in samples collected in the examination room. None of the blood concentrations in the control group exceeded the detection limit of 0.0005 mg/L. For the exposed subjects (data from 13 apartments), indoor air sampling indicated that the mean (7-day TWA) air concentration was 0.7 ppm (standard deviation, 1 ppm) and the median was 0.2 ppm. For the control group, the mean and median values were 0.0005 ppm (standard deviation, 0.0005 ppm) and 0.0003 ppm. There was a good correlation between home indoor air concentrations and blood levels of tetrachloroethylene in the exposed subjects ($r = 0.81$). The correlation was much lower when the examination room blood samples were used ($r = 0.24$).

After adjusting for covariates and possible confounders of age, gender, and education, there were statistically significant group differences between the adjusted mean scores of exposed and control subjects on three neurobehavioral tests (simple reaction time, $p<0.05$ for test 1 and $p<0.01$ for test 2; continuous performance, $p<0.05$; and visual retention, $p<0.05$). In all cases, the exposed subjects had slower response times or more errors than the unexposed controls. No statistically significant differences were observed between the performance of the exposed and control groups on the finger-tapping or eye-hand coordination tests, which are measures of fine motor function or on VEP, which would be expected to be less sensitive than direct measurement of visual function, or on vibration perception at the ankle using a tuning fork.

The relationship between indoor tetrachloroethylene concentration and individual performance was not reported, so it was not possible evaluate concentration-response relationships. Because the responses in the exposed group for the tests highlighted above (simple reaction time, continuous performance, visual retention) were statistically significantly different from those of the control group, whether or not the covariates were considered, an approximate estimate of the impact of the tetrachloroethylene exposures can be derived by comparing the reported response levels for the two groups. The degree of change from control was approximately 15–20% for this subset of tests.

1.1.2.9. ***Spinatonda, G., R. Colombo, E.M. Capodaglio, M. Imbriani, C. Pasetti, G. Minuco and P. Pinelli. 1997. Studio dei processi di produzione della praola: applicazione in un gruppo di soggetti esposti cronicamente a solventi organici (parte II) [Study on speech production processes: application for a group of subjects chronically exposed to organic solvents (part II). Med. Lav. 19:85–88.***

Spinatonda et al. (1997) assessed the effect of tetrachloroethylene exposure on vocal reaction times among 35 dry cleaners and 39 unexposed controls. Controls were matched to exposed individuals for age (mean age of 35 years for both groups) and education. The published paper did not identify the population from which exposed and controls were drawn, the inclusion criteria for exposed subjects and controls, and hence, whether potential study subjects were excluded, nor was information presented as to whether controls were of the same sex as exposed subjects or whether they held jobs similar to those of the tetrachloroethylene-exposed dry cleaners. The investigators did not identify the length of exposure in a tetrachloroethylene-exposed job.

Exposure was assessed by a "grab sample" and not as a weighted average (as expressed in other occupational studies reviewed in this section). Exposure monitoring indicated a median concentration of tetrachloroethylene of 8 ppm (range, 2–136 ppm). An index of cumulative exposure to tetrachloroethylene was also developed for each exposed subject by multiplying the tetrachloroethylene concentration by the number of years worked.

The latency to vocal response to the stimulus (reading) and duration of vocal response were measured in each subject after the presentation of a sequence of words on a computer screen. For each condition, subjects were asked to say the word immediately or following delays of 0.1 or 0.5 seconds. The test was performed using a random sequence of concrete or meaningless disyllabic words. These tests were carried out at the place of employment for dry cleaners and in a clinical setting for controls, indicating that the investigators were not blinded as to a subject's exposure status.

Compared with the control group, the exposed group had statistically significantly longer mean reaction times and/or vocalization durations under all response conditions (immediate or delayed response) with either real or meaningless words. Furthermore, statistically significantly positive correlations were observed between cumulative tetrachloroethylene exposure and immediate reading and delayed reading tasks ($r = 0.69$ and $r = 0.73$, respectively). No information on alcohol consumption or other potential differences between exposed subjects and controls was reported, precluding an analysis of how these factors may have affected the observed association between tetrachloroethylene and reaction time.

1.1.2.10. ***Schreiber, J.S., H.K. Hudnell, A.M. Geller, D.E. House, K.M. Aldous, M.E. Force, K.W. Langguth, E.J. Prohonic and J.C. Parker. 2002. Apartment residents' and day care workers' exposure to tetrachloroethylene (perc) and deficits in visual contrast sensitivity. Environ. Health Perspect. 110: 655–664.***

Schreiber et al. (2002) reported the findings from two different studies that administered visual tests to assess neurologic function in two populations: apartment residents and day care employees who had potential environmental tetrachloroethylene exposure due to close proximity to dry cleaning facilities.[5] All participants—or their guardians in the case of the residential study—signed voluntary consent forms prior to study commencement.

For the residential study, a total of 17 tetrachloroethylene-exposed subjects (11 adults between the ages of 20 and 50, 2 adults over the age of 60, and 4 children) from six families that had resided for an average of 5.8 years (6 years median) in two apartment buildings in New York City. This was an affluent, English-speaking, white population living near New York City's Central Park (telephone communication from K. Hudnell, U.S. EPA, to D. Rice, U.S. EPA). Control subjects were recruited from among NYS DOH employees in Albany, New York, and their families and were age- and gender-matched to exposed apartment residents; control subjects were considered representative of the general population not living near dry cleaning facilities. All controls were white except for one Asian individual. In some cases, more than one control participant was matched to an exposed subject, in which case the visual function test scores of controls were averaged to yield a single point. Mean age was 34.5 years for exposed apartment residents and 33.2 years for control subjects.

Nine adult staff (all females) of a day care facility agreed to participate in the day care study. Controls were age- and gender-matched acquaintances of the exposed participants, local retail shop employees, NYS DOH employees, or staff from other local day care centers with no known tetrachloroethylene exposure. All subjects in the exposed and control groups were white (telephone communication from K. Hudnell, U.S. EPA, to D. Rice, U.S. EPA). Mean age was 27.7 years for control participants and 27.2 years for day care staff; mean duration of employment at the center for exposed subjects was 4 years.

[5] The apartment residents lived in two separate buildings in New York City that each contained a dry cleaning business. The residential study served as a pilot for a larger study that is investigating visual effects among tetrachloroethylene-exposed residents. The day care study was part of an investigation of staff and children carried out by NYS DOH and the Centers for Disease Control and Prevention and reported in Schreiber et al. (2002). The day care facility, located in Albany, New York, was in a building that also housed a business that did dry cleaning. All visual testing for both studies was carried out by the same investigator using the same testing apparatus.

Both study populations and their controls were given a questionnaire to obtain information on sociodemographics; lifestyle factors such as exposure to direct or passive smoke, alcohol consumption, and exercise; medical history; and neurotoxicant exposure in addition to the visual tests. Exposed participants had no known exposure to other neurotoxicants, ongoing illness, current use of neuroactive drugs, or a medical history indicative of neurologic dysfunction, and both exposed participants and controls reported low or moderate alcohol consumption which did not differ between either exposed group and their controls. The investigators also administered visual tests of acuity, contrast sensitivity, and color discrimination to exposed subjects and their referents. The investigators were not blinded as to a subject's status as either exposed or nonexposed.

The assessment of tetrachloroethylene exposure of residents consisted of tetrachloroethylene concentrations in indoor air and personal air samples, exhaled breath, and blood, which were collected at the time of visual testing. Testing was performed during a period of active dry cleaning for four of the families and 1 month after closure of the facility for the remaining two families in the residential study. Additionally, adult residents provided urine samples, which were analyzed for tetrachloroethylene as well as for three products of its metabolism: TCA, trichloroethanol, and the urinary acetyl metabolite. Two exposed participants were mothers who were breastfeeding, and they provided breast milk samples.

Ambient concentrations of tetrachloroethylene were also available for all study participants for an earlier time frame (from 1 to 3 months before the date of visual testing), when active dry cleaning was occurring in both apartment buildings. These measurements were used by NYS DOH to identify study sites. Concentrations of airborne tetrachloroethylene levels in apartment rooms were higher in these samples than in the monitoring data obtained at the time of the visual testing. Median concentrations in these samples, which were taken during the day during active periods of dry cleaning, were 0.21 ppm (mean = 0.36 ppm: range, 0.10–0.9 ppm). Airborne tetrachloroethylene concentrations had decreased in samples collected at the time of visual testing; median tetrachloroethylene concentration was 0.09 ppm (mean = 0.18 ppm; range, 0.01–0.78 ppm). Tetrachloroethylene levels in blood correlated well with levels in room air, personal air, and breath.

Atmospheric monitoring of the day care facility before closure of the dry cleaning business showed airborne concentrations of tetrachloroethylene ranging from 0.27 to 0.35 ppm, with median and mean concentrations of 0.32 ppm. Samples obtained at the time of visual testing, 5 weeks after removal of the dry cleaning machines, approached background concentrations (range, 0.0012–0.0081 ppm).

Visual function testing consisted of visual acuity, contrast sensitivity, and color vision. The visual acuity test assesses the ability to discriminate high frequencies at high contrast; for example, reading successively smaller black-on-white letters as part of an examination for corrective lenses. This typically measures the optics of the eye rather than the neurological integrity of nervous system circuitry. In neither assessment did groups differ in acuity, and individuals wore corrective lenses as appropriate for subsequent testing.

The contrast sensitivity function assesses the integrity of visual pathways. The visual system processes spatial information as a Fourier analysis of sine wave frequencies. Testing of contrast sensitivity is performed by determining the ability of the visual system to detect sine waves of a number of different frequencies tested individually, thereby breaking spatial visual function into its essential components. The stimuli for testing consisted of disks displaying sine waves oriented vertically or 15 degrees to the left or right of the vertical. The subject indicated the orientation of the stimulus either verbally or by a hand gesture. For each of the test frequencies, the contrast between the light and dark portions of the sine wave was decreased until the subject could no longer detect the sine wave pattern. That contrast was considered the threshold for that particular frequency.

Group mean scores for VCS across spatial frequencies were statistically significantly lower in exposed residents than in controls and in day care employees as compared with controls, indicating poorer visual function in the exposed groups. An exposure-response analysis did not show an association between poorer performance and increasing tetrachloroethylene concentration. Among apartment residents, mean scores of VCS in all four children and in both older adults ($\geq$60 years of age) were lower than the 12th percentile score of all control subjects. (The 12th percentile represents the two control subjects with the poorest performance out of the 17 total data points.) In contrast, only 5 of the 11 adults aged less than 60 years scored below the 12th percentile as compared to controls (Figure 1).

The spatial vision of the four children was poor enough that it would likely negatively impact normal activities. For example, at the highest frequency tested, the exposed children required three times as big a difference in the light versus dark part of the grid in order to be able to see the grid. This frequency did not correspond with the detection of fine detail of a scene but rather with the ability to identify small objects. Similar deficits were observed at lower frequencies as well, with the exception of the lowest frequencies that correspond with the ability to distinguish the outlines of large objects. It is unknown whether the difference between groups would have been statistically significant on the basis of the adults under 60 years alone. However, day care employees also had a statistically significantly lower group mean VCS score across all spatial frequencies as compared with the control group (data not shown). No differences between exposed residents or day care employees and their respective controls were observed for visual acuity scores (group means).

Educational differences between residents and their controls were not considered to have confounded the observation of VCS differences between exposed subjects and controls; other studies have looked for but have not found this variable to explain observed differences in VCS in other populations (Mergler et al., 1991; Frenette et al., 1991). Deficits in VCS function are a well-known consequence of solvent exposure in industrial workers (Bowler et al., 1991; Broadwell et al., 1995; Campagna et al., 1995; Donoghue et al., 1995; Frenette et al., 1991; Hudnell et al., 1996a; Mergler et al., 1991). Therefore, the effects of tetrachloroethylene on contrast sensitivity function are not an unexpected finding.

Moreover, urban-rural differences between exposed and control subjects is not thought to strongly bias findings. For example, Kaufman et al. (1988) did not show that urban or rural residence was related to performance on specific subtests of the Wechsler Adult Intelligence Scale, although associations were seen with other variables such as sex, age, and education.

In the residential study, exposed subjects were retested twice after the initial assessment, 6 to 10 months and 17 to 21 months after closure of the dry cleaning facility. Performance across frequencies appeared to worsen over successive episodes (statistical comparisons were not performed) (NYS DOH, 2000a). These results provide evidence that the visual deficits were permanent and perhaps became even worse after closure of the dry cleaning facilities. Control subjects from the initial testing were not retested; however, there is no reason to expect that performance of unexposed subjects would deteriorate. This failure of improvement in function with decreased exposure is consistent with failure of improvement in color vision loss in industrial workers following significant reduction in tetrachloroethylene exposure (Gobba et al., 1998).

Color vision was also assessed in both the residential and the day care groups. Subjects were asked to put a series of small round “caps” in order by color. The types of errors made could distinguish specific types of color vision deficiency: for example, red-green color blindness, which is common in males, or blue-yellow color blindness, which is associated with solvent exposure (Mergler and Blain, 1987; Mergler et al., 1987, 1988a, b, 1991; Campagna et al., 1995, 1996). Neither group was statistically significantly impaired on this test, although the performance of the exposed groups was worse than that of controls, as indicated by the scores on the CCI, particularly in the residential group. These results suggest that VCS is a more sensitive measure of solvent (tetrachloroethylene) exposure than is color vision.

Regarding these permanent changes in contrast sensitivity, it is important to understand that these changes in nervous system pathways are probably not confined to the visual system, but are indicators of nervous system damage in brain areas, which are not as easy to assess as sensory system function, for which normal variability is relatively small compared to other endpoints.

1.2. SUMMARY OF NEUROPSYCHOLOGICAL EFFECTS IN LOW- AND MODERATE-EXPOSURE STUDIES

It is important to compare performance across studies in order to determine whether it is possible to identify a pattern of neuropsychological deficits produced by tetrachloroethylene (Table 1). Deficits in blue-yellow color vision, a well-established effect of solvents, were observed in the Muttray et al. (1997) study of workers previously exposed to a mixture of solvents that contained tetrachloroethylene (not described in Section 1.1.2) and in the high-exposure (7 ppm) but not the low-exposure (5 ppm) groups in Cavalleri et al. (1994). Additionally, the lack of improvement in color vision among dry cleaners studied by Cavalleri et al. (1994) whose exposure to tetrachloroethylene had decreased over a 2-year period (Gobba et al., 1998) suggests impaired color vision may be a persistent chronic effect. In a recent residential study of tetrachloroethylene exposure at a much lower concentration (0.4 ppm) than previously studied (Schreiber et al., 2002), there was a decrement in color vision, although it was not statistically significant. This suggests that color vision impairment might be caused by low tetrachloroethylene concentrations, but more information is needed to confirm the Schreiber et al. (2002) observations.

Deficits in spatial vision, as measured by tests for visual contrast sensitivity (VCS), are also a well-established effect of exposure to solvents (Bowler et al., 1991; Broadwell et al., 1995; Campagna et al., 1995; Donoghue et al., 1995; Frenette et al., 1991; Hudnell et al., 1996a, b; Mergler et al., 1991). Schreiber et al. (2002) was the only study to measure VCS. Moderate deficits were observed in adults in both the day care and residential populations. The severe deficit in the residential study is quite surprising. By comparison, the magnitude of the deficit in VCS was much more severe, for example, than deficits in monkeys exposed to a relatively high dose of methylmercury, a neurotoxicant that affects vision preferentially (Rice and Gilbert, 1990).

Three studies assessed fine motor control using various instruments, and all three found no effect. Two of these studies—an occupational study with relatively higher exposure (Ferroni et al., 1992) and the Altmann et al. (1995) residential study—also assessed simple reaction time, a task that uses a motor response and demands a relatively modest amount of attention; results were positive in both studies.

These findings on simple reaction time are in contrast to those of Lauwerys et al. (1983) who did not observe any statistically significant differences on this test between dry cleaners and their referent. These investigators also did not find a statistically significant difference in the prevalence of self-reported symptoms among exposed subjects compared to controls, an observation inconsistent with Cai et al. (1991), who reported exposure-related increases in the prevalence of subjective symptoms among dry cleaning workers exposed to 20 ppm (mean 8-hour TWA) tetrachloroethylene.

Speed of information processing was assessed in four studies, Seeber (1989), Ferroni et al. (1992), Echeverria et al. (1995), and Spinatonda et al. (1997). Seeber (1989) used two tasks. Effects were observed in both groups on a task requiring recognition of briefly presented stimuli. In a choice reaction time task, effects were borderline in the lower-exposure group and negative in the higher-dose group. Spinatonda et al. (1997) found effects on response to vocal and visual stimuli. Conversely, the times on the finger tapping test were not statistically significantly different between dry cleaner and referents in Ferroni et al. (1992). Speed of information processing also was not shown in Echeverria et al. (1995) to be affected by cumulative tetrachloroethylene exposure.

Ferroni et al. (1992) and Altman et al. (1995) assessed vigilance using a continuous performance procedure in which the subject faces a screen that presents one of several different stimuli at random intervals. The subject must make a response to a specified stimulus and not to the others. This test measures sustained attention and is correlated with performance on tests of executive function. Both studies found deficits as a result of tetrachloroethylene exposure on this task.

Seeber (1989) found effects on two tests of attention that are subsets of the Weschler IQ tests and so were designed to be sensitive to performance within the normal range. These investigators also found positive effects on a visual scanning test that is usually used to assess laterality of brain damage but has also proved sensitive to toxicant (lead) exposure (Bellinger et al., 1994). In contrast, Echeverria et al. (1995) and Ferroni et al. (as described in NYS DOH, 1997) did not find effects on digit span or digit symbol despite higher levels of exposure as compared with Seeber (1989).

The effects of tetrachloroethylene on tests of visuospatial function are of particular interest in light of the effects identified on tests of visual function per se. Echeverria et al. (1995) found effects on tests of pattern memory, visual reproduction, and pattern recognition in the absence of effects on attention (digit symbol and digit span) or executive function (Trailmaking A and B). One hypothesis is that these effects may be the result of deficits in visual function or higher-order processing in the visual system, given that lower exposures produced frank visual deficits. Seeber (1989) also reported impaired visuospatial recognition in both exposure groups, and Altmann et al. (1995) observed deficits on a test of visuospatial function at much lower exposures than those of the other two studies.

The pattern of effects observed in these studies shows a consistency between the occupational studies and studies of residents. The finding of decrements in visuospatial function and visual function per se in occupationally exposed dry cleaners are supportive of the observed deficits in visual function in one residential population (Schreiber et al., 2002) as well as the findings in a second residential population (Altmann et al., 1995). Moreover, contrast sensitivity function may be a more sensitive endpoint than color vision loss, as previously discussed.

The human studies all have limitations. Most importantly, these studies were designed to identify a hazard and not to identify an exposure concentration associated with no adverse effect. In some studies, investigators were not blinded as to subject status, a potential source of bias, particularly in situations in which the investigator interacted directly with the subject during testing. None of these studies included a large number of subjects—fewer than 100 in most cases. All studies used a cross-sectional design, which is weaker than a longitudinal design for a number of reasons, including a greater potential for selection bias and exposure misclassification (the latter of which would bias the results toward the null). Several studies provided insufficient details on the population from which controls were selected (Seeber, 1989; Spinatonda et al., 1997; Ferroni et al., 1992) or the details provided raise concerns regarding the appropriateness of the control group (Seeber, 1989; Spinatonda et al., 1997; Schreiber et al., 2002 [residents only]; Ferroni et al., 1992). For some of the occupational studies, the descriptions of behavioral testing procedures or results were insufficient or ambiguous (Ferroni et al., 1992; Seeber, 1989; Spinatonda et al., 1997).

These studies do have important strengths. They describe susceptibility to tetrachloroethylene toxicity in humans, eliminating the need for quantitative extrapolation from animal models. Moreover, two studies (Cavalleri et al., 1994; Spinatonda et al., 1997) reported exposure response gradients, providing greater confidence of tetrachloroethylene as the causal exposure. Several studies (Altmann et al., 1995; Schreiber et al., 2002; Echeverria et al., 1995) employed multiple measures of exposure (ambient monitoring, personal monitoring, and in some cases, biological monitoring) with a high degree of correlation between ambient concentration and biological metrics such as blood tetrachloroethylene concentration, suggesting ambient exposure as a reasonable exposure metric.

Individual studies have taken appropriate means to minimize bias and potential confounding. Study investigators have either (1) matched exposed and control subjects on a number of important factors such as age, alcohol consumption, and/or education (Cavalleri et al., 1994; Spinatonda et al., 1997; Schreiber et al., 2002; Altmann et al., 1995; Echeverria et al., 1995), (2) excluded subjects whose diseases or conditions may have been associated with neurologic deficits (Altmann et al., 1995; Cavalleri et al., 1994; Ferroni et al., 1992; Echeverria et al., 1995), (3) shown no difference in group means between exposed subjects and their referents on a number of factors such as alcohol consumption (Schreiber et al., 2002; Ferroni et al., 1992), or (4) provided results in which statistical analysis (regression analyses) of the data accounted for a number of joint factors on the outcome measure (Altmann et al., 1995; Seeber, 1989; Echeverria et al., 1995). These measures give greater confidence that the decrement in neurological performance observed in these studies was more likely caused by tetrachloroethylene exposure.

Effects on spatial vision are well-known consequences of solvent exposure in industrial workers (Bowler et al., 1991; Broadwell et al., 1995; Campagna et al., 1995; Donoghue et al., 1995; Frenette et al., 1991; Hudnell et al., 1996a; Mergler et al., 1991). Other organic solvents, as well as alcohol, induce effects on memory and color vision (Altmann et al., 1995; Mergler et al., 1991; Hudnell et al., 1996a, b). Mergler and Blain (1987) also identified several hypotheses for organic solvent-related dyschromatopsia, including effects on the neuron. Both VCS deficits and color discrimination deficits are commonly present prior to detectable pathology in the retina or optic nerve head, making this one of the earliest sign of disease (Regan, 1989). Effects in the visual system may also have “downstream” consequences on neurological tests that use visual stimuli or require a visually mediated response (Grandjean et al., 2001; Hudnell et al., 1996b). The consistency of the human observations suggest a common mode of action of organic solvents, including tetrachloroethylene, to degrade pattern vision. By analogy, these observations support an inference of tetrachloroethylene-induced neurobehavioral effects.

2. ANIMAL STUDIES

2.1. INHALATION STUDIES

Mattsson et al. (1998) studied the effects of exposure to tetrachloroethylene acutely or for 13 weeks on flash-evoked potentials (FEPs), somatosensory-evoked potentials (SEPs), EEGs, and rectal temperature in Fischer 344 rats. During the acute (pilot) study, male rats were exposed to 0 or 800 ppm tetrachloroethylene for 6 hours per day for 4 days and tested before and after exposure on the fourth day. Changes in FEP, SEP, and EEG components were observed. In the subchronic study, the above endpoints plus BAEPs and caudal nerve conduction velocity were determined in male and female rats exposed to 0, 50, 200, or 800 ppm for 6 hours per day for 13 weeks. Testing was performed during the week following cessation of exposure. Changes in FEP were observed at the highest dose. Several measures of BAEP were affected at 50 ppm but not at higher doses. BAEP power was also affected at 800 ppm. Other measures were not affected. The finding of an overall greater effect following short-term (4-day) exposure as compared with longer-term exposure is similar to the findings of Moser et al. (1995) on a number of measures of a neurotoxicity battery.

The effects of exposure to 90–3600 ppm tetrachloroethylene for 1 hour on motor activity was examined in male MRI mice (Kjellstrand et al., 1985). A strong odor (cologne) was used as the control condition. Total activity was monitored during the dark period during exposure and for several hours thereafter. All doses produced increased activity during exposure, which decreased over several hours after cessation of exposure. Although apparently no statistical analyses were performed, it is clear from the figures that the lowest dose produced an *average* performance well outside the boundary of the 95% confidence intervals of the cologne-treated controls and that it was dose-dependent. Tetrachloroethylene induced motor activity at concentrations lower than those of the other organic solvents tested (methylene chloride, toluene, trichloroethylene, 1,1,1-trichloromethane).

De Ceaurriz et al. (1983) exposed male Swiss OF1 mice to 596, 649, 684, or 820 ppm tetrachloroethylene for 4 hours. Immediately following exposure, subjects were immersed in a cylinder filled with water and the duration of immobility was observed for 3 minutes. The term "behavioral despair" has been coined for this initial immobility, and the length of immobility is shortened by antidepressant administration. Tetrachloroethylene exposure also shortened the period of immobility, with a no-observed-effect level (NOEL) of 596 ppm.

Wang et al. (1993) exposed male SD rats to 300 ppm tetrachloroethylene continuously for 4 weeks or to 600 ppm for 4 or 12 weeks. Exposure to 600 ppm at either duration resulted in reduced brain weight gain, decreased regional brain weight, and decreased DNA in frontal cortex and brainstem but not hippocampus. Four specific proteins (S-100, glial fibrallary acidic protein, neurone-specific enolase, and neurofilament 68 kD polypeptide) were decreased at 4- and/or 12-week exposures to 600 ppm; 300 ppm had no effect on any endpoint.

In a study from the same laboratory (Rosengren et al., 1986), Mongolian gerbils of both sexes were exposed to 60 or 300 ppm tetrachloroethylene for 3 months, followed by a 4-month solvent-free period. Changes in both S-100 (an astroglial protein) and DNA concentrations in various brain regions were observed at the higher concentration, and decreased DNA in frontal cortex was observed after exposure to 60 ppm. The higher concentration also produced decreased brain but not body weight. The results at 60 ppm were replicated in a follow-up study (Karlsson et al., 1987).

In a related study (Briving et al., 1986), Mongolian gerbils were exposed for 12 months to tetrachloroethylene at 120 ppm. At the end of exposure, out of a total of 8 amino acids assayed, taurine was significantly decreased in the two brain regions assessed (hippocampus and cerebellum), and glutamine was elevated in the hippocampus. γ-Aminobutyric acid (GABA) levels were unaffected, as were uptake of GABA and glutamate.

The effect of tetrachloroethylene on neurotransmitter levels in the brain was explored in male SD rats exposed continuously to 200, 400, or 800 ppm for a month (Honma et al., 1980a, b). The 800 ppm dose produced a decrease in ACh in the striatum, and there was a dose-related increase in a peak containing glutamine, threonine, and serine in whole-brain preparations. GABA, NE, 5-HT, and other amino acids were not affected.

White male and female MRI mice were exposed to 9, 37, 75, or 150 ppm tetrachloroethylene continuously for 30 days to 150 ppm for one of several exposure periods ranging from 5 to 30 days or to 150 ppm for 30 days with various recovery periods (Kjellstrand et al., 1984). Other groups were exposed intermittently on several dosing and exposure regimens that resulted in a TWA of 150 ppm for 30 days. Plasma butyrylcholinesterase (BuChE) levels, organ weights, liver morphology, and motor activity were assessed. BuChE was elevated after continuous exposure to 37 ppm or greater. Liver weight was increased at all doses following continuous exposure, and body weight decreased at 37 ppm or above. Motor activity results following continuous exposure were not reported. BuChE and liver weight were both elevated at a TWA of 150 ppm for 30 days, regardless of the length of the exposure pulse. This was true even for a 1-hour exposure (at 3600 ppm) as well as at the lowest concentration (225 ppm). All concentrations of intermittent exposure also increased motor activity. A recovery period reversed the effects on BuChE, whereas liver weight was still slightly elevated at 150 days after cessation of exposure. Changes in liver morphology were detected following exposure to 9 ppm for 30 days and reversed after cessation of exposure.

The effects of exposure to 200 ppm tetrachloroethylene 6 hours per day for 4 days in male SD rats were examined on a number of endpoints (Savolainen et al., 1977a, b). Rats were killed on the fifth day following a further 0 to 6 hours of exposure. Tetrachloroethylene levels were highest in fat, followed by liver, cerebrum, cerebellum, lung, and blood. Tissue levels increased in all tissues over the 6 hours of exposure. Brain RNA content decreased, and brain nonspecific cholinesterase was increased on the fifth day, although no statistical comparisons were performed. Locomotion in an open field was increased immediately following the end of exposure on the fourth day, with no difference 17 hours after exposure, although no statistical comparisons were made. Brain protein, GSH, and acid proteinase were unaffected.

A series of experiments was performed on the effects of tetrachloroethylene on brain lipid patterns. Exposure to 320 ppm for 90 days (Kyrklund et al., 1990) or 30 days (Kyrklund et al., 1988) in male SD rats resulted in changes in the fatty acid composition of the cerebral cortex, which persisted after a 30-day recovery period (Kyrklund et al., 1990). Similar results were observed in the cerebral cortex and hippocampus after exposure to 320 ppm in the Mongolian gerbil (sex unspecified) in the presence of reduced brain weight (Kyrklund et al., 1987). Exposure of male Mongolian gerbils to 120 ppm for 12 months also resulted in decreases in long-chain, linolenic acid-derived fatty acids in the cerebral cortex and hippocampus (Kyrklund et al., 1984).

Kyrklund and Haglid (1991) exposed pregnant guinea pigs to airborne tetrachloroethylene continuously from gestation days (GDs) 33 through 65. The exposure was continuous at 160 ppm except for 4 days at the beginning and end of the exposure period, when it was reduced to 80 ppm. In the control group there were three dams with litter sizes of four, three, and two pups, and in the exposed group there were three dams with litter sizes of two each. The pup body weights differed between litters. In the data analysis, three pups in the control group were eliminated and the six pups in the treatment and control groups were assumed to be independent, which is an invalid assumption. According to the authors' analysis, the offspring had a slightly altered brain fatty acid composition, with a statistically significantly reduced stearic acid content in the treatment group, which is consistent with the authors' earlier findings in rats. This conclusion might have been different if the investigators had grouped litters rather than pups as independent groups. The results suggest that tetrachloroethylene could have reduced the litter size, but a much larger study would be necessary to establish reduced litter size as an effect of tetrachloroethylene.

Nelson et al. (1980) of NIOSH investigated developmental neurotoxicity in SD rats by exposing pregnant dams to tetrachloroethylene at concentrations of 100 ppm or 900 ppm during both early pregnancy (GDs 7–13) or late pregnancy (GDs 14–20). The investigators made morphological examinations of the fetuses and performed behavioral testing and neurochemical analysis of the offspring. There were no alterations in any of the measured parameters in the 100 ppm groups. At 900 ppm there were no skeletal abnormalities, but the weight gain of the offspring as compared with controls was depressed about 20% at weeks 3–5. Developmental delay was observed in both the early and late pregnancy groups. Offspring of the early pregnancy-exposed group performed poorly on an ascent test and on a rotorod test, whereas those in the late pregnancy group underperformed on the ascent test only at postnatal day 14. However, later in development (days 21 and 25), their performance was higher than that of the controls on the rotorod test. These pups were markedly more active in the open field test at days 31 and 32.

There were no effects on running in an activity wheel on days 32 or 33 or avoidance conditioning on day 34 and operant conditioning on days 40 to 46. Neurochemical analyses of whole-brain (minus cerebellum) tissue in 21-day-old offspring revealed significant reductions in acetylcholine levels at both exposure periods, whereas dopamine levels were reduced among those exposed on GDs 7–13. Unfortunately, none of the statistics for the 100 ppm treatments were presented. The authors observed that more behavioral changes occurred in offspring exposed during late pregnancy than in those exposed during early pregnancy.

A multigeneration study of the effects on rats exposed to airborne concentrations of tetrachloroethylene was performed by Tinston (1994). The investigators observed several developmental effects. Of interest here were the signs of CNS depression (decreased activity and reduced response to sound) observed for the first 2 weeks in both adult generations and when the exposure was resumed on day 6 postpartum in the F1 generation (adults and pups). These effects disappeared about 2 hours after cessation of the daily exposure. Other overt signs of tetrachloroethylene poisoning among the adults included irregular breathing and piloerection at both 1000 and 300 ppm. These changes stopped concurrently with cessation of exposure or shortly thereafter.

2.1.1. Summary of Animal Inhalation Neurotoxicity Studies

In order to compare the animal inhalation neurotoxicity studies with each other and to discover whether there is any relationship across studies between the lowest-observed-adverse-effect level (LOAEL) and the duration of treatment, the data were summarized (Table 2) and then plotted as the log (duration, weeks) versus log (LOAEL) (Figure 2). The plot shows that there is no systematic trend in the relation between the LOAEL and treatment duration. It also shows that the LOAEL varies over a 22-fold range: from 37 ppm for 30 days for increased brain butyrylcholinesterase in mice observed by Kjellstrand et al. (1984) to 800 ppm for 13 weeks for alteration in the FEP in rats observed by Mattsson et al. (1998). Other observations at comparatively low concentrations are decreased DNA in gerbils by Rosengren et al. (1986) and Karlsson et al. (1987) at 60 ppm and increased motor activity in mice at 90 ppm observed by Kjellstrand et al. (1985). The LOAEL for these studies as a group is therefore in the range of 37 to 90 ppm, and the effects at these levels are changes in neurotransmitter levels and increased motor activity. Changes in fatty acid composition were observed at somewhat higher concentrations (320 ppm).

2.2. ORAL AND INTRAPERITONEAL (i.p.) STUDIES

A study in male SD rats assessed the acute or short-term effects of tetrachloroethylene by gavage on several screening tests (Chen et al., 2002). A single dose of 500 mg/kg to adult rats produced changes on three different tests of pain threshold, locomotor activity, and seizure susceptibility threshold following pentylenetetrazol infusion, whereas 50 mg/kg had statistically significant effects on seizure threshold only. In the short-term study, young 45–50 gm rats were dosed 5 days per week for 8 weeks with 5 or 50 mg/kg. Behavioral testing began 3 days after the last dose. Locomotion was affected only at the high dose, whereas both doses produced effects on the other four endpoints. The 8-week exposure resulted in retarded weight gain in both treated groups, which was about 10% at the end of the dosing period.

The interpretation of these results is problematic. The tests are all observational in nature, requiring scoring by the observer. It does not state in the paper that the observer(s) was blind to the treatment group of the animals, which is essential for such tests to be valid. In fact, because there were differences in weight between control and treated rats, it would probably be easy to distinguish treated from control animals simply by looking at them. Further, the paper does not state whether all animals were tested by the same person for each task or, if not, whether there was any indication of interobserver correlation. The potential effect of the difference in weight between the control and the treated groups on these measures is also unknown. Given that the differences between the control and the treated groups in response latency to painful stimuli is tenths or one-hundredths of a second with no dose-response, these issues are of serious concern.

Umezu et al. (1997) assessed various behavioral endpoints in 8-week-old ICR male mice at the beginning of the experiment. Righting reflex was affected after single-dose i.p. administration of tetrachloroethylene at 4000 but not at 2000 mg/kg or lower, and ability to balance on a wooden rod was decreased at 2000 but not at 1000 mg/kg or lower. Response rate on a fixed-ratio 20 (FR20) schedule—which requires 20 responses for each reinforcement—was affected at 2000 but not at 1000 mg/kg or lower 30 minutes after administration. In a procedure in which a thirsty mouse was shocked every 20th lick of a water spout, mice dosed with 500 mg/kg but not with higher or lower doses received an increased number of shocks. In an FR20-FR20 punishment schedule, responding in the punishment condition was increased at 1000 but not at 500 mg/kg or lower. A puzzling aspect of this study is the mention in the methods section of "breeding animals," with no further explanation. If the investigators bred their own mice, there is no indication of how pups were assigned to treatment groups.

Moser et al. (1995) examined the effects of a number of potentially neurotoxic agents, including tetrachloroethylene, on a neurotoxicity screening battery in adult female Fischer 344 rats following either a single gavage dose (acute exposure) or repeated gavage doses over 14 days (subacute exposure). For the acute study, subjects were tested 4 and 24 hours following exposure. After acute exposure, a lowest-observed-effect level of 150 mg/kg was identified for increased reactivity to being handled 4 hours after dosing, with increased lacrimation, decreased motor activity, abnormal gate, decreased response to an auditory stimulus, decreased ability to right, and increased landing foot splay at higher doses at 4 and/or 24 hours post-dosing. A NOEL was not identified. In the subacute study, no endpoints were significantly different from those of controls at doses of 50–1500 mg/kg. This presumably represents behavioral adaptation following repeated exposure to tetrachloroethylene.

Locomotor activity was monitored in MRI mice gavaged with 5 or 320 mg/kg tetrachloroethylene for 7 days beginning at 10 days of age (Fredriksson et al., 1993). Twelve male pups from three or four litters were assigned to each treatment group. Locomotion, rearing, and total activity (vibration of the cage) were measured for 60 minutes at 17 and 60 days of age.

Locomotor activity of treated mice in both dose groups was statistically significantly increased, and rearing behavior decreased as compared with controls for all three measures at 60 days of age but not at 17 days. However, the results of this study are uninterpretable as an effect of tetrachloroethylene exposure for two reasons: (1) the results at 320 mg/kg were no different than those at 5 mg/kg, indicating that something besides exposure was causing the effect, and (2) littermates were used as independent observations in the statistical analysis. This invalid procedure can increase the apparent α and result in erroneous statistical results. For example, Holson and Pearce (1992) demonstrated that for body weight, using three or four littermates as independent observations, as in the above study, results in the nominal α increasing from 0.05 to 0.23–0.38. Similar litter effects have been demonstrated for behavioral data (Buelke-Sam et al., 1985).

Locomotor activity was assessed in 6-week-old male Wister rats following i.p. doses of 100, 500, or 1000 mg/kg tetrachloroethylene for 3 consecutive days, with activity being monitored for at least 1 week following cessation of administration (Motohashi et al., 1993). Animals were monitored 24 hours per day, and locomotor activity (measured as change in electrical capacitance of a circuit beneath the floor of the cage) was analyzed by time-series analysis and spectral analysis. All doses of tetrachloroethylene changed circadian rhythm in a dose-dependent manner, with the increased activity at the start of the dark period delayed by tetrachloroethylene exposure. Recovery took 3 to 5 days after cessation of exposure.

Operant performance on a fixed-ratio 40 schedule of reinforcement was assessed in adult male SD rats gavaged with 160 or 480 mg/kg tetrachloroethylene immediately before testing (Warren et al., 1996). The lower dose produced no effect on response rate over the 90-minute session, whereas the higher dose produced a transient rate decrease, recovering after 20 to 40 minutes in three of six animals and inducing a complete cessation of response in two of the six animals. Tetrachloroethylene concentrations increased rapidly after administration in blood, brain, fat, liver, and muscle. For the duration of the 90-minute period of testing, blood tetrachloroethylene levels were approximately linearly related to the administered dose, but brain tetrachloroethylene levels were similar for both dose groups.

A summary of the oral neurotoxicity animal studies is presented in Table 3. For the six oral neurotoxicity studies in rodents reviewed here, only one (Fredriksson et al., 1993) described effects lasting more than 1 week. In that study the effect (increased motor activity) was the same at 5 and 320 mg/kg, and the results cannot be interpreted as an effect of tetrachloroethylene treatment, as explained above. The lowest LOAEL occurring in the four remaining studies is 100 mg/kg for delayed onset of circadian activity in rats (Motohashi et al., 1993). This LOAEL is an i.p. dose describing transient neurological effects and is not comparable to inhalation or ingestion LOAELs without pharmacokinetic modeling of an appropriate dose metric. No information is available for irreversible neurological effects via the oral route.

3. PRELIMINARY SUMMARY OF NEUROTOXIC EFFECTS FOR DISCUSSION

Taken together, the preponderance of epidemiologic evidence is supportive of an association between subclinical neurobehavioral system effects and tetrachloroethylene exposure. The pattern of effects on vision may be consistent with decrements in visually mediated functions, as suggested by Echeverria et al. (1995). The test for VCS is sensitive to neurological dysfunction associated with many diseases affecting the nervous system (NYS DOH, 2000b). Moreover, VCS deficits as well as color discrimination deficits are commonly present prior to detectable pathology in the retina or optic nerve head, making this one of the earliest signs of disease (Regan, 1989). Additionally, other organic solvents, as well as alcohol, induce effects on memory and color vision (Altmann et al., 1995; Mergler et al., 1991; Hudnell et al., 1996a, b). The consistency of these observations suggest a common mode of action of organic solvents to degrade pattern vision. Hence, these observations, by analogy, add support to an inference of tetrachloroethylene-induced neurobehavioral effects.

The human studies on dry cleaning workers chronically exposed to tetrachloroethylene indicate that tasks requiring the processing of visual information (color vision, reaction time, coding speed, and visual memory) are particularly vulnerable to alterations from exposure to tetrachloroethylene (Seeber et al, 1989; Ferroni et al., 1992; Cavalleri et al., 1994; Echeverria et al., 1995; Spinatonda et al., 1997).

One study of tetrachloroethylene exposure in residences near a dry cleaning facility (Altmann et al., 1995) and a pilot study of tetrachloroethylene exposure in residences and in a daycare center located near a dry cleaning facility (Schreiber et al., 2002) found decrements in several neurological parameters at lower exposures than did the studies of occupational exposures cited above. This indicates that CNS effects can occur at a lower concentration than inferred from the studies of dry cleaners, which have been of exposures several-fold higher than those in these residential studies. LOAELs in the human studies of CNS effects range from 0.3 ppm to 41 ppm.

Alcohol by itself cannot explain the observed deficits in neurobehavioral functions, because statistical analyses of the epidemiologic observations controlled for this covariate. However, effects from the interaction between tetrachloroethylene exposure and alcohol consumption were not well investigated in these studies. Valic et al. (1997) showed greater decrements in color vision among subjects with both exposures when compared with individuals with solvent exposure only or with neither exposure.

There are no human studies investigating drinking water or other oral exposures to tetrachloroethylene and neurotoxic effects.

The research in animal models (rodents) on the effects of tetrachloroethylene on functional endpoints consists almost exclusively of screening studies (functional observation battery, motor activity) or effects on sensory system function, as assessed by evoked potentials. Effects on motor activity and motor function have been observed with some consistency following either adult or developmental exposure. Changes in VEPs were also reported following acute but not subchronic exposure. In addition, changes in brain DNA or protein levels and lipid composition were altered following inhalation exposure, with changes observed in the cerebellum, hippocampus, and frontal cortex. Although tests of cognitive function have apparently not been performed in rodents, the neurochemistry changes observed in the hippocampus and frontal cortex are consistent with observed effects on cognition and memory in humans. Therefore, effects observed in humans and in rodent models exhibit a reasonable degree of congruence.

Table 1. Summary of neuropsychological effects of tetrachloroethylene in humans

Neurological test	Study, number of subjects, exposure level									
	Cavalleri et al. (1994)	Echeverria et al. (1995)[a]	Ferroni et al. (1992)	Seeber et al. (1989)	Spinatonda et al. (1997)	Altmann et al. (1995)	Schreiber et al. (2002)		Lauwerys et al. (1983)	Nakatsuka et al. (1992)
							Residents	Day care		
	70	65	90	185	74	37	34	18	59	184
	7 pmm	11 ppm 23 ppm 41 ppm	15 ppm	12 ppm 53 ppm	8 ppm	0.7 ppm	0.4 ppm	0.1 ppm	21 ppm	15 ppm
Contrast sensitivity (spatial vision)							+	+		
Color confusion index (Yellow-blue)	+/– [b]						trend +, not statistically significant			– [c]
Fine motor function			–	–		–				
Simple RT (attention, motor)			+			+			--	
Continuous performance (vigilance)			+			+				
Visuospatial function		+, +, + pattern recognition, reproduction, memory		+ digit reproduction		+ Benton				

Table 1. Summary of neuropsychological effects of tetrachloroethylene in humans (continued)

Neurological test	Study, number of subjects, exposure level									
	Cavalleri et al. (1994)	**Echeverria et al. (1995)[a]**	**Ferroni et al. (1992)**	**Seeber, (1989)**	**Spinatonda et al. (1997)**	**Altmann et al. (1995)**	**Schreiber et al. (2002)**		**Lauwerys et al. (1983)**	**Nakatsuka et al. (1992)[b]**
							Residents	**Day care**		
	70	65	90	185	74	37	34	18	59	184
	7 pmm	11 ppm 23 ppm 41 ppm	15 ppm	12 ppm 53 ppm	8 ppm	0.7 ppm	0.4 ppm	0.1 ppm	21 ppm	15 ppm
Information processing speed		–	–	+ perceptual threshold + "delayed reaction" on choice reaction time	+ vocal reproduction					
Digit span, digit symbol	+ dry cleaners[d], - ironers[d]	–, – (both)	–	+/–, +						
Cancellation (visual scanning)				+						
Stress reaction time			+							
Trailmaking (executive function)		–								

[a] Field study, no unexposed controls.
[b] Positive in dry cleaners, negative in ironing workers with lower exposure.
[c] Using less sensitive test instrument and data analysis procedure than the other studies.
[d] Cavalleri et al. (1994) showed an effect in dry cleaners but not ironers with lower exposure.

+ = positive effect, impaired performance in exposed group
– = no effect of tetrachloroethylene

Table 2. Summary of animal inhalation neurotoxicology studies

Subjects	Effect	LOAEL (ppm)	Reference
Fischer 344 rats	Changes in FEP, SEP, EEG Increase in late component of FEP	800, 4 days 800, 13 weeks	Mattsson et al. (1998)
MRI mice, males	Increase in motor activity	90, 1 hour	Kjellstrand et al. (1985)
Swiss OF1 mice, males	Decrease in duration of immobility	649, 4 hours	De Ceaurriz et al. (1983)
SD rats	Decreased weight gain Behavioral changes, more extensive for late pregnancy exposure Decreased brain acetylcholine	0, 100, 900 on days 7–13 or on days 14–20 NOAEL = 100 LOAEL = 900	Nelson et al. (1980)
SD rats, males	Reduced brain weight, DNA, protein	600, 12 weeks	Wang et al. (1993)
	Decrease in brain DNA, increase in brain cholinesterase	200	Savolainen et al. (1977a, b)
	Change in fatty acid composition of cerebral cortex	320, 12 weeks 320, 4 weeks	Kyrklund et al. (1990, 1988)
	Neurotransmitter changes, brain regions	800, 4 weeks	Honma et al. (1980a, b)
Mongolian gerbils	Decrease in DNA, frontal cortex Decrease in brain weight	60, 12 weeks 300, 12 weeks	Rosengren et al. (1986)
	Same as above	60, 12 weeks	Karlsson et al. (1987)
	Taurine, glutamine changes in brain regions	120, 12 months	Briving et al. (1986)
	Decrease in brain weight, change in fatty acids	320, 12 weeks	Kyrklund et al. (1987)

Table 2. Summary of animal inhalation neurotoxicology studies (continued)

Subjects	Effect	LOAEL (ppm)	Reference
Mongolian gerbils (con't)	Decreased brain long-chain fatty acids	120, 52 weeks	Kyrklund et al. (1984)
	Decrease in brain stearic acid after in utero exposure (questionable findings)	160, gestation days 33 to 65	Kyrklund and Hagid (1991)
NMRI mice, males and females	Increase in butyrylcholinesterase	37, 4 weeks	Kjellstrand et al. (1984)
	Motor activity changes	150, 4 weeks	Kjellstrand et al. (1984)
Rats, multigeneration study	CNS depression in first 2 weeks of F1 and F2 generations, which ceased 2 hours after daily exposures	0, 100, 300, 1000	Tinston (1994)

LOAEL = Lowest-observed-adverse-effect level
FEP = Flash-evoked potential
SEP = Somatosensory-evoked potential
EEG = Electroencephalogram
NOAEL = No-observed-adverse-effect level

Table 3. Summary of oral neurotoxicity animal studies

Subjects	Effect	Dose	Reference
SD rats, male	Pain threshold, pain susceptibility, weight gain decrement Interpretation is unclear	5, 50 mg/kg daily for 8 weeks	Chen et al. (2002)
	Operant responses stopped immediately after 480 mg/kg dose, then 2/3 of animals recovered by 40 minutes No effect at 160 mg/kg Brain tetrachloroethylene concentrations were the same at both doses	Gavage single dose at 0, 160, 480 mg/kg	Warren et al. (1996)
ICR mice, male	NOAEL/LOAEL: Righting reflex: 2000/4000 ppm Balance: 1000/2000 ppm Reinforcement: 1000/2000 ppm Punishment: 500/1000 ppm	Single intraperitoneal doses at 0, 500, 1000, 2000, 4000 mg/kg	Umezu et al. (1997)
F344 rats, female	Increased reactivity, decreased motor activity, decreased righting ability, increased landing foot splay, abnormal gait after one dose No effect after repeated doses	Single doses: 150 mg/kg is LOEL Repeated dosing for 14 days: 1500 mg/kg is NOEL	Moser et al. (1995)
NMRI mice, postnatal exposure	Increased locomotion and decreased rearing at day 60 in both dose groups (invalid analysis of data) No effect immediately after treatment	Gavage treatment 5, 320 mg/kg daily for postnatal days 10–16	Fredriksson et al. (1993)
Wistar rats, male	Transient delay in circadian activity, dose-related	Intraperitoneal doses 0, 100, 500, 1000 mg/kg-day for 3 days LOAEL = 100 mg/kg-day	Motohashi et al. (1993)

NOAEL = No-observed-adverse-effect level
LOAEL = Lowest-observed-adverse-effect level
LOEL = Lowest-observed-effect level
NOEL = No-observed-effect level

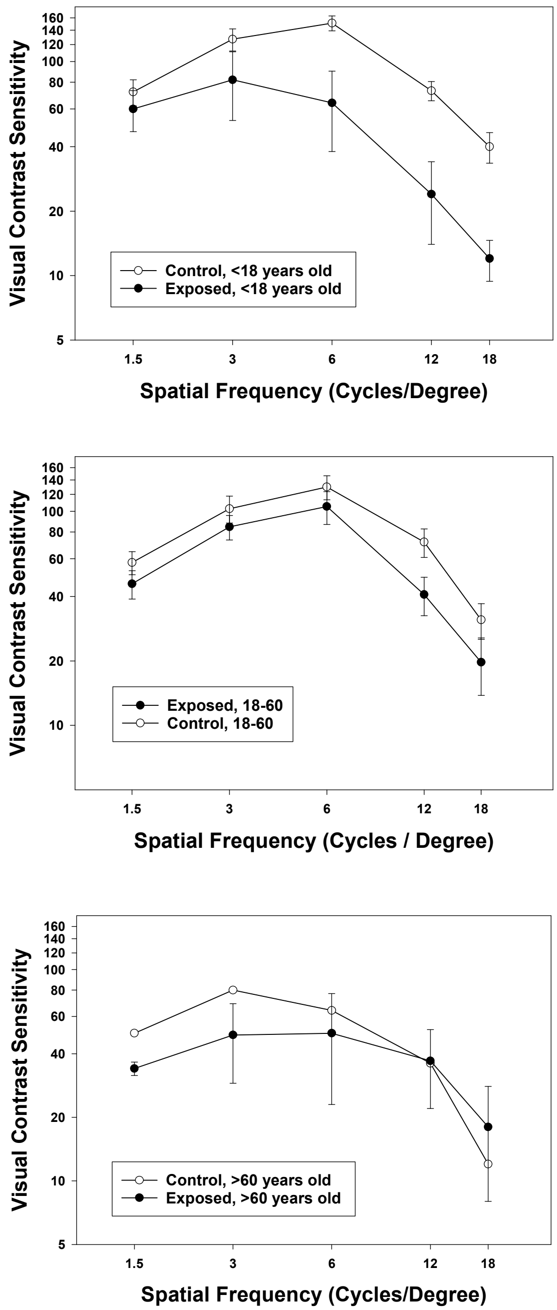

Figure 1. Visual contrast sensitivity functions for control and exposed children (top), adults that were identified as having impaired function (i.e., 5 of the total 11) and their matched controls (middle), and the control and exposed individuals over 60 years of age. The X axis represents the frequency of the stimulus bars, with finer bars toward the right. The Y axis represents the inverse of the contrast at which the subject could no longer distinguish the orientation of the bars (threshold). For any frequency, a higher contrast sensitivity threshold represents better visual function. It is apparent that the group of children is relatively more impaired than the impaired group adults.

Source: Schreiber et al., 2002

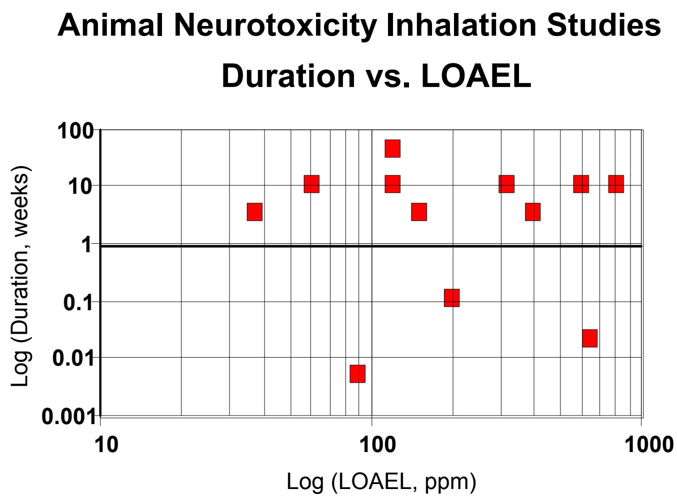

Figure 2. Summary of the relationship between dose levels and treatment duration.

REFERENCES

Aggazzotti, G; Fantuzzi, G; Righi, E; Predieri, G; Gobba, F M; Paltrinieri, M; Cavalleri, A (1994) Occupational and environmental exposure to perchloroethylene (PCE) in dry cleaners and their family members. Arch Environ Health 49:487–493.

Albers, J W; Wald, J J; Werner, R A; Franzblau, A; Berent, S (1999) Absence of polyneuropathy among workers previously diagnosed with solvent-induced toxic encephalopathy. J Occup Environ Med 41:500–509.

Altmann, L; Bottger, A; Wiegand, H (1990) Neurophysiological and psychophysical measurements reveal effects of acute low-level organic solvent exposure in humans. Int Arch Occup Environ Health 62:493–499.

Altmann, L; Weigand, H; Bottger, A; et al. (1992) Neurobehavioral and neurophysiological outcomes of acute repeated perchloroethylene exposure. Applied Psychology: An International Review 41:269–279.

Altmann, L; Neuhann, H F; Kramer, U; Witten, J; Jermann, E (1995) Neurobehavioral and neurophysiological outcome of chronic low-level tetrachloroethylene exposure measured in neighborhoods of dry cleaning shops. Environ Res 69:83–89.

ATSDR (Agency for Toxic Substances and Disease Registry) (1997) Toxicological profile for tetrachloroethylene (update). Prepared by Sciences, International, under subcontract to Research Triangle Institute. Atlanta, GA.

Bellinger, D; Hu, H; Titlebaum, L; Needleman, H L (1994) Attentional correlates of dentin and bone lead levels in adolescents. Arch Environ Health 49:98–105.

Bowler, R M; Mergler, D; Huel, G; Harrison, R; Cone, J (1991) Neuropsychological impairment among former microelectronics workers. Neurotoxicology 12:87–103.

Briving, C; Jacobson, I; Hamberger, A; Kjellstrand, P; Haglid, K G; Rosengren, L E (1986) Chronic effects of perchloroethylene and trichloroethylene on the gerbil brain amino acids and glutathione. Neurotoxicology 7:101–108.

Broadwell, D K; Darcey, D J; Hudnell, H K; Otto, D A; Boyes, W K (1995) Work-site clinical and neurobehavioral assessment of solvent-exposed microelectronics workers. Am J Ind Med 27:677–698.

Buelke-Sam, J; Kimmel, C A; Adams, J; Nelson, C J; Vorhees, C V; Wright, D C; St. Omer, V; Korol, B A; Butcher, R E; Geyer, M A (1985) Collaborative behavioral teratology study: results. Neurobehav Toxicol Teratol 7:591–624.

Cai, S X; Huang, M-Y; Chen, Z; Liu, Y T; Jin, C; Watanabe, T; Nakatsuka, H; Seiji, K; Inoue, O; Ikeda, M (1991) Subjective symptom increase among dry-cleaning workers exposed to tetrachloroethylene vapor. Ind Health 29:111–121.

Cal EPA (California Environmental Protection Agency) (2001) Public health goal for tetrachloroethylene in drinking water. Prepared by Office of Environmental Health Hazard Assessment, California EPA. Available from: http://www.oehha.org/water/phg/pdf/PCEAug2001.pdf.

Campagna, D; Mergler, D; Huel, G; Belanger, S; Truchon, G; Ostiguy, C; Drolet, D (1995) Visual dysfunction among styrene-exposed workers. Scand J Work Environ Health 21:382–390.

Campagna, D; Gobba, F; Mergler, D; Moreau, T; Galassi, C; Cavalleri, A; Huel, G (1996) Color vision loss among styrene-exposed workers neurotoxicological threshold assessment. Neurotoxicology 17:367–373.

Cavalleri, A; Gobba, F; Paltrinieri, M; Fantuzzi, G; Righi, E; Aggazzotti, G (1994) Perchloroethylene exposure can induce colour vision loss. Neurosci Lett 179:162–166.

CFR (Code of Federal Regulations). (   ) Protection of human subjects. CFR 40: §26.

Chen, H H; Chan, M H; Fu, S H (2002) Behavioural effects of tetrachloroethylene exposure in rats: acute and subchronic studies. Toxicology 170:201–209.

De Ceaurriz, J; Desiles, J P; Bonnet, P; Marignac, B; Muller, J; Guenier, J P (1983) Concentration-dependent behavioral changes in mice following short-term inhalation exposure to various industrial solvents. Toxicol Appl Pharmacol 67:383–389.

Donoghue, A M; Dryson, E W; Wynn-Williams, G (1995) Contrast sensitivity in organic-solvent-induced chronic toxic encephalopathy. J Occup Environ Med 37:1357–1363.

Echeverria, D; White, R F; Sampaio, C (1995) A behavioral evaluation of PCE exposure in patients and dry cleaners: a possible relationship between clinical and preclinical effects. J Occup Environ Med 37:667–680.

Ferroni, C; Selis, L; Mutti, A; Folli, D; Bergamaschi, E; Franchini, I (1992) Neurobehavioral and neuroendocrine effects of occupational exposure to perchloroethylene. Neurotoxicology 13:243–247.

Fredriksson, A; Danielsson, B R; Eriksson, P (1993) Altered behaviour in adult mice orally exposed to tri- and tetrachloroethylene as neonates. Toxicol Lett 66:13–19.

Frenette, B; Mergler, D; Bowler, R (1991) Contrast-sensitivity loss in a group of former microelectronics workers with normal visual acuity. Optom Vis Sci 68:556–560.

Geller, A M and Hudnell, H K (1997) Critical issues in the use and analysis of the Lanthony Desaturate Color Vision test. Neurotoxicol Teratol 19:455–465.

Gobba, F; Righi, E; Fantuzzi, G; Predieri, G; Cavazzuti, L; Aggazzotti, G (1998) Two-year evolution of perchloroethylene-induced color-vision loss. Arch Environ Health 53:196–198.

Gobba, F (2000) Color vision: a sensitive indicator of exposure to neurotoxins. Neurotoxicology 21:857–862.

Grandjean, P; White, R F; Sullivan, K; Debes, F; Murata, K; Otto, D A; Weihe, P (2001) Impact of contrast sensitivity performance on visually presented neurobehavioral tests in mercury-exposed children. Neurotoxicol Teratol 23:141–146.

Hake, C L and Stewart, R D (1977) Human exposure to tetrachloroethylene: inhalation and skin contact. Environ Health Perspect 21:231–238.

Holson, R R and Pearce, B (1992) Principles and pitfalls in the analysis of prenatal treatment effects in multiparous species. Neurotoxicol Teratol 14:221–228.

Honma, T; Hasegawa, H; Sato, M; Sudo, A (1980a) Changes of free amino acid content in rat brain after exposure to trichloroethylene and tetrachloroethylene. Ind Health 18:1–7.

Honma, T; Sudo, A; Miyagawa, M; Sato, M; Hasegawa, H (1980b) Effects of exposure to trichloroethylene and tetrachloroethylene on the contents of acetylcholine, dopamine, norepinephrine and serotonin in rat brain. Ind Health 18:171–178.

Hudnell, H K; Boyes, W K; Otto, D A; House, D E; Creason, J P; Geller, A M; Darcey, D J; Broadwell, D K (1996a) Battery of neurobehavioral tests recommended to ATSDR: solvent-induced deficits in microelectronic workers. Toxicol Ind Health 12:235–243.

Hudnell, H K; Otto, D A; House, D E (1996b) The influence of vision on computerized neurobehavioral test scores: a proposal for improving test protocols. Neurotoxicol Teratol 18:391–400.

Karlsson, J E; Rosengren, L E; Kjellstrand, P; Haglid, K G (1987) Effects of low-dose inhalation of three chlorinated aliphatic organic solvents on deoxyribonucleic acid in gerbil brain. Scand J Work Environ Health 13:453–458.

Kaufman AS; McLean JE; Reynolds CR. (1988) Sex, race, residence, region, and education differences on the 11 WAIS-R subtests. J Clin Psychol 44:231–248.

Kjellstrand, P; Holmquist, B; Kanje, M; Alm, P; Romare, S; Jonsson, I; Mansson, L; Bjerkemo, M (1984) Perchloroethylene: effects on body and organ weights and plasma butyrylcholinesterase activity in mice. Acta Pharmacol Toxicol (Copenh) 54:414–424.

Kjellstrand, P; Holmquist, B; Jonsson, I; Romare, S; Mansson, L (1985) Effects of organic solvents on motor activity in mice. Toxicology 35:35–46.

Kyrklund, T; Alling, C; Kjellstrand, P; Haglid, K G (1984) Chronic effects of perchloroethylene on the composition of lipid and acyl groups in cerebral cortex and hippocampus of the gerbil. Toxicol Lett 22:343–349.

Kyrklund, T; Kjellstrand, P; Haglid, K G (1987) Lipid composition and fatty acid pattern of the gerbil brain after exposure to perchloroethylene. Arch Toxicol 60:397–400.

Kyrklund, T; Kjellstrand, P; Haglid, K G (1988) Effects of exposure to Freon 11, 1,1,1-trichloroethane or perchloroethylene on the lipid and fatty-acid composition of rat cerebral cortex. Scand J Work Environ Health 14:91–94.

Kyrklund, T; Kjellstrand, P; Haglid, K G (1990) Long-term exposure of rats to perchloroethylene, with and without a post-exposure solvent-free recovery period: effects on brain lipids. Toxicol Lett 52:279–285.

Kyrklund, T and Haglid, K (1991) Brain lipid composition in guinea pigs after intrauterine exposure to perchloroethylene. Pharmacol Toxicol 68:146–148.

Lauwerys, R; Herbrand, J; Buchet, J P; Bernard, A; Gaussin, J (1983) Health surveillance of workers exposed to tetrachloroethylene in dry- cleaning shops. Int Arch Occup Environ Health 52:69–77.

Lezak M D (1995) Neuropsychological Assessment, 3rd Edition. New York: Oxford University Press.

Lucchini, R; Albini, E; Placidi, D; Alessio, L (2000) Mechanism of neurobehavioral alteration. Toxicol Lett 112-113:35–39.

Mattsson, J L; Albee, R R; Yano, B L; Bradley, G; Spencer, P J (1998) Neurotoxicologic examination of rats exposed to 1,1,2,2- tetrachloroethylene (perchloroethylene) vapor for 13 weeks. Neurotoxicol Teratol 20:83–98.

Mergler, D and Blain, L (1987) Assessing color vision loss among solvent-exposed workers. Am J Ind Med 12:195–203.

Mergler, D; Blain, L; Lagace, J P (1987) Solvent related colour vision loss: an indicator of neural damage? Int Arch Occup Environ Health 59:313–321

Mergler, D; Blain, L; Lemaire, J; Lalande, F (1988a) Colour vision impairment and alcohol consumption. Neurotoxicol Teratol 10:255–260.

Mergler, D; Belanger, S; De Grosbois, S; Vachon, N (1988b) Chromal focus of acquired chromatic discrimination loss and solvent exposure among printshop workers. Toxicology 49:341–348.

Mergler, D; Huel, G; Bowler, R; Frenette, B; Cone, J (1991) Visual dysfunction among former microelectronics assembly workers. Arch Environ Health 46:326–334.

Mergler, D (1995) Behavioral neurophysiology; quantitative measures of sensory toxicity. In: Chang, L and Slikker, W, eds. Neurotoxicology, approaches and methods. New York: Academic Press; pp. 727–736.

Mergler, D; Huel, G; Belanger, S; Bowler, R M; Truchon, G; Drolet, D; Ostiguy, C (1996) Surveillance of early neurotoxic dysfunction. Neurotoxicol 17:803–812.

Moser, V C; Cheek, B M; MacPhail, R C (1995) A multidisciplinary approach to toxicological screening: III. Neurobehavioral toxicity. J Toxicol Environ Health 45:173–210.

Motohashi, Y; Miyazaki, Y; Takano, T (1993) Assessment of behavioral effects of tetrachloroethylene using a set of time-series analyses. Neurotoxicol Teratol 15:3–10.

Muttray, A; Wolff, U; Jung, D; Konietzko, J (1997) Blue-yellow deficiency in workers exposed to low concentrations of organic solvents. Int Arch Occup Environ Health 70:407–412.

Nakatsuka, H; Watanabe, T; Takeuchi, Y; Hisanaga, N; Shibata, E; Suzuki, H; Huang, M-Y; Chen, Z; Qu, Q S; Ikeda, M (1992) Absence of blue-yellow color vision loss among workers exposed to toluene or tetrachloroethylene, mostly at levels below occupational exposure limits. Int Arch Occup Environ Health 64:113–117.

Nelson, B K; Taylor, B J; Setzer, J V; Hornung, R W (1980) Behavioral teratology of perchloroethylene in rats. J Environ Pathol Toxicol 3:233–250.

NYS DOH (New York State Department of Health) (1997) Tetrachloroethylene ambient air criteria document. Final Report. Albany, NY.

NYS DOH (2000a) Evaluation of residential exposure to tetrachloromethane biomarkers of dose and neurological tests. Final deliverable from NYS DOH to U.S. EPA under Cooperative Agreement #CR 824400-01.

NYS DOH (2000b) Pumpkin Patch day care center investigation. Final Report. Available from: U.S. Centers for Disease Control and Prevention, Air Pollution and Respiratory Health Branch, Division of Environmental Hazards and Health Effects, National Center for Environmental Health, Atlanta, GA.

Pokorny, J and Smith, V C (1986) Eye disease and color defects. Vision Res 26:1573–1584.

Regan, D (1989) Human brain electrophysiology. New York: Elsevier Science.

Rice, D C and Gilbert, S G (1990) Effects of developmental exposure to methyl mercury on spatial and temporal visual function in monkeys. Toxicol Appl Pharmacol 102:151–163.

Rosengren, L E; Kjellstrand, P; Haglid, K G (1986) Tetrachloroethylene: levels of DNA and S-100 in the gerbil CNS after chronic exposure. Neurobehav Toxicol Teratol 8:201–206.

Savolainen, H; Pfaffli, P; Tengen, M; Vainio, H (1977a) Biochemical and behavioural effects of inhalation exposure to tetrachlorethylene and dichlormethane. J Neuropathol Exp Neurol 36:941–949.

Savolainen, H; Pfaffli, P; Tengen, M; Vainio, H (1977b) Trichloroethylene and 1,1,1-trichloroethane: effects on brain and liver after five days intermittent inhalation. Arch Toxicol 38:229–237.

Schreiber, J S; Hudnell, H K; Geller, A M; House, D E; Aldous, K M; Force, M E; Langguth, K W; Prohonic, E J; Parker, J C (2002) Apartment residents' and day care workers' exposures to tetrachloroethylene and deficits in visual contrast sensitivity. Environ Health Perspect 110:655–664.

Seeber, A (1989) Neurobehavioral toxicity of long-term exposure to tetrachloroethylene. Neurotoxicol Teratol 11:579–583.

Solet, D; Robins, T G; Sampaio, C (1990) Perchloroethylene exposure assessment among dry cleaning workers. Am Ind Hyg Assoc J 51:566–574.

Spencer, P S; Schaumburg, H H (1978) Distal axonopathy: one common type of neurotoxic lesion. Environ Health Perspect. 26:97–105.

Spinatonda, G; Colombo, R; Capodaglio, E M; Imbriani, M; Pasetti, C; Minuco, G; Pinelli, P (1997) [Processes of speech production: Application in a group of subjects chronically exposed to organic solvents (II)]. G Ital Med Lav Ergon 19:85–88.

Stewart, R D; Baretta, E D; Dodd, H C; Torkelson, T R (1970) Experimental human exposure to tetrachloroethylene. Arch Environ Health 20:225–229.

Stewart R O; Hake, C L; Wu, A; Kalbleisch, J; Newton, P E; Marlow, S K; Vucicevic-Salama, M (1977) Effects of perchloroethylene drug interactions on behavior and neurological function. DHEW (NIOSH) Publ. No. 77-191. Department of Health, Education, and Welfare. Washington, DC. Available from: EPA-IRIS Information Desk.

Tinston, D J (1994) Perchloroethylene: A multigeneration inhalation study in the rat. CTL/P/4097. Available from: EPA-IRIS Information Desk.

Umezu, T; Yonemoto, J; Soma, Y; Miura, T (1997) Behavioral effects of trichloroethylene and tetrachloroethylene in mice. Pharmacol Biochem Behav 58:665–671.

U.S. EPA (Environmental Protection Agency). (2003) Frequently asked questions about dry cleaning. Design for the Environment Program, Office of Pollution Prevention and Toxics. Available from: <http://www.epa.gov/dfe/pubs/garment/ctsa/factsheet/ctsafaq.htm>.-

Valic, E; Waldhor, T; Konnaris, C; Michitsch, A; Wolf, C (1997) Acquired dyschromatopsia in combined exposure to solvents and alcohol. Int Arch Occup Environ Health 70:403–406.

Wang, S; Karlsson, J E; Kyrklund, T; Haglid, K (1993) Perchloroethylene-induced reduction in glial and neuronal cell marker proteins in rat brain. Pharmacol Toxicol 72:273–278.

Warren, D A; Reigle, T G; Muralidhara, S; Dallas, C E (1996) Schedule-controlled operant behavior of rats following oral administration of perchloroethylene: time course and relationship to blood and brain solvent levels. J Toxicol Environ Health 47:345–362.

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