D. Appendix – Neurological Effects of Trichloroethylene

CONTENTS

D.1. Human Studies on the Neurological Effects of Trichloroethylene

There is an extensive body of evidence in the literature on the neurological effects caused by exposure to trichloroethylene (TCE) in humans. The primary functional domains that have been studied and reported are: trigeminal nerve function and nerve conductivity (latency), psychomotor effects, including reaction times (simple and choice), visual and auditory effects, cognition, memory, and subjective neurological symptoms, such as headache and dizziness. This section discusses the primary studies presented for each of these effects. Summary tables for all the human TCE studies are at the end of this section.

D.1.1 Changes in Nerve Conduction

There is strong evidence in the literature that exposure to TCE results in impairment of trigeminal nerve function in humans exposed occupationally, by inhalation, or environmentally, by ingestion. Functional measures such as the blink reflex and masseter reflex tests were used to determine if physiological functions mediated by the trigeminal nerve were significantly impacted. Additionally, trigeminal somatosensory evoked potentials were also measured in some studies to ascertain if nerve activity was directly affected by TCE exposure.

D.1.1.1 *Blink reflex and masseter reflex studies – Trigeminal Nerve*

Barret et al. (1984) conducted a study on 188 workers exposed to TCE occupationally from small and large factories in France (type of factories not disclosed). The average age of the workers was 41 (SD not provided, but authors noted 14% <30 years and 25% >50 years) and the average exposure duration was 7 hours/day for 7 years. The 188 workers were divided into high and low exposure groups for both TCE exposure measured using detector tubes and trichloroacetic acid (TCA) levels measured in urine. There was no unexposed control population, but responses in the high-exposure group were compared response in the low-exposure group. TCE exposure groups were divided into a low exposure group (<150 ppm; n = 134) and a high exposure group (>150 ppm; n = 54). The same workers (n = 188) were also grouped by TCA urine measurements such that a high exposure was ≥100 mg TCA/g creatinine. Personal factors including age, tobacco use and alcohol intake were also analyzed. No mention was made regarding whether or not the examiners were blind to the subjects' exposure status. Complete physical examination including testing visual performance (acuity and color perception), evoked trigeminal potential latencies and audiometry, facial sensitivity, reflexes, and

motoricity of the masseter muscles. Chi squared analysis was used to examine distribution of the different groups for comparing high and low exposed workers followed by one way analysis of variance. Overall, 22 out of 188 workers (11.7%) experienced trigeminal nerve impairment ($p < 0.01$) as measured by facial sensitivity, reflexes (e.g. jaw, corneal, blink) and movement of the masseter muscles. When grouped by TCE exposure, 12 out of 54 workers (22.2%) in the high exposure group (≥150 ppm) and 10 out of 134 workers (7.4%) in the low exposure group had impaired trigeminal nerve mediated responses. When grouped by the presence of TCA in the urine, 41 workers were now in the high TCA group and 10 out of 41 workers (24.4%) experienced trigeminal nerve impairment in comparison to the 12 out of 147 (8.2%) in the low TCA (<100 mg TCA/g creatinine) group. Statistically significant results were also presented for the following symptoms based on TCE and TCA levels: trigeminal nerve impairment ($p < 0.01$), asthenia ($p < 0.01$), optic nerve impairment ($p < 0.001$), and dizziness ($0.05 < p < 0.06$). Statistically significant results were also presented for the following symptoms based on TCA levels: Trigeminal nerve impairment ($p < 0.01$), asthenia ($p < 0.01$), optic nerve impairment ($p < 0.001$), headache ($p < 0.05$), and dizziness ($0.05 < p < 0.06$). Symptoms for which there is a synergistic toxic role for TCE and alcohol ($p < 0.05$) were liver impairment and degreaser flush. This study presents a good statistically significant dose-response relationship between TCE/TCA exposure and trigeminal nerve impairment. TCE concentrations are not available for individual subjects, but exposure assessment was inferred based on occupational standards at the time of the study.

Feldman et al. (1988) conducted an environmental study on 21 Woburn, Massachusetts residents with alleged chronic exposure to TCE in drinking water, resulting from an environmental spill by a local industry. These were from 8 families whose drinking water wells were found to be contaminated with TCE and other solvents. The subjects were self selected, having been referred for clinical evaluation due to suspected neurotoxicity, and were involved in litigation. The control group was 27 unexposed residents from a nearby community with TCE concentrations in drinking water below state standards. TCE in residential well water was measured over a prior 2 year period (1979−1981); the maximum reported concentration for the study population was 267 ppb. The residents' water supply came from two different TCE-contaminated wells that had an average measured concentration of 256 ppb (labeled "Well G"; based on 6 samples) and 111 ppb (labeled "Well H"; based on 4 samples). The residents' exposure ranged from 1−12 years and was dependent on the length of residence and the age of the subject. There were other solvents found to be present in the well water, and TCE data were not available for the entire exposure period. TCE concentrations for the control population were less than the Maximum Contaminant Level (MCL) (5 ppb). The blink reflex (BR) was used to

measure the neurotoxic effects of TCE. The BR was measured using an electrode to stimulate the supraorbital nerve (above the eyelid) with a shock (0.05 ms in duration) resulting in a response and the response was measured using a recording electrode over the orbicularis oculi muscle (the muscle responsible for closing the eyelid and innervated by the trigeminal nerve). The BR generated an R1 and an R2 component from each individual. BRs were recorded and the supraorbital nerve was stimulated with single electrical shocks of increasing intensity until nearly stable R1 and R2 ipsilateral and R2 contralateral responses were obtained. The student's *t* test was used for testing the difference between the group means for the blink reflex component latencies. Because of the variability of R2 responses, this study focused primarily on the R1 response latencies. Highly significant differences in the conduction latency means of the BR components for the TCE exposed population versus control population were observed when comparing means for the right and left side R1 to the controls. The mean R1 BR component latency for the exposed group was 11.35 ms, SD = 0.74 ms, 95% CI = 11.03−11.66. The mean for the controls was 10.21 ms, SD = 0.78 ms, 95% CI = 9.92−10.51; ($p < 0.001$). The study was well conducted with consistency of methods, and statistically significant findings for trigeminal nerve function impairment resulting from environmental exposures to TCE. However, the presence of other solvents in the well water, self selection of subjects involved in litigation, and incomplete characterization of exposure present problems in drawing a clear conclusion of TCE causality or dose-response relationship.

Kilburn and Warshaw (1993) conducted an environmental study on 544 Arizona residents exposed to TCE in well-water. TCE concentrations were from 6 to 500 ppb and exposure ranged from 1 to 25 years. Subjects were recruited and categorized in 3 groups. Exposed group 1 consisted of 196 family members with cancer or birth defects. Exposed group 2 consisted of 178 individuals from families without cancer or birth defects; and exposed group 3 included 170 parents whose children had birth defects and rheumatic disorders. Well-water was measured from 1957 to 1981 by several governmental agencies and average annual TCE exposures were calculated and then multiplied by each individual's years of residence for 170 subjects. A referent group of histology technicians ($n = 113$) was used as a comparison for the blink reflex (BR) test. For this test, recording electrodes were placed over the orbicularis oculi muscles (upper and lower) and the BR was elicited by gently tapping the glabeela (located on the mid-frontal bone at the space between the eyebrows and above the nose). A two sided Student *t* test and linear regression were used for statistical analysis. Significant increases in the R1 component of the BR response was observed in the exposed population as compared to the referent group. The R1 component measured from the right eye appeared within 10.9 ms in TCE-exposed subjects whereas in referents, this component appeared 10.2 ms after the stimulus

was elicited indicating a significant delay ($p < 0.008$) in the reflex response. Similarly, delays in the latency of appearance for the R1 component were also noted for the left eye but the effect was not statistically significant ($p = 0.0754$). This study shows statistically significant differences in trigeminal nerve function between subjects environmentally exposed and non-exposed to TCE. This is an ecological study with TCE exposure inferred to subjects by residence in a geographic area. Estimates of TCE concentrations in drinking water to individual subjects are lacking. Additionally, litigation is suggested and may introduce a bias, particularly if no validity tests were used.

Kilburn (2002a) studied 236 residents (age range: 18−83 years old) lived nearby manufacturing plants (e.g. microchip plants) in Phoenix, AZ. Analysis of the groundwater in the residential area revealed contamination with many volatile organic compounds including TCE. Concentrations of TCE in the well water ranged from 0.2 ppb to more than 10,000 ppb and the exposure duration varied between 2 to 37 years. Additional associated solvents included dichloroethane (DCE), perchloroethylene (PERC), and vinyl chloride. A group-match design was used to compare the 236 TCE-exposed residents to 161 unexposed regional referents and 67 referents in NE Phoenix in the blink reflex (BR) test. The BR response was recorded from surface electrodes placed over the location of the orbicularis oculi muscles. The reflex response was elicited by gently tapping the left and right supraorbital notches with a small hammer. The R1 component of the BR response was measured for both the left and right eye. Statistically significant increases in latency time for the R1 component was observed for residents exposed to TCE in comparison to the control groups. In unexposed individuals, the R1 component occurred within 13.4 ms from the right eye and 13.5 ms from the left eye. In comparison, the residents near the manufacturing plant had latency times of 14.2 ms ($p < 0.0001$) for the right eye and 13.9 ms ($p < 0.008$) for the left eye. This study shows statistically significant differences between environmentally exposed and unexposed populations for trigeminal nerve function, as a result of exposures to TCE. This is an ecological study with TCE exposure potential to subjects inferred by residence in a geographic area. Estimates of TCE concentrations in drinking water to individuals are lacking. Additionally, litigation is suggested and may introduce a bias, particularly if no validity tests were used.

Feldman et al. (1992) evaluated the BR reflex in 18 subjects occupationally exposed to neurotoxic chemicals (e.g. degreasers, mechanics and pesticide sprayers among many others). Eight of the subjects were either extensively ($n = 4$) or occupationally ($n = 4$) exposed to TCE. The remaining subjects ($n = 10$) were exposed to other neurotoxic chemicals, but not TCE. Quantitative exposure concentration data were not reported in the study, but TCE exposure was

characterized as either "extensive" or "occupational." Subjects in the "extensive" exposure group were chronically exposed (≥1 year) to TCE at least 5 days a week and for at greater than 50% of the workday (n = 3) or experienced a direct, acute exposure to TCE for greater than 15 minutes (n = 1). Subjects in the "occupational" group were chronically exposed (≥1 year) to TCE for 1−3 days/week and for greater than 50% of the workday. The BR responses from the TCE-exposed subjects were compared to a control group consisting of 30 nonexposed subjects with no noted neurological disorders. BR responses were measured using surface electrodes over the lower lateral portion of the orbicularis oculi muscle. Electrical shocks with durations of 0.05 ms were applied to the supraorbital nerve to generate the R1 and R2 responses. All of the subjects that were extensively exposed to TCE had significantly increased latency times in the appearance of the R1 component (no p value listed) and for 3 subjects this increased latency time persisted for at least one month and up to 20 years post-exposure. However, none of the subjects occupationally exposed to TCE had changes in the BR response in comparison to the control group. In comparing the remaining neurotoxicant exposed subjects to the TCE-exposed individuals, the sensitivity, or the ability of a positive blink reflex test to identify correctly those who had TCE exposure was 50%. However, in workers with no exposure to TCE, 90% demonstrated a normal R1 latency.

Mixed results were obtained in a study by Ruitjen et al. (1991) on 31 male printing workers exposed to TCE. The mean age was 44; mean exposure duration was 16 years and had at least 6 years of TCE exposure. The control group consisted of 28 workers with a mean age 45 yrs. Workers in the control group were employed at least 6 years in print factories (similar to TCE-exposed), had no exposure to TCE, but were exposed to "turpentine-like organic solvents." TCE exposure potential was inferred from historical monitoring of TCE at the plant using gas detection tubes. These data indicated TCE concentrations in the 1960s of around 80 ppm, mean concentration of 70 ppm in the next decade, with measurements from 1976 and 1981 showing a mean concentration of 35 ppm. The most recent estimate of TCE concentrations in the factory was 17 ppm (stable for three years) at the time of the report. The authors calculated that mean cumulative TCE exposure would be 704 ppm × years worked in factory. The masseter and blink reflexes were measured to evaluate trigeminal nerve function in TCE-exposed and control workers. For measurement of the masseter reflex, surface electrodes were attached over the right masseter muscle (over the cheek area). A gentle tap on a roller placed under the subject's chin was used to elicit the masseter reflex. For measurement of the blink reflex, surface electrodes were placed on the muscle near the upper eyelid. Electrical stimulation of the right supraorbital nerve was used to generate the blink reflex. There was a significant increase in the latency of the masseter reflex to appear for the TCE-exposed workers ($p < 0.05$). However, there was no

significant change in the blink reflex measure between TCE-exposed workers and control. Although no change in the blink reflex measures were observed between the two groups, it should be noted that the control group was exposed to other volatile organic solvents (not specified) and this VOC exposure could be a possible confounder for determination of TCE-induced effects.

There are two studies that reported no effect of TCE exposure on trigeminal nerve function (El-Ghawabi et al., 1973; Rasmussen et al., 1993c). El-Ghawabi et al. (1973) conducted a study on 30 money printing shop workers occupationally exposed to TCE. Metabolites of total trichloroacetic acid and trichloroethanol were found to be proportional to TCE concentrations up to 100 ppm (550 mg/m^3). Controls were 20 age- and Socio-Economic Status (SES)-matched non-exposed males and 10 control workers not exposed to TCE. Trigeminal nerve involvement was not detected, but the authors failed to provide details as to how this assessment was made. It is mentioned that each subject was clinically evaluated and trigeminal nerve involvement may have been assessed through a clinical evaluation. As a result, the conclusions of this study are tempered since the authors did not provide details as to how trigeminal nerve function was evaluated in this study.

Rasmussen et al. (1993c) conducted an historical cohort study on 99 metal degreasers. Subjects were selected from a population of 240 workers from 72 factories in Denmark. The participants were divided into three groups based on solvent exposure durations where low exposure was up to 0.5 years, medium was 2.1 years and high was 11.0 years (mean exposure duration). Most of the workers (70 out of 99) were primarily exposed to TCE with an average exposure duration of 7.1 years for 35 hours/week. TCA and TCOH levels were measured in the urine samples provided by the workers and mean TCA levels in the high group was 7.7 mg/L and was as high as 26.1 mg/L. Experimental details of trigeminal nerve evaluation were not provided by the authors. It was reported that 1 out of 21 people (5%) in the low exposure, 2 out of 37 (5%) in the medium exposure and 4 out of 41 (10%) in the high exposure group experienced abnormalities in trigeminal nerve sensory function. No linear association was seen on trigeminal nerve function (Mantel-Haenzel test for linear association, $p = 0.42$). However, the trigeminal nerve function findings were not compared to a control (no TCE exposure) group and it should be noted that some of the workers (29 out of 99) were not exposed to TCE.

D.1.1.2. *Trigeminal Somatosensory Evoked Potential Studies – Trigeminal Nerve*

In a preliminary study, Barret et al. (1982) measured trigeminal sensory evoked potentials (TSEPs) in eleven workers that were chronically exposed to TCE. Nine of these workers were suffering effects from TCE intoxication (changes in facial sensitivity and clinical changes in trigeminal nerve reflexes), and two were TCE-exposed without exhibiting any clinical manifestations from exposure. A control group of 20 non-exposed subjects of varying ages were used to establish the normal response curve for the trigeminal nerve function. In order to generate a TSEP, a surface electrode was placed over the lip and a voltage of 0.05 ms in duration was applied. The area was stimulated 500 times at a rate of two times per second. TSEPs were recorded from a subcutaneous electrode placed between the international CZ point (central midline portion of the head) and the ear. In eight of the eleven workers, an increased voltage ranging from a 25 to a 45 V increase was needed to generate a normal TSEP. Two of the eleven workers had an increased latency of appearance for the TSEP and three workers had increases in TSEP amplitudes. The preliminary findings indicate that TCE exposure results in abnormalities in trigeminal nerve function. However, the study does not provide any exposure data and lacks information with regards to the statistical treatment of the observations.

Barret et al. (1987) conducted a study on 104 degreaser machine operators in France (average age = 41.6 years; range = 18−62 years) who were highly exposed to TCE with an average exposure of 7 hours/day for 8.23 years. Although TCE exposure concentrations were not available, urinary concentrations of trichloroethanol (TCOH) and trichloroacetic acid (TCA) were measured for each worker. A control group consisting of 52 subjects without any previous solvent exposure and neurological deficits was included in the study. Trigeminal nerve symptoms and trigeminal sensory evoked potentials (TSEPs) were collected for each worker. Trigeminal nerve symptoms were clinically assessed by examining facial sensitivity and reflexes dependent on this nerve such as the jaw and blink reflex. TSEPs were elicited by electrical stimulation (70−75 V for 0.05 ms) of the nerve using an electrode on the lip commissure. Eighteen out of 104 TCE-exposed machine operators (17.3%) had trigeminal nerve symptoms. The subjects that experienced trigeminal nerve symptoms were significantly older (47.8 years vs. 40.5; $p < 0.001$). Both groups had a similar duration of exposure with a mean of 9.2 years in the sensitive group and 7.8 years in the non-sensitive group. Urinary concentrations of TCOH and TCA were also statistically similar although the levels were slightly higher in the sensitive group (245 mg/g creatinine vs. 162 mg/g creatinine for TCOH; 131 mg/g creatinine versus 93 mg/g creatinine for TCA). However, in the same group, 40 out of 104 subjects (38.4%) had an abnormal TSEP. Abnormal TSEPs were characterized as potentials that exhibited changes in latency and/or amplitude that were at least 2.5 times the standard deviation of the normal TSEPs obtained from the control group. Individuals with abnormal TSEP were significantly older (45

years vs. 40.1 years; $p < 0.05$) and were exposed to TCE longer (9.9 years vs. 5.6 years; $p < 0.01$). Urinary concentrations TCOH and TCA were similar between the groups with sensitive individuals having average metabolite levels of 195 mg TCOH/g creatinine and 98.3 mg TCA/g creatinine in comparison to 170 mg TCOH/g creatinine and 96 mg TCA/g creatinine in non-sensitive individuals. When a comparison was made between workers that had normal TSEP and no trigeminal symptoms and workers that had an abnormal TSEP and experienced trigeminal symptoms, it was found that in the sensitive individuals (abnormal TSEP and trigeminal symptoms) there was a significant increase in age (48.5 vs. 39.5 years old, $p < 0.01$), duration of exposure (11 vs. 7.5 years, $p < 0.05$) and an increase in urinary TCA (313 vs. 181 mg TCA/g creatinine). No significant changes were noted in urinary TCOH, but the levels were slightly higher in sensitive individuals (167 vs. 109 mg TCOH/g creatinine). Overall, it was concluded that abnormal TSEPs were recorded in workers who were exposed to TCE for a longer period (average duration 9.9 years). This appears to be a well designed study with statistically significant results reported for abnormal trigeminal nerve response in TCE exposed workers. Exposure assessment to TCE is by exposure duration and mean urinary TCOH and TCA concentrations. TCE concentrations to exposed subjects as measured by atmospheric or personal monitoring are lacking.

Mhiri et al. (2004) measured TSEPs from 23 phosphate industry workers exposed to TCE for 6 hours/day for at least two years while cleaning tanks. Exposure assessment was based on measurement of urinary metabolites of TCE, which were performed 3 times/worker, and air measurements. Blood tests and hepatic enzymes were also collected. The mean exposure duration was 12.4 ± 8.3 years (exposure duration range = 2−27 years). Although TCE exposures were not provided, mean urinary concentrations of TCOH, TCA, and total trichlorides were 79.3 ± 42, 32.6 ± 22, and 111.9 ± 55 mg/g urinary creatinine, respectively. The control group consisted of 23 unexposed workers who worked in the same factory without being exposed to any solvents. TSEPs were generated from a square wave pulses (0.1 ms in duration) delivered through a surface electrode that was placed 1 cm under the corner of the mouth. The responses to the stimuli (TSEPs) were recorded from another surface electrode that was placed over the contralateral parietal area of the brain. The measured TSEP was divided into several components and labeled according to whether it was 1) a positive (P) or negative (N) potential and 2) the placement of the potential in reference to the entire TSEP (e.g. P1 is the first positive potential in the TSEP). TSEPs generated from the phosphate workers that were ± 2.5 times the standard deviation from the TSEPs obtained from the control group were considered abnormal. Abnormal TSEP were observed in 6 workers with clinical evidence of trigeminal involvement and in 9 asymptomatic workers. Significant increases in latency were noted for all TSEP

potentials (N1, P1, N2, P2, N3, $p < 0.01$) measured from the phosphate workers. Additionally, significant decreases in the P1 ($p < 0.02$) and N2 ($p < 0.05$) amplitudes were observed. A significant positive correlation was demonstrated between duration of exposure and the N2 latency ($p < 0.01$) and P2 latency ($p < 0.02$). Only one subject had urinary TCE metabolite levels over tolerated limits. TCE air contents were over tolerated levels, ranging from 50−150 ppm (275−825 mg/m^3). The study is well presented with statistically significant results for trigeminal nerve impairment resulting from occupational exposures to TCE. Exposure potential to TCE is defined by urinary biomarkers, TCA, total trichloro-compounds, and TCOH. The study lacks information on atmospheric monitoring of TCE in this occupational setting.

D.1.1.3 *Nerve conduction velocity studies*

Nerve conduction latencies were also studied in two occupational studies by Triebig et al. (1982, 1993) using methods for measurement of nerve conduction which differ from most published studies, but the results indicate a potential impact on nerve conduction following occupational TCE exposure. There was no impact seen on latencies in the 1982 study, but a statistically significant response was observed in the latter study. The latter study, however, is confounded by multiple solvent exposures.

In Triebig et al. (1982), twenty-four healthy workers (20 males, 4 females) were exposed to TCE occupationally at three different plants. The ages ranged from 17−56, and length of exposure ranged from 1 month to 258 months (mean 83 months). TCE concentrations measured in air at work places ranged from 5−70 ppm (27−385 mg/m^3). A control group of 144 healthy, complaint-free individuals were used to establish 'normal' responses on the nerve conduction studies. The matched control group consisted of twenty-four healthy nonexposed individuals (20 males, 4 females), chosen to match the subjects for age and sex. TCA, TCE, and trichloroethanol were measured in blood, and TCE and TCA were measured in urine. Nerve conduction velocities were measured for sensory and motor nerve fibers using the following tests: MCV_{max} (U): Maximum NLG of the motor fibers of the N. ulnaris between the wrist joint and the elbow; dSCV (U): Distal NLG of mixed fibers of the N. ulnaris between finger V and the wrist joint; pSCV (U): Proximal NLG of sensory fibers of the N. medianus between finger V and Sulcus ulnaris; and dSCV (M): Distal NLG of sensory fibers of the N. medianus between finger III and the wrist joint. Data were analyzed using parametric and nonparametric tests, rank correlation, linear regression, with 5% error probability. Results show no statistically significant difference in nerve conduction velocities between the exposed and unexposed groups. This study has measured exposure data, but exposures/responses are not reported by dose levels.

Triebig et al. (1983) has a similar study design to the previous study (Triebig et al., 1982) in the tests used for measurement of nerve conduction velocities, and in the analysis of blood and urinary metabolites of TCE. However, in this study, subjects were exposed to a mixture of solvents, including TCE, specifically "ethanol, ethyl acetate, aliphatic hydrocarbons (gasoline), methyl ethyl ketone (MEK), toluene, and trichloroethene." The exposed group consists of 66 healthy workers selected from a population of 112 workers. Workers were excluded based on polyneuropathy (n = 46) and alcohol consumption (n = 28). The control group consisted of 66 healthy workers with no exposures to solvents. Subjects were divided into three exposure groups based on length of exposure, as follows: 20 employees with "short-term exposure" (7−24 months); 24 employees with "medium-term exposure" (25−60 months); 22 employees with "long-term exposure" (over 60 months). TCA, TCE, and trichloroethanol were measured in blood, and TCE and TCA were measured in urine. Subjects were divided into exposure groups based on length of exposures, and results were compared for each exposure group to the control group. In this study, there was a dose response relationship observed between length of exposure to mixed solvents and statistically significant reduction in nerve conduction velocities observed for the medium and long term exposure groups for the NCV (ulnar nerve). Interpretation of this study is limited by the mixture of solvent exposure, with no results reported for TCE alone.

D.1.2 Auditory Effects

There are three large environmental studies reported which assessed the potential impact of TCE exposures through groundwater ingestion on auditory functioning. They present mixed results. All three studies were conducted on the population in the TCE Subregistry from the National Exposure Registry (NER) developed by the Agency for Toxic Substances Disease Registry (ATSDR). The two studies conducted by Burg et al. (1995; Burg and Gist, 1999) report an increase in auditory effects associated with TCE exposure, but the auditory endpoints were self reported by the population, as opposed to testing of measurable auditory effects in the subject population. The third of these studies, reported by ATSDR (2003) conducted measurements of auditory function on the subject population, but failed to demonstrate a positive relationship between TCE exposure and auditory effects. Results from these studies strongly suggest that children ≤ 9 years are more susceptible to hearing impairments from TCE exposure than the rest of the general population. These studies are described below.

Burg et al. (1995) conducted a study on registrants in the NHIS TCE subregistry of 4,281 (4,041 living and 240 deceased) residents environmentally exposed to TCE via well water in

Indiana, Illinois, and Michigan. Morbidity baseline data were examined from the TCE Subregistry from the National Exposure Registry (NER) developed by the Agency for Toxic Substances Disease Registry (ATSDR). Participants were interviewed in the National Health Interview Survey (NHIS), which consists of 25 questions about health conditions. Data were self reported via face-to-face interviews. Neurological endpoints were hearing and speech impairments. This study assessed the long-term health consequences of long-term, low-level exposures to trichloroethylene (TCE) in the environment. The collected data were compared to the National Health Interview Survey (NHIS), and the National Household Survey on Drug Abuse (NHSDA). Poisson Regression analysis model was used for registrants 19 and older. The statistical analyses performed treated the NHIS population as a standard population and applied the age- and sex-specific period prevalence and prevalence rates obtained from the NHIS data to the corresponding age- and sex-specific denominators in the TCE Subregistry. This one-sample approach ignored sampling variability in the NHIS data because of the large size of the NHIS database when compared to the TCE Subregistry data file. A binomial distribution was assumed in estimating standard errors for the TCE Subregistry data. Weighted age- and sex-specific period prevalence and prevalence rates by using the person-weights were derived for the TCE subregistry. These "standard" rates were applied to the corresponding TCE Subregistry denominators to obtain expected counts in each age and sex combination. In the NHIS sample, 18% of the subjects were nonwhite. In the TCE Subregistry sample, 3% of the subjects were nonwhite. Given this discrepancy in the proportion of nonwhites and the diversity of races reported among the nonwhites in the TCE Subregistry, the statistical analyses included 3,914 exposed white TCE registrants who were alive at baseline. TCE registrants that were 9 years old or younger had a statistically significant increase in hearing impairment as reported by the subjects. The relative risk (RR) in this age group for hearing impairments was 2.13. The RR decreased to 1.12 for registrants aged 10−17 years and to 0.32 or less for all other age groups. As a result, the effect magnitude was lower for children 10−17 yrs and for all other age groups. The study reports a dose-response relationship, but the hearing effects are self-reported, and exposure data are modeled estimates.

Burg and Gist (1999) reported a study conducted on the same subregistry population described for Burg et al. (1995). It investigated intrasubregistry differences among 3,915 living members of the National Exposure Registry's Trichloroethylene Subregistry (4,041 total living members). The participants' mean age was 34 yrs (SD = 19.9 yrs.), and included children in the registry. All registrants had been exposed to TCE through domestic use of contaminated well water. All were Caucasian. All registrants had been exposed to TCE though domestic use of contaminated well water; there were four exposure Subgroups, each divided into quartiles: 1)

Maximum TCE measured in well water, exposure subgroups: 2−12 ppb; 12−60 ppb; 60−800 ppb; 2) Cumulative TCE exposure subgroups: <50 ppb, 50−500 ppb, 500−5,000 ppb, >5,000 ppb; 3) Cumulative chemical exposure subgroups: include TCA, DCE, DCA, in conjunction with TCE, with the same exposure Categories as in # 2; and 4) Duration of exposure subgroups: <2 yrs, 2−5 yrs, 5−10 yrs., >10 yrs.; 2,867 had TCE exposure of ≤50 ppb; 870 had TCE exposure of 51−500 ppb; 190 had TCE exposure of 501−5,000 ppb; 35 had TCE exposure >5,000 ppb. The lowest quartile was used as a control group. Interviews included occupational, environmental, demographic, and health information. A large number of health outcomes were analyzed, including speech impairment and hearing impairment. Statistical methods used include Logistic Regression and Odds Ratios. The primary purpose was to evaluate the rate of reporting health-outcome variables across exposure categories. The data were evaluated for an elevation of the risk estimates across the highest exposure categories or for a dose-response effect, while controlling for potential confounders. Estimated prevalence odds ratios for the health outcomes, adjusted for the potential confounders, were calculated by exponentiating the β-coefficients from the exposure variables in the regression equations. The standard error of the estimate was used to calculate 95% confidence intervals (CIs). The referent group used in the logistic regression models was the lowest exposure group. The results variables were modeled as dichotomous, binary dependent variables in the regression models. Nominal, independent variables were modeled, using dummy variables. The covariables used were sex, age, occupational exposure, education level, smoking history, and the sets of environmental subgroups. The analyses were restricted to persons 19 years of age or older when the variables of occupational history, smoking history, and education level were included. When the registrants were grouped by duration of exposure to TCE, a statistically significant association (adjusted for age and sex) between duration of exposure and reported hearing impairment was found. The prevalence odds ratios were 2.32 (95% Cl = 1.18, 4.56) (>2 to <5 yr); 1.17 (95% Cl = 0.55, 2.49) (>5 to <10 yr); and 2.46 (95% Cl = 1.30, 5.02)(>10 yr). Higher rates of speech impairment (although not statistically significant) were associated with maximum and cumulative TCE exposure, and duration of exposure. The study reports dose-response relationships, but the effects are self reported, and exposure data are estimates. No information was reported on presence or absence of additional solvents in drinking water.

ATSDR (2003) conducted a follow-up study to the TCE subregistry findings (Burg et al., 1995, 1999) and focused on the subregistry children. Of the 390 subregistry children (≤ 10 years at time of original study), 116 agreed to participate. TCE exposure ranged from 0.4 to 5,000 ppb from the drinking water. The median TCE exposure for this subgroup was estimated to be 23 ppb per year of exposure. To further the hearing impairments reported in Burg et al. (1995,

1999), comprehensive auditory tests were conducted with the 116 children and compared to a control group of 182 children that was age-matched. The auditory tests consisted of a hearing screening (typanometry, pure tone and distortion product otoacoustic emissions [DPOAE]) and a more in-depth hearing evaluation for children that failed the initial screening. Ninety percent of the TCE-exposed children passed the typanometry and pure tone tests, and there were no significant differences between control and TCE-exposed groups. Central auditory processing (CAP) tests were also conducted and consisted of a test for acoustic reflexes and a screening test for auditory processing disorders (SCAN). The acoustic reflex tested the ipsilateral and contralateral auditory pathway at 1,000 Hz for each ear. In this test, each subject hears the sound frequency and determines if the sound causes the stapedius muscle to tighten the stapes (normal reflex to noise). Approximately 20 percent of the children in the TCE subregistry and 5−7 percent in the controls exhibited an abnormal acoustic reflex, and this increased abnormality in the test was a significant effect ($p = 0.003$). No significant effects were noted in the SCAN tests. The authors concluded that the significant decrease in the acoustic reflex for the TCE subregistry children is reflective of potential abnormalities in the middle ear, which may reflect abnormalities in lower brainstem auditory pathway function. Lack of effects with the pure tone and typanometry tests suggests that the cochlea is not affected by TCE exposure.

Although auditory function was not directly measured, Rasmussen et al. (1993b) used a psychometric test to measure potential auditory effects of TCE exposure in an environmental study. Results from 96 workers exposed to TCE and other solvents were presented in this study. The workers were divided into three exposure groups: low, medium, and high. Details of the exposure groups and exposure levels are provided in Table 4.2−3 (under study description of Rasmussen et al., 1993b). Three auditory-containing tasks were included in this study, but only the acoustic motor function test could be used for evaluation of auditory function. In the acoustic motor function test, high and low frequency tones were generated and heard through a set of earphones. Each individual then had to imitate the tones by knocking on the table using the flat hand for a low frequency and using a fist for a high frequency. A maximal score of 8 could be achieved through this test. The tones were provided in either a set of 1 or 3 groups. In the one group acoustic motor function test, the average score for the low exposure group was 4.8 in comparison to 2.3 in the high exposure group. Similar decrements were noted in the 3 group acoustic motor function test. A significant association was reported for TCE exposure and performance on the one group acoustic motor function test ($p < 0.05$) after controlling for confounding variables.

D.1.3 Vestibular Effects

The data linking acute TCE exposure with transient impairment of vestibular function are quite strong based on human chamber studies, occupational exposure studies, and laboratory animal investigations. It is clear from the human literature that these effects can be caused by exposures to TCE, as they have been reported extensively in the literature.

The earliest reports of neurological effects resulting from TCE exposures focused on subjective symptoms, such as headaches, dizziness, and nausea. These symptoms are subjective and self-reported, and, therefore, offer no quantitative measurement of cause and effect. However, there is little doubt that these effects can be caused by exposures to TCE, as they have been reported extensively in the literature, resulting from occupational exposures (Grandjean et al., 1955; Liu et al., 1988; Rasmussen and Sabroe, 1986, and Smith, 1970), environmental exposures (Hirsch et al., 1996), and in chamber studies (Stewart et al., 1970; Kylin et al., 1967). These studies are described below in more detail.

Grandjean et al. (1955) reported on 80 workers exposed to TCE from 10 different factories of the Swiss mechanical engineering industry. TCE air concentrations varied from 6 ppm−1,120 ppm (33−6,200 mg/m^3) depending on time of day and proximity to tanks, but mainly averaged between 20−40 ppm (100−200 mg/m^3). Urinalysis (TCA) varied from 30 mg/L to 300 mg/L. This study does not include an unexposed referent group, although prevalences of self-reported symptoms or neurological changes among the higher-exposure group are compared to the lower-exposure group. Workers were classified based on their exposures to TCE and there were significant differences ($p = 0.05$) in the incidence of neurological disorder between Groups I (10−20ppm), II (20−40ppm; 110−220mg/m3) and III (>40ppm; (220mg/m3). Thirty-four percent of the workers had slight or moderate psycho-organic syndrome; 28% had neurological changes. Approximately 50% of the workers reported incidences of vertigo and 30% reported headaches (primarily an occasional and/or minimal disorder). Based on TCA eliminated in the urine, results show that subjective, vegetative, and neurological disorders were more frequent in Groups II (40−100mg/L) and III (101−250mg/L) than in Group I (10−39mg/L). Statistics do support a dose-effect relationship between neurological effects and TCE exposure, but exposure data are questionable.

Liu et al. (1988) evaluated the effects of occupational TCE exposure on 103 factory workers in Northern China. The workers (79 men, 24 women) were exposed to TCE during vapor degreasing production or operation. An unexposed control group of 85 men and 26 women was included for comparison. Average TCE exposure was mostly at less than 50 ppm (275mg/m^3). The concentration of breathing zone air during entire shift was measured by

diffusive samplers placed on the chest of each worker. Subjects were divided into three exposure groups; 1 ppm−10 ppm (5.5−55mg/m^3), 11 ppm−50 ppm (60−275mg/m^3) and 51 ppm−100ppm (280−550mg/m^3). Results were based on a self-reported subjective symptom questionnaire. The frequency of subjective symptoms, such as nausea, drunken feeling, light-headedness, floating sensation, heavy feeling of the head, forgetfulness, tremors and/or cramps in extremities, body weight loss, changes in perspiration pattern, joint pain, & dry mouth (all $\geq$3 times more common in exposed workers); reported as 'prevalence of affirmative answers', was significantly greater in exposed workers than in unexposed ($p < 0.01$). *Bloody strawberry jam-like feces"* was borderline significant in the exposed group and *"frequent flatus"* was statistically significant. Dose response relationships were established (but not statistically significant) for symptoms. Most workers were exposed below 10 ppm, and some at 11 ppm−50ppm. The differences in exposure intensity between men and women was of borderline significance ($0.05 < p < 0.10$). The study appears to be well done, although the self reporting of symptoms and the 'prevalence of affirmative answers' metric is not standard practice.

Rasmussen et al. (1986) conducted a cross-sectional study on 368 metal degreasers working in various factories in Denmark (industries not specified) with chlorinated solvents. The control group consisted of 94 randomly selected semi-skilled metal workers from same area. The mean age was 37.7 (range: 17−65+). Neurological symptoms of the subjects were assessed by questionnaire. The workers were categorized into 4 groups as follows: 1)currently working with chlorinated solvents (n = 171; average duration: 7.3 yrs, 16.5 hrs./wk; 57 % TCE & 37% 1,1,1-trichloroethane), 2) currently working with other solvents (n = 131; petroleum, gasoline, toluene, xylene), 3) previously (1−5 yrs.) worked with chlorinated or other solvents (n = 66), 4) never worked with organic solvents (n = 94). A dose-response relationship was observed between exposure to chlorinated solvents and chronic neuropsychological symptoms including vestibular system effects such as dizziness ($p < 0.005$), and headache ($p < 0.01$). The authors indicated that TCE exposure resulted in the most overall symptoms. Significant associations were seen between previous exposure and consumption of alcohol with chronic neuropsychological symptoms. Results are confounded by exposures to additional solvents.

Smith (1970) conducted an occupational study on 130 workers (108 males, 22 females) exposed to TCE (industry not reported). The control group consisted of 63 unexposed men working at the same factories matched by age, marital status and other non-specified criteria. A referent group was included and consisted of 112 men and women exposed to low concentration of lead and matched to the TCE exposed group in age and sex distribution. Seventy-three out of 130 workers (56.2%) reported dizziness and 23 workers reported having headaches (17.7%).

The number of complaints reported by subjects was greater for those with 60 mg/L or greater TCA than for those with less than 60 mg/L TCA. There was no difference in the number of symptoms reported between those with shorter durations of exposure and those with longer durations of exposure. No statistics were reported.

Hirsh et al. (1996) evaluated the vestibular effects of an environmental exposure to TCE in Roscoe, IL residents. A medical questionnaire was mailed to 103 residents of Roscoe with 100 percent response. These 103 and an additional 15 residents, not previously surveyed, brought the subject population to 118 residents. During the course of testing, 12 subjects (young children and uncooperative patients) were excluded bringing the total number of subjects to 106 all of whom were in the process of taking legal action against the company whose industrial waste was assumed to be the source of the polluting TCE. This was a case series report with no controls. Random testing of the wells between 1983−84 revealed groundwater in wells to have levels of TCE between 0 to 2,441 ppb. The distance of residence from contaminated well was used to estimate exposure level. Sixty-six subjects (62%) complained of headaches at the time of evaluation. Diagnosis of TCE-induced cephalagia was considered credible for 57 patients (54%). Forty-seven of these had a family history of headaches. Retrospective TCE level of well water or well's distance from the industrial site analysis did not correlate with the occurrence of possibly-TCE induced headaches. This study shows a general association between headaches and exposure to TCE in drinking water wells. There were no statistics to support a dose-response relationship. All subjects were involved in litigation.

Stewart et al. (1970) evaluated vestibular effects in 13 subjects who were exposed to TCE vapor 100 ppm (550mg/m^3) and 200 ppm (1,100mg/m^3) for periods of 1 hour to a five-day work week. Experiments 1−7 were for a duration of 7 hours with a mean TCE concentration of 198 ppm−200 ppm (1,090−1,100mg/m^3). Experiments 8 and 9 exposed subjects to 190 ppm−202 ppm (1,045−1,110mg/m^3) TCE for a duration of 3.5 and 1 hour, respectively. Experiment 10 exposed subjects to 100 ppm (550mg/m^3) TCE for 4 hours. Experiments 2−6 were carried out with the same subjects over 5 consecutive days. Gas chromatography of expired air was measured. There were no self controls. Subjects reported symptoms of lightheadedness, headache, eye, nose & throat irritation. Prominent fatigue and sleepiness by all were reported above 200ppm (1,100mg/m^3). There were no quantitative data or statistics presented regarding dose and effects of neurological symptoms.

Kylin et al. (1967) exposed 12 volunteers to 1,000ppm (5,500mg/m^3) TCE for two hours in a 1.5x2x2 meters chamber. Volunteers served as their own controls since 7 of the 12 were

pre-tested prior to exposure and the remaining 5 were post-tested days after exposure. Subjects were tested for optokinetic nystagmus, which was recorded by electronystogmography, that is, "the potential difference produced by eye movements between electrodes placed in lateral angles between the eyes." Venous blood was also taken from the volunteers to measure blood TCE levels during the vestibular task. The authors concluded that there was an overall reduction in the limit ("fusion limit") to reach optokinetic nystagmus when individuals were exposed to TCE. Reduction of the "fusion limit" persisted for up to 2 hours after the TCE exposure was stopped and the blood TCE concentration was 0.2 mg/100 mL.

D.1.4 Visual Effects

Kilburn (2002a) conducted an environmental study on 236 people exposed to TCE in groundwater in Phoenix, AZ. Details of the TCE exposure and population are described earlier in Section D.1.1.1 (See Kilburn [2002a]). Among other neurological tests, the population and 161 nonexposed controls was tested for color discrimination using the desaturated Lanthony 15-hue test, which can detect subtle changes in color vision deficiencies. Color discrimination errors were significantly increased in the TCE exposed population ($p < 0.05$) with errors scores averaging 12.6 in the TCE exposed in comparison to 11.9 in the control group. This study shows statistically significant differences in visual response between exposed and non-exposed subjects exposed environmentally. Estimates of TCE concentrations in drinking water to individual subjects are lacking.

Reif et al. (2003) conducted a cross sectional environmental study on 143 residents of the Rocky Mountain Arsenal community of Denver whose water was contaminated with TCE and related chemicals from nearby hazardous waste sites between 1981 and 1986. The residents were divided into three groups based on TCE exposure with the lowest exposure group at <5 ppb, the medium exposure group at 5 to15 ppb and the high exposure group defined as >15 ppb TCE. Visual performance was measured by two different contrast sensitivity tests (C and D) and the Benton visual retention test. In the two contrast sensitivity tests, there was a 20 to 22 percent decrease in performance between the low and high TCE exposure groups and approached statistical significance ($p = 0.06$ or 0.07). In the Benton visual retention test, which measures visual perception and visual memory, scores, dropped by 10% from the lowest exposure to the highest TCE exposure group and was not statistically significant. It should be noted that the residents were potentially exposed to multiple solvents including TCE and a non-exposed TCE group was not included in the study. Additionally, modeled exposure data are only a rough

estimate of actual exposures, and possible misclassification bias associated with exposure estimation may limit the sensitivity of the study.

Rasmussen et al. (1993b) conducted a cross-sectional study on 96 metal workers, working in degreasing at various factories in Denmark (industries not specified) with chlorinated solvents. These subjects were identified from a larger cohort of 240 workers. Details of the exposure groups and TCE exposure levels are presented in Section D.1.1.1 (under Rasmussen et al., 1993c). Neuropsychological tests including the visual gestalts (test of visual perception and retention) and the stone pictures test (test of visual learning and retention) were administered to the metal workers. In the visual gestalts test, cards with a geometrical figure containing four items were presented and workers had to redraw the figure from memory immediately (learning phase) after presentation and after 1 hour (retention phase). In the learning phase, the figures were redrawn until the worker correctly drew the figure. The number of total errors significantly increased from the low group (3.4 errors) to the high exposure group (6.5 errors; $p = 0.01$) during the learning phase (immediate presentation). Similarly, during the retention phase of this task (measuring visual memory), errors significantly increased from an average of 3.2 in the low group to 5.9 in the high group ($p < 0.001$). In the stone pictures test, slides of 10 stones (different shapes and sizes) were shown and the workers had to identify the 10 stones out of a lineup of 25 stones. There were no significant changes in this task, but the errors increased from 4.6 in the low exposure group to 6.3 in the high exposure group during the learning phase of this task. Although this study identifies visual performance deficits, a control group (no TCE exposure) was not included in this study and the presented results may actually underestimate visual deficits from TCE exposure.

Troster and Ruff (1990) presented case studies conducted on two occupationally exposed workers to TCE and included a third case study on an individual exposed to 1,1,1-trichloroethane. Case #1 was exposed to TCE (concentration unknown) for eight months and Case #2 was exposed to TCE over a three month period. Each patient was presented with a visual-spatial task (Ruff-Light Trail Learning test as referenced by the authors). Both of the individuals exposed to TCE were unable to complete the visual-spatial task and took the maximum number of trials (10) to attempt to complete the visual task. A control group of 30 individuals and the person exposed to 1,1,1-trichloroethane were able to complete this task accordingly. The lack of quantitative exposure data and a small sample size severely limits the study and does not allow for statistical comparisons.

Vernon and Ferguson (1969) exposed eight male volunteers (ages 21−30) to 0, 100, 300, and 1,000 ppm TCE for 2 hours. Each individual was exposed to all TCE concentrations and a span of at least three days was given between exposures. The volunteers were presented with 6 visuo-motor tests during the exposure sessions. When the individuals were exposed to 1,000 ppm TCE (5,500 mg/m^3), significant abnormalities were noted in depth perception as measured by the Howard-Dolman test ($p < 0.01$), but no effects on the flicker fusion frequency test (threshold frequency at which the individual sees a flicker as a single beam of light) or on the form perception illusion test (volunteers presented with an illusion diagram). This is one of the earliest chamber studies of TCE. This study included only healthy young males, is of a small size, limiting statistical power, and reports mixed results on visual testing following TCE exposure.

D.1.5 Cognition

There is a single environmental study in the literature that presents evidence of a negative impact on intelligence resulting from TCE exposure. Kilburn and Warshaw (1993 – study details in Section D.1.1.1) evaluated the effects on cognition for 544 Arizona residents exposed to TCE in well-water. Subjects were recruited and categorized into three groups. Exposed group 1 consisted of 196 family members with cancer or birth defects. Exposed group 2 consisted of 178 individuals from families without cancer or birth defects; and exposed group 3 included 170 parents whose children had birth defects and rheumatic disorders. Sixty-eight referents were used as a comparison group for the clinical memory tests. Several cognitive tests were administered to these residents in order to test memory recall skills and determine if TCE exposure resulted in memory impairment. Working or short-term memory skills were tested by asking each individual to recall two stories immediately after presentation (verbal recall) and also draw three diagrams immediately after seeing the figures (visual recall). Additionally, a digit span test where increasing numbers of digits were presented and then the subject had to recall the digits was conducted to the extent of the short-term memory. Exposed subjects had lower intelligence scores and there were significant impairments in verbal recall ($p = 0.001$), visual recall ($p = 0.03$) and with the digit span test ($p = 0.07$). Significant impairment in short-term memory as measured by three different cognitive test was correlated with TCE exposure. Lower intelligence scores ($p = 0.0001$) as measured by the Culture Fair IQ test may be a possible confounder in these findings. Additionally, the large range of TCE concentrations (6−500 ppb) and exposure durations (1 to 25 years) and overall poor exposure characterization precludes a NOAEL/LOAEL from being estimated from this study on cognitive function.

Rasmussen et al. (1993a, b) and Troster and Ruff (1990) present results of positive findings in occupational studies for cognitive effects of TCE. Rasmussen et al. (1993a) reported an historical cohort study conducted on 96 metal degreasers, identified 2 years previously. Subjects were selected from a population of 240 workers from 72 factories in Denmark, and is described above. They reported psychoorganic syndrome, a mild syndrome of dementia characterized by cognitive impairment, personality changes, and reduced motivation, vigilance, and initiative, was increased in the 3 exposure groups. The medium and high exposure groups were compared with the low exposure group. Neuropsychological tests included WAIS (original version, Vocabulary, Digit Symbol, Digit Span), Simple Reaction Time, Acoustic-motor function (Luria), Discriminatory attention (Luria), Sentence Repetition, Paced Auditory Serial Addition Test (PASAT), Text Repetition, Rey's Auditory Verbal Learning, Visual Gestalts, Stone Pictures (developed for this study, non-validated), revised Santa Ana, Luria motor function, and Mira. The prevalence of psychoorganic syndrome was 10.5% in low exposure group; 38.9% in medium exposure group; 63.4% in high exposure group. (x^2 trend analysis: low vs. medium exposure $x^2 = 11.0$, p value <0.001; low vs. high exposure $x^2 = 19.6$, p value <0.001). Psychoorganic syndrome increased with age ($p < 0.01$). Age was strongly correlated with exposure.

Rasmussen et al. (1993b) used a series of cognitive tests to measure effects of occupational TCE exposure. Short-term memory and retention following an latency period of one hour was evaluated in several tests including a verbal recall (auditory verbal learning test), visual gestalts, visual recall (stone pictures), and the digit span test. Significant cognitive performance decreases were noted in both short-term memory and memory retention. In the verbal recall test immediate memory and learning were significantly decreased ($p = 0.03$ and 0.04, respectively). No significant effects were noted for retention following a one hour latency period was noted. Significant increases in errors were noted in both the learning ($p = 0.01$) and memory ($p < 0.001$) phases for the visual gestalts test. No significant effects were found in the visual recall test in either the learning or memory phases or in the digit span test. As a result, there were some cognitive deficits noted in TCE-exposed individuals as measured through neuropsychological tests.

Troster and Ruff (1990) provides additional supporting evidence in an occupational study for cognitive impairment, although the results reported in a qualitative fashion are limited in their validity. In the two case studies that were exposed to TCE, there were decrements (no statistical analysis performed) in cognitive performance as measured in verbal and visual recall tests that

were conducted immediately after presentation (learning phase) and one hour after original presentation (retention/memory phase).

Triebig et al. (1977b) presents findings of no impairment of cognitive ability resulting from TCE exposure in an occupational setting. This study was conducted on 8 subjects occupationally exposed to TCE. Subjects were 7 men and 1 woman with an age range from 23−38 years. Measured TCE in air averaged 50 ppm (260 mg/m^3). Length of occupational exposure was not reported. There was no control group. Results were compared after exposure periods, and compared to results obtained after periods removed from exposure. TCA and TCE metabolites in urine and blood were measured. The testing consisted of: the Syndrome Short Test, which consists of nine subtests through which amnesic and simple perceptive and cognitive functional deficits are detected; the "Attention Load Test" or "d2 Test" from Brickenkamp is a procedure that measures attention, concentration, and stamina. Number recall test, letter recall test, the "Letter Reading Test", "Word Reading Test". Data were assessed using Wilcoxon and Willcox nonparametric tests. Due to the small sample size a significance level of 1% was used. The concentrations of trichloroethylene (TCE), trichloroethanol, and trichloroacetic acid (TCA) in the blood and total TCE and total TCA elimination in the urine were used to assess exposure in each subject. The mean values observed were 330 mg trichloroethanol and 319 mg TCA /g creatinine, respectively, at the end of a work shift. The psychological tests showed no statistically significant difference in the results before or after the exposure-free time period. The small sample size may limit the sensitivity of the study.

Salvini et al. (1971), Gamberale et al. (1976), and Stewart et al. (1970) reported positive findings for the impairment of cognitive function following TCE exposures in chamber studies. Salvini et al. (1971) reported a controlled exposure study conducted on six male university students. TCE concentration was 110 ppm (550 mg/m^3) for 4-hour intervals, twice per day. Each subject was examined on two different days, once under TCE exposure, and once as self controls, with no exposure. Two sets of tests were performed for each subject corresponding to exposure and control conditions. Perception test with tachistoscopic presentation, Wechsler memory scale, complex reaction time test (CRT), and manual dexterity test. Statistically significant results were observed for perception tests learning ($p < 0.001$), mental fatigue ($p < 0.01$), subjects ($p < 0.05$); and CRT learning ($p < 0.01$), mental fatigue ($p < 0.01$), subjects ($p < 0.05$). This is controlled exposure study with measured dose (110 ppm; 600 mg/m^3) and clear, statistically significant impact on neurological functional domains. However, it only assesses acute exposures.

Gamberale et al. (1976) reported a controlled exposure study conducted on 15 healthy men aged 20−31 yrs old, employed by the Department of Occupational Medicine in Stockholm, Sweden. Controls were within subjects (15 self-controls), described above. Test used included Reaction time (RT) Addition and short term memory using an electronic panel. Subjects also assessed their own conditions on a 7-point scale. Researchers performed ANOVA for the 4 performance tests based on a 3 x 3 Latin square design with repeated measures. In the short-term memory test (version of the digit span test), a series of numbers lasting for one second was presented to the subject. The volunteer then had to reproduce the numerical sequence after a latency period (not specified). No significant effect on the short-term memory test was observed with TCE exposure in comparison to air exposure. Potential confounders from this study include repetition of the same task for all exposure conditions, volunteers served as their own controls, and TCE exposure preceded air exposure in two of the three exposure experimental designs. This is a well controlled study of short term exposures with measured TCE concentrations and significant response observed for cognitive impairment.

Additional qualitative support for cognitive impairment is provided by Stewart et al. (1970). This was a controlled exposure study conducted on 13 subjects in 10 experiments, which consisted of ten chamber exposures to TCE vapor of 100 ppm (550 mg/m^3) and 200 ppm (1,100 mg/m^3) for periods of 1 hour to a five-day work week. Experiments 1−7 were for 7 hours with a mean TCE concentration of 198 ppm−200 ppm (1,090−1,100 mg/m^3). Experiments 8 and 9 exposed subjects to 190 ppm−202 ppm (1,045−1,110 mg/m^3) TCE for a duration of 3.5 and 1 hour, respectively. Experiment 10 exposed subjects to 100 ppm (550 mg/m^3) TCE for 4 hours. Experiments 2−6 were carried out with the same subjects over 5 consecutive days. Gas chromatography of expired air was measured. There were no self controls. All had normal neurological tests during exposure, but 50% reported greater mental effort was required to perform a normal modified Romberg test on more than one occasion. There were no quantitative data or statistics presented regarding dose and effects of neurological symptoms.

Two chamber studies conducted by Triebig et al. (1976, 1977a) report no impact of TCE exposure on cognitive function. Triebig et al. (1976) was a controlled exposure study conducted on 7 healthy male and female students (4 females, 3 males) exposed for 6 hours/day for 5 days to 100 ppm (550 mg/m^3 TCE). The control group was 7 healthy students (4 females, 3 males) exposed to hair care products. This was assumed as a zero exposure, but details of chemical composition were not provided. Biochemical and psychological testing was conducted at the beginning and end of each day. Biochemical tests included TCE, TCA, and trichloroethanol in blood. Psychological tests included the d2 test, which was an attention load test; the short test is

used to record patient performance with respect to memory and attention; daily Fluctuation Questionnaire measured the difference between mental states at the start of exposure and after the end of exposure is recorded; The MWT-A is a repeatable short intelligence test; Culture Fair Intelligence Test (CFT-3) is a nonverbal intelligence test that records the rather "fluid" part of intelligence, that is, finding solution strategies; Erlanger Depression Scale. Results were not randomly distributed. The median was used to describe the mean value. Regression analyses were conducted. In this study the TCE concentrations in blood reported ranged from 4 to14 μg/mL. A range of 20 to 60 μg/mL was obtained for TCA in the blood. There was no correlation seen between exposed and unexposed subjects for any measured psychological test results. The biochemical data did demonstrate subjects' exposures. This is a well controlled study with excellent exposure data, although the small sample size may have limited sensitivity.

Triebig et al. (1977a) is an additional report on the seven exposed subjects and seven controls evaluated in Triebig et al. (1976). Additional psychological testing was reported. The testing included the Syndrome Short Test, which consists of nine subtests, described above. Statistics were conducted using Whitney Mann. Results indicated the anxiety values of the placebo random sample group dropped significantly more during the course of testing ($p < 0.05$) than those of the active random sample group. No significantly different changes were obtained with any of the other variables. Both these studies were well controlled with excellent exposure data, which may provide some good data for establishing a short term NOAEL. The small sample size may have limited the sensitivity of the study.

Additional reports on the impairment of memory function as a result of TCE exposures have been reported, and provide additional evidence of cognitive impairment. The studies by Chalupa et al. (1960), Rasmussen et al. (1986, 1993b), and Troster and Ruff (1990) report impairment of memory resulting from occupational exposures to TCE. Kilburn and Warshaw (1993) and Kilburn (2002a) report impairment of memory following environmental exposures to TCE. Salvini et al. (1971) reports impairment of memory in a chamber study, although Triebig et al. (1976) reports no impact on memory following TCE exposure in a chamber study.

D.1.6 Psychomotor Effects

There is evidence in the literature that TCE can have adverse psychomotor effects in humans. The effects of TCE exposure on psychomotor response have been studied primarily as the impact on reaction times (RT), which provide a quantitative measure of the impact TCE exposure has on motor skills. Studies on motor dyscoordination resulting from TCE exposure

are more subjective, but provide additional evidence that TCE may cause adverse psychomotor effects. These studies are described below.

D.1.6.1 Reaction Time

There are several reports in the literature that report an increase in reaction times following exposures to TCE. The best evidence for TCE exposures causing an increase in choice reaction times comes from environmental studies by Kilburn (2002a), Kilburn and Warshaw (1993), Reif et al. (2003), and Kilburn and Thornton (1996), which were all conducted on populations which were exposed to TCE through groundwater contaminated as the result of environmental spills. Kilburn (2002a – study details described in section D.1.1) evaluated reaction times in a Phoenix, Arizona population exposed to TCE through groundwater. Volunteers were tested for response rates in the simple reaction time (SRT) and 2 choice reaction time (CRT) tests. Various descriptive statistics were used, as well as ANCOVA and a step-wise adjustment of demographics. The principal comparison, between the 236 exposed persons and the 161 unexposed regional controls, revealed significant differences ($p < 0.05$) indicating that SRTs and CRTs were delayed. Balance was also abnormal with excessive sway speed (eyes closed), but this was not true when both eyes were open. This study shows statistically significant differences in psychomotor responses between exposed and non-exposed subjects exposed environmentally. However, it is limited by poor exposure characterization.

Kilburn and Warshaw (1993 – study details described in section D.1.1.1) evaluated reaction times in 170 Arizona residents exposed to TCE in well-water. A referent group of 68 people was used for comparison. TCE concentration was from 6 to 500 ppb and exposure ranged from 1 to 25 years. SRT was determined by presenting the subject a letter on a computer screen and measuring the time (in msec) it took for the person to type that letter. SRT significantly increased from 281 ± 55 msec to 348 ± 96 msec in TCE-exposed individuals ($p < 0.0001$). Similar increases were reported for CRT where subjects were presented with two different letters and required to make a decision as to which letter key to press. CRT of the exposed subjects was 93 msec longer in the third trial ($p < 0.0001$) than referents. It was also longer in all trials, and remained significantly different after age adjustment. This study shows statistically significant differences for neurological test results between subjects environmentally exposed and non-exposed to TCE, but is limited by poor exposure data on individual subjects given the ecological design of this study. Additionally, litigation is suggested and may introduce a bias, particularly if no validity tests were used.

Kilburn and Thornton (1996) conducted an environmental study that attempts to use reference values from two control groups in assessing neurological responses for chemically exposed subjects using neurophysiological and neuropsychological testing on three groups. Group A: randomly selected registered voters from Arizona and Louisiana with no exposure to TCE: $n = 264$ unexposed volunteers aged 18−83: Group B volunteers from California $n = 29$ (17 males & 12 females) used to validate the equations; Group C exposed to TCE and other chemicals residentially for 5 years or more $n = 237$. Group (A), was used to develop the regression equations for Simple Reaction Time (SRT) and Choice Reaction Time (CRT). A similarly selected comparison group B was used to validate the equations. Group C, the exposed population, was submitted to SRT and CRT tests ($n = 237$) and compared to the control groups. All subjects were screened by a questionnaire. Reaction speeds were measured using a timed computer visual-stimulus generator. No exposure data were presented. The Box-Cox transformation was used for dependent variables (DV) and independent variables (IV). They evaluated graphical methods to study residual plots. Cook's distance statistic was used as a measure of influence to exclude outliers with undue influence and none of the data were excluded. Lack-of-fit test was performed on Final model and F statistic was used to compare estimated error to lack-of-fit component of the model's residual sum of squared error. Final models were validated using group B data and paired *t* test to compare observed values for SRT and CRT. F statistic was used to test the hypothesis that parameter estimates obtained with group B were equal to those of Group A, the model. The results are as follows: Group A: SRT = 282 ms; CRT = 532 ms. Group B: SRT = 269 ms; CRT = 531 ms. Group C: SRT = 334 ms; CRT = 619 ms. TCE exposure produced a step increase in reaction times (SRT and CRT). The coefficients from Group A were valid for group B. The predicted value for SRT and for CRT, plus 1.5 SDs selected 8% of the model group as abnormal. The model produced consistent measurement ranges with small numerical variation. This study is limited by lack of any exposure data, and does not provide statistics to demonstrate dose response effects.

Kilburn (2002a) conducted an environmental study on 236 residents chronically exposed to TCE-associated solvents in the groundwater resulting from a spill from a microchip plant in Phoenix, AZ. Details of the TCE exposure and population are described earlier in Section D.1.1.1 (See Kilburn [2002a]). The principal comparison, between the 236 exposed persons and the 161 unexposed regional controls, revealed significant differences indicating that simple reaction times (SRTs) and choice reaction times (CRTs) were increased. SRTs significantly increased from 283 ± 63 msec in controls to 334 ± 118 msec in TCE exposed individuals ($p < 0.0001$). Similarly, CRTs also increased from 510 ± 87 msec to 619 ± 153 msec with exposure to TCE ($p < 0.0001$). This study shows statistically significant differences in

psychomotor responses as measured by reaction times between TCE-exposed and non-exposed subjects. Estimates of TCE concentrations in drinking water to individual subjects were not reported in the paper. Since the TCE exposure ranged from 0.2 to over 10,000 ppb in well water, it is not possible to determine a NOAEL for increased reaction times through this study. Additionally, litigation is suggested and may introduce a bias, particularly if no validity tests were used.

Reif et al. (2003) conducted a cross sectional study on 143 residents of the Rocky Mountain Arsenal (RMA) community of Denver exposed environmentally to drinking water contaminated with TCE and related chemicals from nearby hazardous waste sites between 1981 and 1986. The referent group was at the lowest estimated exposure concentration (<5 ppb). The socioeconomic profile of the participants closely resembled those of the community in general. "A total of 3393 persons was identified through the census, from which an age- and gender-stratified sample of 1267 eligible individuals who had lived at their current residence for at least 2 years was drawn. Random selection was then used to identify 585 persons from within the age–gender strata, of whom 472 persons aged 2–86 provided samples for biomonitoring. Neurobehavioral testing was conducted on 204 adults who lived in the RMA exposure area for a minimum of 2 years. Among the 204 persons who were tested, 184 (90.2%) lived within the boundaries of the LWD and were originally considered eligible for the current analysis. Therefore, participants who reported moving into the LWD after 1985 were excluded from the total of 184, leaving 143 persons available for study." An elaborate hydraulic simulation model (not validated) was used in conjunction with a geographic information system (GIS) to model estimates of residential exposures to TCE. The TCE concentration measured in community wells exceeded the Maximum Contaminant Level (MCL) of 5 ppb in 80% of cases. Approximately 14% of measured values exceeded 15 ppb. Measured values were used to model actual exposure estimates based on distance of residences from sampled wells. The estimated exposure for the high exposure group was >15 ppb; the estimate for the low exposure referent group was < 5ppb. The medium exposure group was estimated at exposures 5< x <15 ppb TCE. The test battery consisted of the Neurobehavioral Core Test Battery (NCTB), which consists of 7 neurobehavioral tests including simple reaction time. Results were assessed using the Multivariate Model. Results were statistically significant ($p < 0.04$) for the simple reaction time tests. The results are confounded by exposures to additional solvents and modeled exposure data, which while highly technical, are still only a rough estimate of actual exposures, and may limit the sensitivity of the study.

Gamberale et al. (1976) conducted a controlled exposure (chamber) study on 15 healthy men aged 20−31 yrs old, employed by the Department of Occupational Medicine in Stockholm, Sweden. Controls were within subjects (15 self-controls). Subjects were exposed to TCE for 70 minutes via a breathing valve to 540 mg/m^3 (97 ppm), 1,080 mg/m^3 (194 ppm), and to ordinary atmospheric air (0 ppm). Sequence was counterbalanced between the 3 groups, days, and exposure levels. Concentration was measured with a gas chromatographic technique every third minute for the first 50 minutes, then between tests thereafter. Test used were reaction time (RT) addition, simple RT, choice RT and short term memory using an electronic panel. Subjects also assessed their own conditions on a 7 point scale. The researchers performed Friedman two-way analysis by ranks to evaluate differences between the 3 conditions. The results were non-significant when tested individually, but significant when tested on the basis of six variables. Nearly half of the subjects could distinguish exposure/nonexposure. Researchers performed ANOVA for the 4 performance tests based on a 3x3 Latin square design with repeated measures. In the RT-Addition test the level of performance varied significantly between the different exposure conditions ($F(2.24) = 4.35$; $p < 0.05$) and between successive measurement occasions ($F(2.24) = 19.25$; $p < 0.001$). The level of performance declined with increased exposure to TCE, whereas repetition of the testing led to a pronounced improvement in performance as a result of the training effect. No significant interaction effects were observed between exposure to TCE and training. This is a good study of short term exposures with measured TCE concentrations and significant response observed for reaction time.

Gun et al. (1978) conducted an occupational study on 8 TCE-exposed workers who operated degreasing baths in two different plants. Four female workers were exposed to TCE only in one plant and four female workers were exposed to TCE and nonhalogenated hydrocarbon solvents in the second plant. The control group ($n = 8$) consisted of 4 female workers from each plant who did not work near TCE. Each worker worked 2 separate 4 hour shifts daily, with one shift exposed to TCE and the second 4-hour shift not exposed. Personal air samples were taken continuously over separate 10-minute sessions. Readings were taken every 30 seconds. Eight-choice reaction times were carried out in four sessions; at the beginning and end of each exposure to TCE or TCE + solvents; a total of 40 reaction time trials were completed. TCE concentrations in the TCE only plant 1 (148−418 ppm (800−2,300 mg/m^3)) were higher than in the TCE + solvent plant 2 (3−87 ppm (16−480mg/m^3). Changes in choice reaction times (CRT) were compared to level of exposure. The TCE only group showed a mean increase in reaction time, with a probable cumulative effect. In the TCE + solvent group, mean reaction time shortened in session 2, then increased to be greater than at the start. Both control groups showed a shortening in mean choice reaction time in session 2 which was sustained in

session 3 & 4 consistent with a practice effect. This is a study with well defined exposures and reports of cause and effect (TCE exposure on reaction time); however, no statistics were presented to support the conclusions or the significance of the findings, and the small sample size is a limitation of the study.

D.1.6.2 Muscular Dyscoordination

Effects on motor dyscoordination resulting from TCE exposure have been reported in the literature. These impacts are subjective, but may provide additional evidence that TCE can cause adverse psychomotor effects. There are three reports summarized below which suggest that muscular dyscoordination resulted from TCE exposure, although all three have significant limitations due to confounding factors. Rasmussen et al. (1993c) presented findings on muscular dyscoordination as it relates to TCE exposure. This was a historical cohort study conducted on 96 metal degreasers, identified 2 years previously. Subjects were selected from a population of 240 workers from 72 factories in Denmark. Although the papers report a population of 99 participants, tabulated results were presented for a total of only 96. No explanation was provided for this discrepancy. These workers had chronic exposure to fluorocarbon (cfc 113) (n = 25) and mostly TCE (n = 70; average duration: 7.1 years.). There were no external controls. The range of working full-time degreasing was 1 month to 36 years. Researchers collected data regarding the workers' occupational history, blood and urine tests, as well as biological monitoring for TCE and TCE metabolites. A CEI (chronic exposure index) was calculated based on number of hours per week worked with solvents multiplied by years of exposure multiplied by 45 weeks per year. No TCE air concentrations were reported. Participants were categorized into three groups: 1) "Low exposure": n = 19, average full-time exposure = 0.5 years. 2) "Medium exposure": n = 36, average full-time exposure = 2.1 years. 3) "High exposure": n = 41, average full-time exposure = 11 years. The mean trichloroacetic acid (TCA) level in the "high" exposure group was 7.7 mg/L (max = 26.1 mg/L). TWA measurements of CFC 113 levels were 260−420 ppm (US & Danish TLV was 500 ppm). A significant trend of dyscoordination from low to high solvent exposure was observed (p = 0.003). This study provides evidence of causality for muscular dyscoordination resulting from exposure to TCE, but no measured exposure data were reported.

Additional evidence of the psychomotor effects caused by exposure to TCE are presented in Gash et al. (2007) and Troster and Ruff (1990). There are, however, significant limitations with each of these studies. In Gash et al. (2007), the researchers evaluated the clinical features of 1 Parkinson's disease (PD) patient, identified in a phase 1 clinical trial study, index case, and an

additional 29 coworkers of the patient, all with chronic occupational exposures to TCE. An additional 2 subjects with Parkinson's Disease were included, making the total of 3 Parkinson's disease patients, and 27 non-Parkinson's co-workers making up the study population. Co-workers for the study were identified using a mailed questionnaire to 134 former co-workers. No details are provided in the paper on selection criteria for the 134 former co-workers. Of the 134 former workers sent questionnaires, 65 responded. Twenty-one self-reported no symptoms, 23 endorsed 1−2 symptoms, and 21 endorsed 3 or more signs of Parkinsonism. Fourteen of the 21 with 3 or more signs and 13 of the 21 without any signs agreed to a clinical exam; this group comprises the 27 additional workers examined for Parkinsonian symptoms. No details were provided on non-responders. All subjects were involved in degreasing with long-term chronic exposure to TCE through inhalation and dermal exposure (14 symptomatic: age range = 31−66, duration of employment range: 11−35 yrs) (13 asymptomatic: age range = 46−63, duration of employment range: 8−33 yrs). The data were compared between groups and with data from 110 age- matched controls. Exposure to TCE is self-reported and based on job proximity to degreasing operations. The paper lacks any description of degreasing processes including TCE usage and quantity. Mapping of work areas indicated that workers with PD worked next to the TCE container, and all symptomatic workers worked close to the TCE container. Subjects underwent a general physical exam, neurological exam and Unified Parkinson's Disease Rating Scale (UPDRS), timed motor tests, occupational history survey, and mitochondrial neurotoxicity. ANOVA analysis was conducted, comparing symptomatic versus non-symptomatic workers, and comparing symptomatic workers to age-matched non-exposed controls. No description of the control population (n = 110), nor how data were obtained for this group, was presented. The symptomatic non-Parkinson's group was significantly slower in fine motor hand movements than age-matched non-symptomatic group ($p < 0.001$). The symptomatic group was significantly slower ($p < 0.0001$) than age-matched unexposed controls as measured in fine motor hand movements on the Movement Analysis Panel. All symptomatic workers had positive responses to 1 or more questions on UPDRS Part II (diminished activities of daily life), and/or deteriorization of motor functions on Part III. The fine motor hand movement times of the asymptomatic TCE-exposed group were significantly slower ($p < 0.0001$) than age-matched non-exposed controls. Also, in TCE-exposed individuals, the asymptomatic group's fine motor hand movements were slightly faster ($p < 0.01$) than those of the symptomatic group. One symptomatic worker had been tested 1 yr. prior and his UPDRS score had progressed from 9 to 23. Exposures are based on self-reported information, and no information on the control group is presented. One of the PD patients predeceased the study and had a family history of PD.

Troster and Ruff (1990) reported a case study conducted on two occupationally exposed workers to TCE. Patients were exposed to low levels of TCE. There were 2 groups of $n = 30$ matched controls (all age and education matched) whose results were compared to the performance of the exposed subjects. Exposure was described as "Unknown amount of TCE for 8 months." Assessment consisted of the San Diego Neuropsychological Test Battery (SDNTB), "1 or more of: Thematoc Apperception Test (TAT), Minnesota Multiphasic Personal Inventory (MMPI), and Rorschach. Medical examinations were conducted, including neurological, CT scan, and/or chemo-pathological tests, and occupational history was taken, but not described. There were no statistical results reported. Results were reported for each test, but no tests of significance were included, therefore the authors presented their conclusions for each 'case' in qualitative terms, as such: Case 1: intelligence "deemed" to drop from pre-morbid function at 1 yr 10 months after exposure. Impaired functions improved for all but reading comprehension, visuospatial learning and categorization (abstraction). Case 2: Mild deficits in motor speed, but symptoms subsided after removal from exposure.

D.1.7 Summary Tables

Table D.1.1 Epidemiological Studies: Neurological Effects of Trichloroethylene

Reference	Study Population	Exposure Assess. & biomarkers	Tests used	Statistics	Results
Barret et al., 1984	188 workers exposed to TCE occupationally from small and large factories in France (type of factories not disclosed); average age = 41; 6 yrs average exposure time The workers were divided into high and low exposure groups for both trichloroethylene (TCE) and urinary trichloroacetic acid (TCA). No control group was mentioned.	Review of medical records and analysis of TCE atmospheric levels (detector tubes) and level of urinary metabolites measurement (TCA). TCE exposure groups included high exposure group (>150ppm; *n* = 54) and low exposure group <150 ppm; *n* = 134) Personal factors including age, tobacco use and alcohol intake were also analyzed; Exposure duration = 7 hours/day for 7 years; no mention was made regarding whether or not the examiners were blind to the subjects' exposure status	Complete physical examination including testing visual performance (acuity and color perception), evoked trigeminal potential latencies and audiometry, facial sensitivity, reflexes, and motoricity of the masseter muscles.	X^2 examined distribution of the different groups for comparing high and low exposed workers, one way analysis of variance, Mann Whitney U & t-test for analyzing personal factors	Symptoms for which TCE role is statistically significant: Trigeminal nerve impairment was reported in 22.2% (*n* = 12) of workers in the high-exposure group for TCE , 7.4% (*n* = 10) in the low-exposure group for TCE , 24.4% (*n* = 10) in the high-exposure group for TCA and 8.2% (*n* = 12) in the low-exposure group for TCA. TCE Results — High dose% — Low dose% — P Trigeminal nerve Impairment — 22.2 — 7.4 — <0.01 Asthenia — 18.5 — 4.5 — <0.01 Optic nerve Impairment — 14.8 — 0.75 — <0.001 Headache — 20.3 — 19.4 — NS Dizziness — 13 — 4.5 — 0.05<P<0.06 Symptoms for which TCE role is possible, but not statistically significant = deafness, nystagmus, GI symptoms, morning cough, change in tumor, eczema, palpitations, conjunctivitis, Symptoms for which there's a synergistic toxic role for TCE and alcohol (P < 0.05) = liver impairment and degreaser flush. Trigeminal sensory evoked potentials are suggested as a good screening test.

Barret et al., 1987	104 occupationally exposed workers highly exposed to TCE during work as degreaser machine operators in France. Controls: 52 healthy, nonexposed controls of various ages who were free from neurological problems	Urinary analysis determined TCE and TCA rates. The average of the last 5 measurements were considered indicative of the average level of past exposure; Mean exposure 8.2 yrs, average daily exposure 7 hrs/day. Mean age 41.6 yrs.	Evoked trigeminal potentials were studied while eyes closed & fully relaxed. Also, physical exams with emphasis on nervous system, a clinical study of facial sensitivity, and of the reflexes depending on the trigeminal nerve were systematically performed; Normal latency and amplitude values for TSEP obtained from data from control population. Normal response characterized from 4 main peaks, alternating from negative to positive, respective latency of 12.8 ms (SD = 0.6), 19.5 ms (SD = 1.3), 27.6 ms (SD = 1.6) & 36.8 ms (SD = 2.2), mean amplitude of response is 2.5 μv (SD = 0.5 μv). Pathological responses were results 2 ½ SDs over the normal value.	Students t test & one-way ANOVA used as well as nonparametric tests Mann-Whitney U test & Kruskal-Wallis test. Also decision matrix and the analysis of the receiver operating curve to appreciate the accuracy of the TSEP method. The distribution of the different populations was compared by a chi square test.	Dizziness (71.4%), Headache (55.1%), Asthenia (46.9%), insomnia (24.4%), mood perturbation (20.4%), and sexual problems (12.2%) were found. Symptomatic patients had significantly longer exposure periods and were older than asymptomatic patients. 17.3% of patients had trigeminal nerve symptoms. Bilateral hypoesthesia with reflex alterations in 9 cases. Hypoesthesia was global and predominant in the mandibular and maxillary nerve areas. Several reflex abolitions were found without facial palsy and without convincing hypoesthesia in 9 cases. Corneal reflexes were bilaterally abolished in 5 cases as were naso-palpebral reflexes in 6 cases; length of exposure positively correlated with functional manifestations ($P < 0.01$; correlation between symptoms and exposure levels were non-significant; 40 (38.4%) subjects had pathological response to TSEP with increased latencies, amplitude or both; of these 28 had normal clinical trigeminal exam and 12 had abnormal exam; TSEP was positively correlated with length of exposure ($p < 0.01$); and with age ($p < 0.05$), but not with exposure concentration; trigeminal nerve symptoms ($n = 18$) were positively correlated with older age ($p < 0.001$).

Barret, et al., 1982	Eleven workers with chronic TCE exposure; 9 were suffering effects of solvent intoxication; 2 were work place controls. Control group was 20 unexposed subjects of all ages.	Selected following clinical evaluations of their facial sensitivity and trigeminal nerve reflexes; exposures verified by urinalysis. Presence of TCE and TCA found. (Exposure rates not reported)	Somatosensory evoked potential (SEP) following stimulation of the trigeminal nerve through the lip alternating right and left by a bipolar surface electrode utilizing voltage, usually 75 to 80 V, just below what is necessary to stimulate the orbicularis oris muscle. Duration was approx. 0.05 ms stimulated 500 times (2x/sec)	SEP recordings illustrated from trigeminal nerve graphs.	3 pathological abnormalities present in exposed (TCE intoxicated) workers: 1) in 8 workers higher voltage required to obtain normal response, 2) excessive delay in response observed twice 3) excessive graph amplitude noted in three cases. One subject exhibited all three abnormalities. Correlation was reported between clinical observation and test results. Most severe SEP alternations observed in subjects with the longest exposure to TCE (although exposure levels or exposure durations are not reported). No statistics presented.
Burg et al., 1995	From an NHIS TCE subregistry of 4,281 (4,041 living & 240 deceased) residents environmentally exposed to TCE via well water in Indiana, Illinois, & Michigan; compared to NHIS registrants	Morbidity baseline data were examined from the TCE Subregistry from the National Exposure Registry (NER) developed by the Agency for Toxic Substances Disease Registry (ATSDR); were interviewed in the National Health Interview Survey (NHIS)	Self report via face-to-face interviews - 25 questions about health conditions; were compared to data from the entire NHIS population; neurological endpoints were hearing and speech impairments	Poisson Regression analysis model used for registrants 19 and older. Maximum likelihood estimation and likelihood ratio statistics and Wald C.I.; TCE subregistry population was compared to larger NHIS registry population	Speech impairments showed statistically significant variability in age-specific risk ratios with increased reporting for children $\leq$9 yrs (RR = 2.45, 99% CI = 1.31, 4.58) and for registrants $\geq$35 yrs (data broken down by 10 yr ranges). Analyses suggest a statistically significant increase in reported hearing impairments for children $\leq$9 yrs (RR = 2.13, 99% CI = 1.12, 4.06). It was lower for children 10−17 yrs (RR = 1.12, 99% CI = 0.52, 2.44) and $\leq$0.32 for all other age groups.

Burg & Gist, 1999	4,041 living members of the National Exposure Registry's Trichloroethylene Subregistry; 97% white; mean age 34 yrs (sd = 19.9 yrs.); divided in 4 groups based on type and duration of exposure; analysis reported only for 3,915 white registrants; lowest quartile used as control group	All registrants exposed to TCE though domestic use of contaminated well water; 4 exposure Subgroups, each divided into quartiles: 1) Maximum TCE measured in well water, exposure subgroups: 2−12 ppb; 12−60 ppb; 60−800 ppb; 2) Cumulative TCE exposure subgroups: <50 ppb, 50−500 ppb, 500−5,000 ppb, >5,000 ppb; 3) Cumulative chemical exposure subgroups: include TCA, DCE, DCA, in conjunction with TCE, with the same exposure Categories as in # 2; 4) Duration of exposure subgroups: <2 yrs, 2−5 yrs, 5−10 yrs., >10 yrs.; 2,867 had TCE exposure of ≤50 ppb; 870 had TCE exposure of 51−500 ppb; 190 had TCE exposure of 501−5,000 ppb; 35 had TCE exposure >5,000 ppb	Interviews (occupational, environmental, demographic, & health information); A large number of health outcomes analyzed, including speech impairment and hearing impairment	Logistic Regression, Odds Ratios; lowest quartile used as reference population	When the registrants were grouped by duration of exposure to TCE, a statistically significant association (adjusted for age and sex) between duration of exposure and reported hearing impairment was found. The prevalence odds ratios were 2.32 (95% Cl = 1.18, 4.56) (>2 to <5 yr); 1.17 (95% Cl = 0.55, 2.49) (>5 to <10 y); and 2.46 (95% Cl := 1.30, 5.02)(>10 yr); Higher rates of speech impairment (not statistically significant) associated with maximum and cumulative TCE exposure, and duration of exposure

Buxton and Hayward, 1967	This was a case study on four workers exposed to very high concentrations of TCE, which resulted from an industrial accident. No controls were evaluated.	Case 1 was a 44 year old man exposed for 10 minutes; Case 2 was a 39 year old man exposed for 30 minutes; Case 3 was a 43 year old man exposed for 2.5 hours; Case 4 was a 39 year old man exposed for 4 hours. TCE concentrations were not reported.	Clinical evaluations were conducted by a physician when patients presented with symptoms; numbness of face, ocular pain, enlarged right blind spot, nausea, loss of taste, headache, dizziness, unsteadiness, facial diplesia, loss of gag and swallowing reflex, absence of corneal reflex, and reduction of trigeminal response.	There was no statistical assessment of results presented.	Case 1 exhibited headaches and nausea for 48 hours, but had a full recovery. Case 2 exhibited nausea and numbness of face, but had a full recovery. Case 3 was seen and treated at a hospital with numbness of face, insensitivity to pin prick over the trigeminal distribution, ocular pain, enlarged right blind spot, nausea, and loss of taste. No loss of mental faculty was observed. Case 4 was seen and treated for headache, nausea, dizziness, unsteadiness, facial diplesia, loss of gag and swallowing reflex, facial analgesia, absence of corneal reflex, and reduction of trigeminal response. The patient died and was examined postmortem. There was demyelination of the 5th cranial nerve evident.
Chalupa et al., 1960	This was a case study conducted on 22 patients with acute poisoning caused by carbon monoxide and industrial solvents. Six subjects were exposed to TCE (doses not known). Average age 38.	No exposure data were reported	Medical and psychological exams were given to all subjects. These included EEGs, measuring middle voltage theta activity of 5−6 second duration. Subjects were tested for memory disturbances.	No statistics were performed.	80% of those with pathological EEG displayed memory loss; 30% of those with normal EEGs displayed memory loss. Pathology and memory loss were most pronounced in subjects exposed to carbon monoxide.

El Ghawabi et al., 1973	30 money printing shop workers occupationally exposed to TCE; Controls: 20 age and SES matched non-exposed males and 10 control workers not exposed to TCE but exposed to inks used in printing	Air samples on 30 workers. Mean TCE air concentrations ranged from 41 ppm to 163 ppm throughout the Intalgio process Colorimetric determination of both Trichloroacetic acid and total trichloro-compounds in urine with Fujiware reaction	Inquiries about occupational, past and present medical histories, and family histories in addition to age and smoking habits. EKGs were performed on 25 of the workers. Lab investigations included complete blood and urine analysis, and routine liver function tests.	Descriptive statistics and central tendency evaluation for metabolites; no stats reported for neurological symptoms	Most frequent symptoms: prenarcotic headache (86% vs 30% for controls), dizziness (67 % vs 6.7% for controls), and sleepiness (53% vs 6% for controls) main presenting symptoms in addition to suppression of libido. Trigeminal nerve involvement was not detected. The concentration of total trichloro-compounds increased toward mid-week & was stationary during the last 2 working days. Metabolites of total trichloroacetic acid and trichloroethanol are only proportional to TCE concentrations up to 100 ppm.
Feldman et al., 1988	21 Massachusetts residents with alleged chronic exposure to TCE in drinking water; 27 laboratory controls	TCE in residential well water was 30−80 times greater than EPA MCL; maximum reported concentration was 267 ppb; other solvents also present	Blink reflex (BR) used as an objective indicator of neurotoxic effects of TCE; clinical neurological exam, EMGs to evaluate blink reflex, nerve conduction studies, and extensive neuropsychological testing.	Students t test used for testing the difference between the group means for the Blink reflect component latencies	Highly significant differences in the conduction latency means of the BR components for the TCE exposed population vs control population, when comparing means for the right and left side R1 to the controls ($p < 0.001$). The mean R1 BR component latency for the exposed group was 11.35 ms, SD = 0.74 ms, 95% CI = 11.03−11.66. The mean for the controls was 10.21 ms, SD = 0.78 ms, 95% CI = 9.92−10.51; $p < 0.001$. Suggests a subclinical alteration of the trigeminal nerve function (V) due to chronic, environmental exposure to TCE.

Feldman et al., 1992	18 workers occupationally exposed to TCE; 30 laboratory controls	Reviewed exposure histories of each worker (job type, length of work) and audited medical records to categorize into three exposure categories: "extensive", "occasional", and "chemical other than TCE"	Blink Reflexes using TECA 4 EMG.	Non-Gaussian distribution and high coefficient of variance data were log-transformed and then compared to the log-transformed control mean values. MRV was calculated by subtracting the subjects value (x) from the control group mean (M), and the difference is divided by the control group standard deviation.	The "extensive" group revealed latencies greater than 3 SD above the non-exposed group mean on R1 component of blink reflex; none of the "occasional" group exhibited such latencies, however two of them demonstrated evidence of demyelinating neuropathy on conduction velocity studies; the sensitivity, or the ability of a positive blink reflex test to correctly identify those who had TCE exposure, was 50%. However, the specificity was 90%, which means that of those workers with no exposure to TCE, 90% demonstrated a normal K1 latency. Subclinical alteration of the Vth cranial nerve due to chronic occupational exposure to TCE is suggested.
Gash et al., 2007	30 Parkinson's Disease patients and 27 non-Parkinson coworkers exposed to TCE; No unexposed controls	Mapping of work areas	General physical exam, neurological exam and Unified Parkinson's Disease Rating Scale (UPDRS), timed motor tests, and occupational history survey; mitochondrial neurotoxicity; Questionnaire mailed to 134 former non-Parkinson's workers, (14 symptomatic of parkinsonism: age range = 31−66, duration of employment range: 11−35 yrs) (13 asymptomatic: age range = 46−63,	Workers' raw scores given; ANOVA comparing symptomatic versus non-symptomatic workers	Symptomatic non-Parkinson's group was significantly slower in fine motor hand movements than age-matched non-symptomatic group ($p < 0.001$); All symptomatic workers had positive responses to 1 or more questions on UPDRS Part I and Part II, and/or had signs of parkinsonism on Part III; One symptomatic worker had been tested 1 yr. prior & his UPDRS score had progressed from 9 to 23.

			duration of employment range: 8−33 yrs);		

Grandjean et al., 1955	80 workers employed in 10 different factories of the Swiss mechanical engineering industry exposed to TCE, seven of whom stopped working with TCE from 3 wks to 6 yrs prior; no unexposed control group	Vapors were collected in ethylic alcohol 95%. Volume of air was checked using a flowmeter, and quantitatively measured according to the method of Truhaut (1951), which is based on a colored reaction between TCE and the pyridine in an alkaline medium (with modifications). Urine analysis of TCA levels; TCE air concentrations varied from 6 ppm−1,120 ppm depending on time of day and proximity to tanks, but mainly averaged between 20−40 ppm. Urinalysis varied from 30 mg/L to 300 mg/L; Could not establish a relationship between TCE eliminated through urine and TCE air levels. Four exposure groups estimated based on air sampling data	Medical exam, including histories; Blood and biochem. tests, & psychiatric exam. Psychological exam; Meggendorf, Bourdon, Rorschach, Jung, Knoepfel's "thirteen mistakes" test, and Bleuler's test	Coefficient of determination, Regression coefficient;	Men working all day with TCE showed on average larger amounts of TCA than those who worked part time with TCE. Relatively high frequency of subjective complaints, of alterations of the vegetative nervous system, and of neurological and psychiatric symptoms. 34% had slight or moderate psycho-organic syndrome; 28% had neurological changes; There is a relationship between the frequency of those alterations and the degree of exposure to TCE. There were significant differences ($p = 0.05$) in the incidence of neurological disorder between Groups I and III, while between Groups II and III there were significant differences ($p = 0.05$) in vegetative and neurological disorders. Based on TCA eliminated in the urine, results show that subjective, vegetative, and neurological disorders were more frequent in Groups II and III than in Group I. Statistical analysis revealed the following significant differences ($p < 0.01$) : subjective disorders between I and II ; vegetative disorders between I and II and between I and III ; neurological disorders between I and (II & III). Vegetative, neurological, and psychological symptoms increased with the length of exposure to TCE. The following definite differences were shown by statistical analysis ($p < 0.03$) : vegetative disorders between I and IV ; neurological disorders between I and II and between I and IV; psychological disorders between I and III and between I and IV.

Gun, el al., 1978	8 exposed: 4 female workers from one plant exposed to TCE and 4 female workers from another plant exposed to TCE + nonhalogenated hydrocarbon solvent used in degreasing; control group (n = 8) consisted of 4 female workers from each plant who did not work near TCE.	Air sampled continuously over separate 10 min. durations drawn into a Davis Halide Meter. Readings taken every 30 sec.; ranged from 3 ppm−419 ppm	Eight-Choice reaction times carried out in four sessions-40 reaction time trials completed.	Variations in RT by level of exposure; ambient air exposure TCE concentrations & mean air TCE values;	TCE only group had consistently high mean ambient air TCE levels (which exceeded the 1978 TLV of 100 ppm) and showed a mean increase in reaction time, with a probable cumulative effect. In TCE + solvent group, ambient TCE was lower (did not exceed 100 ppm) and mean reaction time shortened in Session 2, then rose subsequently to be greater than at the start. Both control groups showed a shortening in mean choice reaction time in Session 2 which was sustained in Session 3 & 4 consistent with a practice effect; No stats provided

Hirsch et al., 1996	106 residents of Roscoe, a community in Illinois on the Rock River, in direct proximity to an industrial plant that released an unknown amount of TCE into the River. All involved in litigation. Case series report; No unexposed controls	Random testing of the wells between 1983−84 revealed groundwater in wells to have levels of TCE between 0 to 2,441 ppb; distance of residence from well used to estimate exposure level	Medical, neurologic, and psychiatric exams and histories. For those who complained of headaches, a detailed headache history was taken, and an extensive exam of nerve-threshold measurements of toes, fingers, face, olfactory threshold tests for phenylethyl methylethyl carbinol, brain map, Fast Fourier Transform (FFT), P300 Cognitive auditory evoked response, EEG, Visual Evoked Response (VER), Somato sensory Evoked Potential (SSER), Brainstem Auditory Evoked Response (BAER), MMPI-II, MCMI-II, and Beck Depression Inventory were also given.	Student t-test, Chi square analysis, nonparametric t-test & ANOVA, correlating all history, physical exam findings, test data, TCE levels in wells, and distance from plant.	66 subjects (62%) complained of headaches, Diagnosis of TCE-induced cephalagia was considered credible for 57 patients (54%). Retrospective TCE level of well water or well's distance from the industrial site analysis did not correlate with the occurrence of possibly-TCE induced headaches. Studies that were not statistically significant with regard to possible TCE-cephalalgia included P300, FFT, VER, BAER, MMPI, MCMI, Beck Depression Inventory, SSER and nerve threshold measurements. Headache might be associated with exposure to TCE at lower levels than previously reported. Headaches mainly occurred without sex predominance, gradual onset, bifrontal, throbbing, without associated features; No quantitative data presented to support statement of headache in relation to TCE exposure levels, except for incidences of headache reporting and measured TCE levels in wells.

Kilburn & Thornton, 1996	Group A: Randomly selected registered voters from Arizona and Louisiana with no exposure to TCE : *n* = 264 unexposed volunteers aged 18−83 : Group B volunteers from California *n* = 29 17 males & 12 females to validate the equations; Group C exposed to TCE & other chemicals residentially for 5 years or more *n* = 237	No exposure or groundwater analyses reported	Reaction speed using a timed computer visual-stimulus generator; Compared groups to plotted measured SRT & CRT Questionnaire to eliminate those exposed to possibly confounding chemicals	Box-Cox transformation for DV & IV . Evaluated graphical methods to study residual plots. Cooks distance statistic measured influence of outliers examined. Lack- of-fit test performed on Final model & F statistic to compare estimated error to lack-of-fit component of the model's residual sum of squared error. final models were validated using group B data and paired t test to compare observed values for SRT & CRT. F statistic to test hypothesis that parameter estimates obtained with group b were equal to those of the model.	Group A: SRT = 282ms CRT = 532ms Group B: SRT = 269ms CRT = 531ms Group C: SRT = 334 CRT = 619 Lg(SRT) = 5.620, SD = 0.198 Regression equation for Lg(CRT) = 6.094389 + 0.0037964 × age. TCE exposure produced a step increase in SRT and CRT, but no divergent lines. Coefficients from Group A were valid for group B. Predicted value for SRT and for CRT, plus 1.5 SDs. selected 8% of the model group as abnormal.

Kilburn & Warshaw, 1993	Well-water exposed subjects to 6 to 500 ppb of TCE for 1 to 25 years; 544 recruited test subjects; Group 1 = 196 exposed family members of subjects with cancer or birth defects; Group 2 = 178 from exposed families without cancer or birth defects; Group 3 = 170 exposed parents whose children had birth defects and rheumatic disorders; Controls: 68 referents and 113 histology technicians (HTs) without environmental exposure to TCE	Well-water was measured from 1957 to 1981 by several governmental agencies, and average annual TCE exposures were calculated and then multiplied by each individual's years of residence for 170 subjects.	Neurobehavioral testing- augmented NBT:Eye Closure and Blink using EMG Neuropsychological (NPS) test- Portions of Wechsler's Memory Scale, and WAIS & embedded figures test, grooved pegboard, Trail Making A and B, POMS, and Culture Fair Test Neurophysiological (NPH) testing- Simple visual reaction time, body balance apparatus, cerebellar function, proprioception, visual, associative links and motor effector function	Two sided student "t" test with a $p < 0.05$. Linear regression coefficients to test how demographic variables or other factors may contribute.	Exposed subjects had lower intelligence scores and more mood disorders NPH: Significant impairments in sway speed with eyes open and closed, blink reflex latency (R-1), eye Closure speed, and two choice visual reaction time. NPS: Significant impairments in Culture Fair (intelligence) scores, recall of stories, visual recall, digit span, block design, recognition of fingertip numbers, grooved pegboard, and Trail making A and B. POMS: all subtests, but the fatigue, were elevated Mean speeds of sway were greater with eyes open at <0.0001) and with eyes closed $p < 0.05$) in the exposed group compared to the combined referents. The exposed group mean simple reaction time was 67 milliseconds (msec) longer than the referent group $p < 0.0001$). Choice reaction time (CRT) of the exposed subjects was 93 msec longer in the third trial ($p < 0.0001$) than referents. It was also longer in all trials, and remained significantly different after age adjustment. Eye closure latency was slower for both eyes in the exposed and significantly different ($p < 0.0014$) on the right compared to the HT referent group.

Kilburn, 2002b	236 residents chronically exposed to TCE and associated solvents, including DCE, PCE, and vinyl chloride, in the environment from a nearby microchip plant, some involved in litigation, prior to 1983 and those who lived in the area between 1983 and 1993 during which time dumping of chlorinated solvents had supposedly ceased and clean-up activities had been enacted; Controls: 67 referents from northeast Phoenix, who had never resided near the 2 plants (mean distance = 2,000 m, range = 1,400−3,600 m from plants) and 161 regional referents from Wickenburg, AZ up-wind of Phoenix, recruited via random calls made to numbers	Exposure estimate based on groundwater plume based on contour mapping; concentrations between 0.2−10,000 ppb of TCE over a 64 km^2 area; additional associated solvents, including DCE, PCE, and vinyl chloride, No air sampling;	Simple reaction time, choice reaction time, Balance sway speed (with eyes open & eyes closed), color errors, blink reflex latency, Supra orbital tap (left & right), Culture Fair A, Vocabulary, Pegboard, Trail Making A & B, Immediate verbal recall, POMS; Pulmonary Function; The same examiners who were blinded to the subjects' exposure status examined the Phoenix group, but the Wickenburg referents' status was known to the examiners. Exact order or timing of testing not stated.	Descriptive statistics; ANCOVA; step-wise adjustment of demographics;	The principal comparison, that was between the 236 exposed persons and the 161 unexposed regional controls, revealed 13 significant differences ($p < .05$). SRTs and CRTs were delayed. Balance was abnormal with excessive sway speed (eyes closed), but this was not true when both eyes were open. Color discrimination errors were increased. Both right and left blink reflex latencies (R-1) were prolonged. Scores on Culture Fair 2A, vocabulary, grooved pegboard (dominant hand), trail making A and B, and verbal recall (i.e., memory) were decreased in the exposed subjects. Litigation is suggested but not stated & study paid by lawyers. Litigation status may introduce a bias, particularly if no validity tests were used.

	on voter registration rolls, matched to exposed subjects by age and years of education, records showed no current or past water contamination in the areas.				

Kilburn, 2002b	236 residents exposed environmentally from a nearby microchip plant (exact number of litigants not stated); 156 individuals exposed for >10 yrs. compared to 80 individuals <10 yrs of exposure; Controls: 58 non-claimants in 3 areas within exposure zone (Zones A, B, and C)	No discussion of exposure assessment methods and results. Solvents included TCE, DCE, PCE, and vinyl chloride; concluded exposure is primarily due to groundwater plume rather than air releases	Simple reaction time, choice reaction time, Balance sway speed (with eyes open & eyes closed), color errors, blink reflex latency, Supra orbital tap (left & right), Culture Fair A, Vocabulary, Pegboard, Trail Making A & B, Immediate verbal recall, POMS;	Descriptive statistics, Regression analysis; Similar study to the one reported above with the exception of looking at the effects of duration of residence, proximity to the microchip plant, and being involved in litigation	Insignificant effects of longer duration of residence. No effect of proximity and litigation. Effects of longer duration of residence modest and insignificant. No effect of proximity. No litigation effect. Zone A- 100 clients were not different from the 9 non-clients Zone B, non-clients were more abnormal in color different than clients and right-sided blink was less abnormal in non-clients. Zone C, 9 of the 13 measurements were not significantly different. 26 of the original 236 subjects re-tested in 1999: maintained impaired levels of functioning and mood; No tests of effort and malingering used, limiting interpretations Again, no tests of effort and malingering were used, thus limiting interpretation. Litigation is suggested but not stated & study paid by lawyers; Litigation status may introduce a bias, particularly if no validity tests were used.

Landrigan et al., 1987	13 Pennsylvania residents exposed through drinking & bathing water contaminated by approximately 1,900 gallon TCE spill; Feb 1980: 9 workers exposed to TCE while degreasing metal in pipe manufacturing plant and 9 unexposed controls (mean ages were 42.7 exposed and 46.4 yr. old unexposed; mean durations of employment = 4.4, exposed, and 9.4 yrs, unexposed.; May 1980: 10 exposed workers & same 9 unexposed worker controls from Feb monitoring.	Community Evaluation: Nov 1979- Questionnaires on TCE & other chemical exposures, & occurrence of signs and symptoms of exposure to TCE, morning urine samples, urine samples analyzed coloreimetrically for total trichloro-compounds Occupational Evaluations (In workers): breathing-zone air samples(mean 205 mg/m3; 37 ppm); medical evaluations, pre and post shift spot urine samples in Feb and again in May, mid and post shift venous blood samples during the May survey	Community evaluation, occupational evaluations; urine evaluations for TCE metabolites; Questionnaires to evaluate neurologic effects & symptoms; ISO concentrations, Map of TCE in groundwater	Descriptive statistics	Community Evaluation: No urinary TCA detected in community population except for 1 resident also working at plant and 1 resident with no exposure; Occupational Evaluation: Range 117−357 mg/m^3 – (21−64 ppm) Feb: airborne exposures exceeded NIOSH limit by up to 222 mg/m^3 (40 ppm)(NIOSH TWA <135 $mg/m^{3)}$ (24 ppm). Short term exposure exceeded NIOSH values of 535 mg/m^3 (96 ppm) by up to 1,465 mg/m3 (264 ppm) Personal breathing zone of other workers within recommended limits (0.5−125 mg/m^3) (0.1−23 ppm). 7 exposed workers reported acute symptoms, including fatigue, light-headedness, sleepiness, nausea, headache, consistent with TCE exposure; No control workers reported such symptoms; Prevalence of 1 or more symptoms 78% in exposed worker group, 0% in control worker group; Symptoms decreased after recommendations were in place for 3 months (may testing) for reduced exposures.

Liu et al., 1988	103 workers from factories in Northern China, exposed to TCE (79 men, 24 women), during vapor degreasing production or operation- The unexposed control group included 85 men and 26 women	Exposed to TCE, mostly at less than 50 ppm; concentration of breathing zone air during entire shift measured by diffusive samplers placed on the chest of each worker; divided into three exposure groups; 1 ppm−10 ppm, 11 ppm−50 ppm & 51 ppm−100ppm; Also, hematology, serum biochemistry, sugar, protein and occult blood in urine were collected.	Self-reported subjective symptom questionnaire	Prevalence of affirmative answers = total number of affirmative answers divided by (number of respondents x number of questions); X^2	Dose response relationship established in symptoms such as nausea, drunken feeling, light-headedness, floating sensation, heavy feeling of the head, forgetfulness, tremors &/or cramps in extremities, body weight loss, changes in perspiration pattern, joint pain, & dry mouth (all $\geq$3 times more common in exposed workers); *"bloody strawberry jam-like feces"* was borderline significant in the exposed group and *"frequent flatus"* was statistically significant. Exposure ranged up to 100 ppm, however most workers were exposed below 10 ppm, and some at 11 ppm−50ppm. Contrary to expectations, production plant men had significantly higher levels of exposure (24 had levels of 1 ppm−10 ppm, 15 had levels of 11 ppm−50 ppm, 4 had levels of 51 ppm−100 ppm) than degreasing plant men (31 had levels of 1 ppm−10 ppm, 2 had levels of 11 ppm−50 ppm, 0 had levels of 51 ppm−100 ppm); $p < 0.05$ by chi-square test. No significant difference ($p > 0.10$) was found in women workers. The differences in exposure intensity between men and women was of borderline significance ($0.05 < p < 0.10$). .

McCunney, 1988	This is a case study conducted on three young white male workers exposed to TCE in degreasing operations. There were no controls included. Case 1 was a 25 year old male, Case 2 was a 28 year old white male, Case 3 was a 45 year old white male	Case 1: TCE in air at the work place was measured at 25 ppm, but his TCA in urine was measured at 210 mg/L. This is likely due to dermal exposure while cleaning metal rods in TCE. Case 2: no TCE exposure data presented, TCA at 9 mg/L after 6 months; Case 3: no TCE exposure data presented.	Clinical evaluation of loss of balance, light headedness, resting tremor, blurred vision, and dysdiadochokinesia, change in demeanor and loss of coordination, cognitive changes were noted, as well as depression; CT scan, EEG, nerve conductivity, and visual and somatosensory evoked response. Neurological exams included sensitivity to pinprick over the face; Ophthalmic evaluation.	There were no statistical analyses of results presented.	Case 1 was a 25 year old male, who presented with a loss of balance, light headedness, resting tremor, blurred vision, and dysdiadochokinesia. The subject had been in a car accident and suffered head injuries. He later returned with a change in demeanor and loss of coordination. He showed a normal CT scan, EEG, nerve conductivity, and visual and somatosensory evoked response. Neurological exams revealed reduced sensitivity to pinprick over the face, deep tendon reflexes were reduced, mild to moderate cognitive changes were noted, as well as depression. Ophthalmic evaluation was normal. He was removed form the TCE exposure and appeared to recover. Case 2 was a 28 year old white male who presented with numbness and shooting pains in fingers. He exhibited anorexia, tiredness. He worked in a degreasing operation for a jeweler using open containers filled with TCE in a small, unventilated room. There were no exposure data provided, but his TCA was 9 mg/L at six months after exposure. He had been hospitalized with hepatitis previously. No neurological tests were administered. Case 3 was a 45 year old white male who presented with numbness in hands and an inability to sleep. He exhibited slurred speech. He was positive for blood in stool, but had a history of duodenal ulcers.

Mhiri et al., 2004	23 phosphate industry workers exposed to TCE for 6 hours/day for at least two years while cleaning walls to be painted; Controls: 23 unexposed workers from the department of neurology	Measurement of urinary metabolites of TCE were performed 3 times/worker. Blood tests and hepatic enzymes were also collected.	Trigeminal somatosensory evoked potentials recorded using Nihon-Kohden EMG- evoked potential system; baseline clinical evaluations regarding facial burn or numbness, visual disturbances, restlessness, concentration difficulty, fatigue, mood changes, assessment of cranial nerves, quality of life; biological tests described under biomarkers	Paired or unpaired Student's t-test as appropriate. P value set at <0.05. Spearman rank-correlation procedure was used for correlation analysis.	Abnormal TSEP were observed in 6 workers with clinical evidence of Trigeminal involvement and in 9 asymptomatic workers. A significant positive correlation between duration of exposure and the N2 latency ($p < 0.01$) and P2 latency <0.02) was observed. Only one subject had urinary TCE metabolite levels over tolerated limits. TCE air contents were over tolerated levels, ranging from 50−150 ppm.
Mitchell and Parsons-Smith, 1969	This was a case study of one male patient, age 33, occupational exposed to TCE during degreasing. There were no controls.	No exposure data are presented.	Trigeminal nerve, loss of taste, X-rays of the skull, EEG, hemoglobin, and Wassermann reaction	No statistics provided.	The patient had complete analgesia in the right trigeminal nerve and complete loss of taste, patient complained of loss of sensation on right side of face, and uncomfortable right eye, as well as vertigo and depression. X-rays of the skull, EEG, hemoglobin, and Wassermann reaction were all normal.

Nagaya et al., 1990	84 male workers ages 18−61 (mean 36.2) constantly using TCE in their jobs. Duration of employment (i.e. exposure) 0.1−34.0 years, (mean 6.1 yrs; SD = 5.9). Controls: 83 age-matched office workers and students with no exposure	Workers exposed to about 22 ppm TCE in air. Serum dopamine-β-hydroxylase (DBH) activity levels measured from blood. Urinary total trichloro-compounds (U-TTC) also measured.	Blood drawn during working time and DBH activities were analyzed; Spot urine collected at time of blood sampling and urinary total trichloro-compounds (U-TTC) determined by alkaline-pyridine method.	Student's t-test and linear correlation coefficient. Results of U-TTC presented by age groups: ≤25; 26−40; ≥41	A slight decrease in serum DBH activity with age was noted in both groups. Significant inverse correlation of DBH activity and age was found in workers ($r = -0.278$, $0.01 < P < 0.02$), but not in controls ($r = -0.182$, $0.05 < P < 0.1$). No significant differences between mean serum DBH activity levels by age groups for workers and corresponding controls in any age group. Workers' U-TTC levels: 3.8 to 1,066.4 mg/L (M = 133.6 mg/L); U-TTC not detected in controls. Serum DBH activity levels in workers independent of U-TTC levels and duration of employment. Results suggest that chronic occupational exposure to TCE did not influence sympathetic nerve activity.
Reif et al., 2003	143 residents of the Rocky Mountain Arsenal community of Denver whose water was contaminated with TCE and related chemicals from nearby hazardous waste sites between 1981 & 1986; Referent group at lowest concentration (<5 ppb)	Hydraulic simulation model used in conjunction with a geographic information system (GIS) estimated residential exposures to TCE; Approximately 80% of the sample exposed to TCE exceeding MCL of 5 ppb & approximately 14% exceeded 15 ppb. High exposure group >15 ppb, low exposure referent group <5 ppb, medium exposure group $5 < x < 15$ ppb	Neurobehavioral Core Test Battery (NCTB), tests of visual contrast sensitivity, POMS	Multivariate Model	Statistical significance was approached as a result of high TCE exposure vs referent group; poorer performance on the digit symbol ($p = 0.07$), contrast sensitivity C test ($p = 0.06$), and contrast sensitivity D test ($p = 0.07$), and higher mean scores for depression ($p = 0.08$). Alcohol was an effect modifier in high-exposed individuals- statistically significant on the Benton, digit symbol, digit span, and simple reaction time tests, as well as for confusion, depression, and tension.

Rasmussen & Sabroe, 1986	368 metal workers working in degreasing at various factories in Denmark (industries not specified) with chlorinated solvents; 94 controls randomly selected semi-skilled metal workers from same area; mean age: 37.7 (range: 17−65+). Total 443 men; 19 women.	Questionnaire; categorized in 4 groups; three exposure groups plus control:1)currently working with chlorinated solvents (n = 171; average. duration: 7.3 yrs, 16.5 hrs./wk; 57 % TCE & 37% 1,1,1-trichloroethane), 2) currently working with other solvents (n = 131; petroleum, gasoline, toluene, xylene), 3) previously (1−5 yrs.) worked with chlorinated or other solvents (n = 66) 4) never worked with organic solvents (n = 94)	Questionnaire: 74 items about neuropsychological symptoms (memory, concentration, irritability, alcohol intolerance, sleep disturbance, fatigue)	Chi-square; Odds ratios; t test; logistic regression	Neuropsychological symptoms significantly more prevalent in the chlorinated solvents-exposed group; TCE caused the most "inconveniences and symptoms"; dose-response between exposure to chlorinated solvents and chronic neuropsychological symptoms (memory ($p < 0.001$), concentration ($p < 0.02$), irritability ($p < 0.004$), alcohol intolerance ($p < 0.004$), forgetfulness ($p < 0.001$), dizziness ($p < 0.005$), and headache ($p < 0.01$); Significant associations between previous exposure & consumption of alcohol with chronic neuropsychological symptoms

Rasmussen et al., 1993a	96 Danish workers involved in metal degreasing with chlorinated solvents, mostly TCE (*n* = 70); (industries not specified), age range: 19−68; no external controls	Chronic exposure to TCE (*n* = 70); CFC (*n* = 25); HC (*n* = 1); average duration: 7.1 yrs.); range of full-time degreasing: 1 month to 36 yrs.; occupational history, blood and urinary metabolites (TCA); biological monitoring for TCE and TCE metabolites; CEI calculated based on number of hrs/week worked with solvents x yrs. of exposure x 45 weeks per yr.; 3 groups: 1) low exposure: *n* = 19, average full-time expo 0.5 yrs; 2) medium exposure: *n* = 36, average full-time exposure 2.1 yrs.; 3) high exposure: *n* = 41, average full-time exposure 11 yrs.; Mean trichloroacetic acid (TCA) in high exposure group = 7.7 mg/L (max = 26.1 mg/L); TWA measurements of CFC 113 levels: 260−420 ppm (US & Danish TLV is 500 ppm)	Medical interview, neurological exam, neuropsychological exam; **Tests:** WAIS: Vocabulary, Digit Symbol; Simple Reaction Time, acoustic-motor function, discriminatory attention, Sentence Repetition, Paced Auditory Serial Addition Test , Text Repetition, Rey's Auditory Verbal Learning, visual gestalt, Stone Pictures (developed for this study, non-validated), revised Santa Ana, Luria motor function, Mira; Blind study	Fisher's exact test, Chi-square trend test, t test, ANOVA, logistic regression, odds ratios, Chi-square goodness-of-fit test; Confounders examined: age, primary intellectual level, arteriosclerosis, neurological/psychiatric disease, alcohol abuse, & present solvent exposure	After adjusting for confounders, the high exposure group has significantly increased risk for psychoorganic syndrome following exposure (OR = 11.2); OR for medium exposed group = 5.6; Significant increase in risk with age and with decrease in WAIS Vocabulary scores; Prevalence of psychoorganic syndrome: 10.5% in low exposure group, 38.9 in medium exposure group, 63.4% in high exposure group; no significant interaction between age & solvent exposure

Rasmussen et al., 1993b	96 Danish workers involved in metal degreasing with chlorinated solvents (industries not specified), age range: 19−68; No external controls	Chronic exposure to TCE (*n* = 70); CFC (*n* = 25); HC (*n* = 1); average duration: 7.1 yrs.); range of full-time degreasing: 1 month to 36 yrs.; occupational history, blood and urinary metabolites (TCA); biological monitoring for TCE and TCE metabolites; CEI calculated based on number of hrs/week worked with solvents x yrs. of exposure x 45 weeks per yr.; 3 groups: 1) low exposure: *n* = 19, average full-time expo 0.5 yrs; 2) medium exposure: *n* = 36, average full-time exposure 2.1 yrs.; 3) high exposure: *n* = 41, average full-time exposure 11 yrs.; Mean trichloroacetic acid (TCA) in high exposure group = 7.7 mg/L (max = 26.1 mg/L); TWA measurements of CFC 113 levels: 260−420 ppm (US & Danish TLV is 500 ppm)	WAIS (original version): Vocabulary, Digit Symbol, Digit Span; Simple Reaction Time, Acoustic-motor function (Luria), Discriminatory attention (Luria), Sentence Repetition, Paced Auditory Serial Addition Test (PASAT) , Text Repetition, Rey's Auditory Verbal Learning, Visual Gestalts, Stone Pictures (developed for this study, non-validated), revised Santa Ana, Luria motor function, Mira; Blind study	Linear regression analysis; Confounding variables analyzed: age, primary intellectual function, word blindness, education, arteriosclerosis, neurological/psychiatric disease, alcohol use, present solvent exposure	Dose-response with 9 of 15 tests; Controlling for confounds, significant relationship of exposure was found with Acoustic-motor function ($p < 0.001$), PASAT ($p < 0.001$), Rey AVLT ($p < 0.001$), vocabulary ($p < 0.001$) and visual gestalts ($p < 0.001$); significant age effects

Rasmussen et al., 1993c	96 Danish workers involved in metal degreasing with chlorinated solvents (industries not specified), age range: 19−68; No external controls	Chronic exposure to TCE (*n* = 70); CFC (*n* = 25); HC (*n* = 1); average duration: 7.1 yrs.); range of full-time degreasing: 1 month to 36 yrs.; occupational history, blood and urinary metabolites; biological monitoring for TCE and TCE metabolites; CEI calculated based on number of hrs/week worked with solvents x yrs. of exposure x 45 weeks per yr.; 3 groups: 1) low exposure: *n* = 19, average full-time expo 0.5 yrs; 2) medium exposure: *n* = 36, average full-time exposure 2.1 yrs.; 3) high exposure: *n* = 41, average full-time exposure 11 yrs.; Mean trichloroacetic acid (TCA) in high exposure group = 7.7 mg/L (max = 26.1 mg/L); TWA measurements of CFC 113 levels: 260−420 ppm (US & Danish TLV is 500 ppm)	Medical interview, clinical neurological exam, neuropsychological exam	Multiple regression; Fisher's exact test; Mantel-Haenzel test for linear association	Significant dose-response between exposure and motor dyscoordination remained after controlling for confounders; Bivariate analysis showed increased vibration threshold with increased exposure, but with multivariate analysis, age was a significant factor for the increase

Ruijten, et al., 1991	31 male printing workers exposed to TCE. Mean age 44; Mean duration 16 years; Controls: 28; mean age 45 yrs.	Relied on exposure data from past monitoring activities conducted by plant personnel using gas detection tubes. Estimated 17ppm for past 3 years, 35ppm for preceding 8 years and 70 ppm before that. Individual cumulative exposure was calculated as time spent in different exposure periods & the estimated exposure in those periods. Mean cumulative exposure = 704 ppm x years (SD 583, range: 160−2,150 ppm x years	General questionnaire, cardiotachogram recorded on ink writer to measure Autonomic nerve function, including forced respiratory sinus arrhythmia (FRSA), Muscle heart reflex (MHR), resting arrhythmia; Trigeminal nerve function measured using masseter reflex and blink reflex; electrophysiological testing of peripheral nerve functioning using motor nerve conduction velocity of the peroneal nerve.	Combined Z score = individual Z scores of the FRSA and MHR; ANCOVA to calculate difference between exposed/non-exposed workers; Cumulative exposure effect calculated by multiple linear regression analysis. Controlled for age, alcohol consumption, and nationality by including them as covariables. Quetelet-index included for AN parameters; Body length & skin temperature used for all peripheral nerve functions; one-sided significance level of 5% used. Non-normal distributions were log or square root transformed.	Slight reduction in Sural nerve conduction velocity was found and a prolongation of the Sural refractory period (SRP). Latency of the masseter reflex had increased. No prolongation of the blink reflex was found; no impairment of autonomic or motor nerve function were found. Long term exposure to TCE at threshold limit values (approximately 35 ppm) may slightly affect the trigeminal and sural nerves.

Smith, 1970	130 (108 males, 22 females); Controls: 63 unexposed men working at the same factory matched by age, marital status	Trichloroacetic acid (TCA) metabolite levels in urine were measured: 60.8% had levels up to 20mg/L, and 82.1% had levels up to 60 mg/L.	Cornell Medical Index Questionnaire (Psychiatric section), Heron's Personality Questionnaire, Fluency Test, 13-Mistake Test, Serial Sevens, Digit Span, General Knowledge Test, tests of memory;	Descriptive Statistics;	Of the 130 subjects exposed 27% had no complaints of symptoms, 74.5% experienced fatigue, 56.2% Dizziness, 17.7% Headache, 25.4% Gastro-intestinal problems, 7.7% autonomic effects, and 24.9% had other symptoms. The number of complaints reported by subjects were statistically significant between those with 20mg/L or less TCA (M = 1.8 complaints) and those 60mg/L or more (M = 2.7). Each group, however, had a similar proportion of subjects who reported having only 'slight' symptoms. The total time of continuous exposure to TCE (ranging from less than 1 year to more than 10 years) appeared to have little influence on frequency of symptoms. No results of the tests are reported; Author postulates that symptom assessment raises the possibility of "errors of subjective judgment"
Triebig, 1977 Int Arch Occup Environ Health 38(3):149−162	This study was conducted on 8 subjects occupationally exposed to TCE. Subjects were 7 men and 1 woman with an age range from 23−38 years. There was no control group.	Measured TCE in air averaged 50 ppm (260 mg/m^3). Length of occupational exposure was not reported.	Results were compared after exposure periods, and compared to results obtained after periods removed from exposure. TCA and TCE metabolites in urine and blood were measured. Psychological tests included d2, MWT-A, and short test.	Wilcoxon and Willcox nonparametric tests. Due to the small sample size a significance level of 1% was used.	Mean values observed were 330 mg trichloroethanol and 319 mg TCA /g creatinine, respectively, at the end of a work shift. The psychological tests showed no statistically significant difference in the results before or after the exposure-free time period.

Triebig, 1982	This study was conducted on 24 healthy workers (20 males, 4 females) exposed to TCE occupationally at three different plants. The ages 17−56; length of exposure ranged from 1 month to 258 months (mean 83 months). A control group of 144 controls used to establish 'normal' responses on the nerve conduction studies. The matched control group consisted of twenty-four healthy nonexposed individuals (20 males, 4 females), chosen to match the subjects for age and sex.	length of exposure ranged from 1 month to 258 months (mean 83 months). TCE concentrations measured in air at work places ranged from 5−70 ppm. TCA, TCE, and trichloroethanol were measured in blood, and TCE and TCA were measured in urine.	Nerve conduction velocities were measured for sensory and motor nerve fibers using the following tests: MCV_{max}(U):Maximum NLG of the motor fibers of the N. ulnaris between the wrist joint and the elbow; dSCV (U):Distal NLG of mixed fibers of the N. ulnaris between finger V and the wrist joint; pSCV (U): Proximal NLG of sensory fibers of the N. medianus between finger V and Sulcus ulnaris; and dSCV (M): Distal NLG of sensory fibers of the N. medianus between finger III and the wrist joint.	Data were analyzed using parametric and nonparametric tests, rank correlation, linear regression, with 5% error probability.	Results show no statistically significant difference in nerve conduction velocities between the exposed and unexposed groups. This study has measured exposure data, but exposures/responses are not reported by dose levels.

Triebig, 1983	The exposed group consists of 66 healthy workers selected from a population of 112 workers. Workers were excluded based on polyneuropathy (*n* = 46) and alcohol consumption (*n* = 28). The control group consisted of 66 healthy workers with no exposures to solvents.	subjects were exposed to a mixture of solvents, including TCE, specifically "ethanol, ethyl acetate, aliphatic hydrocarbons (gasoline), methyl ethyl ketone (MEK), toluene, and trichloroethene." Subjects were divided into three exposure groups based on length of exposure, as follows: 20 employees with "short-term exposure" (7−24 months); 24 employees with "medium-term exposure" (25−60 months); 22 employees with "long-term exposure" (over 60 months). TCA, TCE, and trichloroethanol were measured in blood, and TCE and TCA were measured in urine.	Nerve conduction velocities were measured for sensory and motor nerve fibers using the following tests: MCV_{max}(U):Maximum NLG of the motor fibers of the N. ulnaris between the wrist joint and the elbow; dSCV (U):Distal NLG of mixed fibers of the N. ulnaris between finger V and the wrist joint; pSCV (U): Proximal NLG of sensory fibers of the N. medianus between finger V and Sulcus ulnaris; and dSCV (M): Distal NLG of sensory fibers of the N. medianus between finger III and the wrist joint.	Data were analyzed using parametric and nonparametric tests, rank correlation, linear regression, with 5% error probability.	there was a dose response relationship observed between length of exposure to mixed solvents and statistically significant reduction in nerve conduction velocities observed for the medium and long-term exposure groups for the NCV (ulnar nerve).

Troster & Ruff, 1990	3 occupationally exposed workers to TCE or TCA: 2 patients acutely exposed to low levels of TCE & 1 patient exposed to TCA; Controls: 2 groups of *n* = 30 matched controls; (all age & education matched)	"Unknown amount of TCE for 8 months"	San Diego Neuropsychological Test Battery (SDNTB), "1 or more of": TAT, MMPI, Rorschach, & Interviewing questionnaire, Medical examinations (including neurological, CT scan, &/or Chemo-pathological tests & occupational history	Not reported	Case 1: Intelligence "deemed" to drop from pre-morbid function at 1 yr 10 months after exposure. Impaired functions improved for all but reading comprehension, visuospatial learning and categorization (abstraction). Case 2: Mild deficits in motor speed, verbal learning, and memory; "marked" deficits in visuospatial learning; good attention; diagnosis of mild depression and adjustment disorder, but symptoms subsided after removal from exposure. Case 3: Manual dexterity and logical thinking borderline impaired; no emotional changes, cognitive function spared, diagnosis of somatoform disorder.
White et al., 1997	Group 1: 28 individuals in Massachusetts exposed to contaminated well water; source: tanning factory & chemical plant; age range: 9−55 Group 2: 12 individuals in Ohio exposed to contaminated well water; source: degreasing; age range: 12−68 Group 3: 20 individuals in Minnesota exposed to contaminated well water; *n* = 14 for nerve conduction studies & *n* = 6 for neuropsychological	Group 1: 2 wells tested in 1979: 267 ppb TCE, 21 ppb Tetrachloroethylene, 12 ppb chloroform, 29 ppb Dichloroethylene, 23 ppb Trichlorotrifluoroethane ; 2 yr. average TCE 256 ppb for well G, and 111 ppb for well H Group 2: 13 wells with 1,1,1-trichloroethane (up to 2,569 ppb) & TCE (up to 760 ppb); blood analysis of individuals 2 yrs. after end of exposure and soon after exposure showed normal or mild elevations of TCE, elevations of 1,1,1-trichloroethane, ethylbenzene, & xylenes;	Occupational & environmental questionnaire, neurological exam, neuropsychological exam: WAIS-R, WISC-R, WMS, WMS-R, Wisconsin Card Sorting, COWAT, Boston Naming, Boston Visuospatial Quantitative Battery, Milner Facial Recognition Test, Sticks Visuospatial Orientation Task, Word triads, Benton Visual Retention Test, Santa Ana, Albert's Famous Faces, Peabody Picture Vocabulary Test, WRAT, POMS, MMPI, Trail-making,	Data shown in proportion in three communities, clinical diagnostic categories, analysis of central tendencies, & descriptive statistics	Group 1: Some individuals with subclinical peripheral neuropathy; 92.8% with reflex abnormalities; 75% total diagnosed with peripheral neuropathy; 88.9 % with impairment in at least 1 memory test; Impairments: attention & executive function in 67.9%; motor function in 60.71%, visuospatial in 60.71%, mild to moderate encephalopathy in 85.7% Group 2: 25% with abnormal nerve conduction; Impairments: attention & executive function in 83.33%, memory in 58.33%, language/verbal in 50% Group 3: 35.7% with peripheral neuropathy; neuropsychological: all 6 tested had memory impairment, attention & executive function impairment, 3 had manual motor slowing; Participants younger at time of exposure with wider range of deficits; Language deficits in younger, but not in older participants

	testing; source: ammunition plant; age range: 8−62; No controls	Group 3: mean TCE for one well 261 ppb; 1,1-Dichloroethylene 9.0 ppb; 1,2-dichloroethylene 107 ppb	Fingertapping, Delayed Recognition Span Test; Neurophysiological exam: eyeblink, evoked potentials, nerve conduction; Other: EKG, EEG, medical tests		

Winneke, 1982	This is a review article reporting on multiple studies conducted to evaluate neurological effects of toluene, TCE, and methylene chloride. Only the TCE results are summarized herein.	"Two experiments were run in our laboratory on behavioral and electrophysiological effects of low-level TCE-exposure. In experiment (Schlipkater, et al., 1974) effects of 3 1/2 hours of exposure to 50 ppm TCE were studied in 18 Ss, whereas in experiment II (Winneke, et al., 1974, 1976, 1978) TCE-effects (50 ppm; 3 1/2 hours) were compared to those of alcohol (0.76mL ethanol/kg) in 12 Ss; blood-alcohol - levels (BAL) measured at the end of the exposure, i.e. . 3 hours after alcohol-consumption averaged 24 mg%.	The following were measured: "Perceptual measures (e.g. critical flicker fusion = CFF), measures of sustained attention (vigilance), measures of psychomotor performance (as e.g., reaction time, motor speed, coordination) as well as EEG-measures (sensory evoked potentials) are used to illustrate the main effects from such studies."	No statistical details were reported.	The authors concluded "No consistent behavioral deficit has been reported for trichloroethylene below 300 ppm; instead, visual and auditory evoked potentials were found to be affected at TCE vapor-concentrations between 50 and 100 ppm (3 1/2−7 1/2 hours of exposure). (200−800 ppm; 2−4 hours)".

ATSDR, 2003	116 children from registry of 14 hazardous waste sites with TCE in groundwater; under 10 yrs of age at time of registry; Control population (*n* = 177); communities with no evidence of TCE in groundwater (measured below MCL); matched by age and race; there were other chlorinated solvents present in the exposed group wells	Exposures were modeled using tap water TCE concentrations and GIS for spatial interpolation, and LaGrange for temporal interpolation to estimate exposures from gestation to 1990 across the area of subject residences, modeled data were used to estimate lifetime exposures (ppb-years) to TCE in residential wells; 3 exposure level groups; control = 0 ppb; low exposure group = 0 <23 ppb-years; and high exposure group = >23 ppb-years; confounding exposure was a concern	Fisher Logemann test; OSME-R; CSP; D-COME-T; hearing screening; DPOAE; SCAN	Screening results as binary variables using logistic regression within SAS; independent variables included exposure measures, age, gender, case history; chi square test, Fisher's exact test, t-tests, linear models	Exposed children had higher abnormalities for D-COME-T ($p < 0.002$), CSP ($p < 0.008$), velopharyngeal function ($p < 0.04$), high palatal arch ($p < 0.04$), abnormal outer ear cochlear function; No difference observed in exposed and non-exposed populations for speech or hearing function; No difference found in OSH function
Epidemiological Studies: Controlled Exposure Studies; Neurological Effects of Trichloroethylene					

Gamberale, et al., 1976	15 healthy men aged 20−31 yrs old employed by the Department of Occupational Medicine in Stockholm, Sweden; Controls**:** Within Subjects (15 self-controls)	Exposed for TCE 70 minutes via a breathing valve to 540 mg/m^3 (97 ppm), 1,080 mg/m^3 (194 ppm), and during ordinary atmospheric air. Sequence was counterbalanced between the 3 groups, days, and exposure levels. Concentration was measured with a gas chromatographic technique every third minute for the 1st 50 min., then between tests thereafter	Reaction time (RT)-Addition, Simple RT, Choice RT & short term memory using an electronic panel Subjects also assessed their own conditions on a 7 pt scale	Friedman two-way analysis by ranks to evaluate difference between 3 conditions, non-significant when tested individually, but significant when tested on the basis of six variables. Nearly half of the subjects could distinguished exposure/nonexposure. ANOVA for 4 performance tests based on a 3x3 Latin square design with repeated measures	In the RT-Addition test the level of performance varied significantly between the different exposure conditions [$F(2.24) = 4.35$; $p < 0.051$ and between successive measurement occasions $tF(2.24) = 19.25$;$p < 0.001$; The level of performance declined with increased exposure to TCE, whereas repetition of the testing led to a pronounced improvement in performance as a result of the training effect; No significant interaction effects between exposure to TCE and training

Konietzko, et al., 1975	This is a controlled exposure study conducted on 20 healthy male students and scientific assistants with a mean age of 27.2 years	Subjects were exposed to a constant TCE concentration of 95.3 ppm (520 mg/m^3) for up to twelve hours, and Blood concentrations of TCE were also analyzed at hourly intervals	evaluated for changes in alpha waves (<14 Hz) in the EEG recordings; EEG recordings were performed hourly for a period of 1 minute with the eyes closed. This was used as a potential measure of psychomotor disturbance		The alpha segment increased over time of exposure (from 0800 to 0900 and 1000 hours [military time]) (P = 0.05). There were no significant differences for the other time spans or for other parameters. Subjects with highest and lowest TCE blood levels <2 µg/mL and >5 µg/mL were compared to determine if they showed different responses, but no case were the differences statistically different.

Kylin et al., 1967	12 subjects exposed to 1,000ppm TCE for two hours in a 1.5 x 2 x 2 meters chamber; 2 subjects were given alcohol (0.7 gm of body weight); Controls**:** 7 of the 12 were tested some days prior to exposure and 5 of the 12 were tested some days after exposure	1,000 ppm of TCE was blown into a chamber via an infusion unit and vaporizing system. Ostwald's distribution factor for TCE- the quotient of the amount of solvent in the blood by the amount of alveolar air.	Optokinetic Nystagmus; Venus blood and alveolar air specimens were taken at various times after exposure and analyzed in a gas chromatograph with a flame ionization detector.	Ostwald's distribution factor for TCE (the quotient of the amount of solvent in the blood in mg/L by the amount of the alveolar air in mg/L) = 9.7 (1mg/L blood = 0.69 v/v; 1 mg/L air = 186 ppm, v/v.); Significant relationship between TCE in air & blood (0.88)	"A number" of subjects showed reduction in Fusion limit although more pronounced in the two subjects who consumed alcohol. "Others" however showed little if any effect. No stats

Salvini, 1971	This is a controlled exposure study conducted on six male university students. Each subject was examined on two different days, once under TCE exposure, and once as self controls, with no exposure.	TCE concentration was 110 ppm for 4 hour intervals, twice per day. 0 ppm control exposure for all as self controls.	Two sets of tests were performed for each subject corresponding to exposure and control conditions. Perception test with tachistoscopic presentation, Wechsler memory scale, complex reaction time test (CRT), and manual dexterity test.	Analysis of variance	A decrease in function for all measured effects was observed. Statistically significant results were observed for perception tests learning ($p < 0.001$), mental fatigue ($p < 0.01$), subjects ($p < 0.05$); and CRT learning ($p < 0.01$), mental fatigue ($p < 0.01$), subjects ($p < 0.05$).

Stewart et al., 1970	13 subjects in 10 experiments	Ten chamber exposures to TCE vapor (100 ppm and 200 ppm) for periods of 1 hour to a five-day work week. Experiments 1−7 were for a duration of 7 hours with a mean TCE concentration of 198 ppm−200 ppm. Experiments 8 and 9 exposed subjects to 190 ppm−202 ppm TCE for a duration of 3.5 and 1 hour, respectively. Experiment 10 exposed subjects to 100 ppm TCE for 4 hours. Experiments 2−6 were carried out with the same subjects over 5 consecutive days.; Gas chromatography of expired air; No self controls	Physical examination 1 hour prior to exposure. Blood analysis for complete blood cell count (CBC), sedimentation rate, total serum lipid, total serum protein, serum electrophoresis, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT). 24-hour urine collection for urobilinogen, trichloroacetic acid (TCA), and TCE. Also a preexposure expirogram, tidal volume measurement, and an alveolar breath sample for TCE; Short neurological exam including modified Romberg test, heel-to-toe test, finger-to-nose test;	Descriptive statistics	Ability to perceive TCE odor diminished as duration of expo increased; 40% had dry throat after 30 min. exposure; 20% reported eye irritation; Urine specimens showed progressive increase in amounts of TCE metabolites over the 5 consecutive exposures. Concentrations of TCA and TCE decreased exponentially after last exposure, but still present in abnormal amounts in urine specimens 12 days after exposure. Loss of smelling TCE: >1hr. = 33%; >2hrs. = 80%; >6.5 hrs. = 100%; Symptoms of lightheadedness, headache, eye, nose & throat irritation. Prominent fatigue & sleepiness by all after 200 ppm. These symptoms may be of clinical significance. All had normal neurological tests during exposure, but 50% reported greater mental effort was required to perform a normal modified Romberg test on more than one occasion.

Triebig, 1976	This was a controlled exposure study conducted on 7 healthy male and female students (4 females, 3 males) The control group was 7 healthy students (4 females, 3 males)	Subjects exposed for 6 hours/day for 5 days to 100 ppm (550 mg/m3 TCE). Controls were exposed in chamber to zero TCE. Biochemical tests included TCE, TCE, and trichloroethanol in blood. In this study the TCE concentrations in blood reported ranged from 4 to 14 µg/mL. A range of 20 to 60 µg/mL was obtained for TCA in the blood.	Psychological tests were: the d2 test was an attention load test; the short test is used to record patient performance with respect to memory and attention; daily Fluctuation Questionnaire measured the difference between mental states at the start of exposure and after the end of exposure is recorded; The MWT-A is a repeatable short intelligence test; the Freiburg Personality Inventory (FPI) is a test for 12 independent personality traits; Culture Fair Intelligence Test (CFT-3) is a nonverbal intelligence test;; Erlanger Depression Scale.	Regression analyses were conducted.	There was no correlation seen between exposed and unexposed subjects for any measured psychological test results. The biochemical data did demonstrate that exposed subjects' exposures.

Triebig, 1977 *Zbl. Bakt. Hyg.*, I. Abt. Orig. B 164, 314–327	This was a controlled exposure study conducted on 7 healthy male and female students (4 females, 3 males) The control group was 7 healthy students (4 females, 3 males)	Subjects exposed for 6 hours/day for 5 days to 100 ppm (550 mg/m3 TCE). Controls were exposed in chamber to zero TCE. Biochemical tests included TCE, TCE, and trichloroethanol in blood. In this study the TCE concentrations in blood reported ranged from 4 to 14 µg/mL. A range of 20 to 60 µg/mL was obtained for TCA in the blood.	The testing consisted of: the Syndrome Short Test;; the "Attention Load Test" or "d2 Test"; Number recall test, letter recall test, The "Letter Reading Test," "Word Reading Test" ,Erlanger Depression Scale (EDS). Scale for Autonomic Dysfunction (SVF,) Anxiety Scale, Pain Short Scale, and Information on Daily Fluctuations.	Statistics were conducted using Whitney Mann.	Results indicated the anxiety values of the placebo random sample group dropped significantly more during the course of testing ($p < 0.05$) than those of the active random sample group. No significantly different changes were obtained with any of the other variables.

Vernon & Ferguson, 1969	8 male volunteers age range 21−30; **s**elf controls: 0 dose	TCE administered as Trilene air-vapor mixtures through spirometers administered at random concentrations of 0, 100 ppm, 300 ppm or 1,000 ppm of TCE for two hours at a time, during which testing took place. Concentrations were measured with a halide meter. Medical history, exam including Complete blood count (CBC), urinalysis, Blood urea nitrogen (BUN), and serum glutamic-oxaloacetic transaminase (SGOT).	Flicker Fusion with Krasno-Ivy Flicker Photometer, Howard-Dolman depth perception apparatus, Muller-Lyer two-dimensional illusion, groove-type steadiness test, Purdue Pegboard, Written "code substitution", blood studies	ANOVAs, Dunnett's test	TCE did not produce any appreciable effects at lower concentrations. Compared to controls, participants exposed to 1,000 ppm of TCE had adverse effects on the Howard-Dolman, steadiness, and part of the pegboard, but no effects on Flicker Fusion, from perception or code substitution. No appreciable changes in CBC, urinalysis, SGOT, or BUN

Windemuller & Ettema, 1978	Pilot study: 24 healthy male volunteers; age range = 19−26 yrs, 4 groups with 6 volunteers in each: 1) control, 2) exposed to TCE, 3) exposed to alcohol, 4) exposed to TCE and alcohol; Final study: 15 other volunteers, each exposed to all 4 conditions;	Chamber study; Group 1 no exposure; Group 2 TCE exposure: 2.5 hrs. with 200 ppm; Group 3 alcohol exposure: 0.35 g/kg body weight; Group 4 TCE & alcohol: same as above levels; Blood alcohol levels taken with breathalyzer; exhaled air sampled for levels of TCE and trichloroethanol; TCE exposure: average measured TCE in exhaled air = 29 µg/L (SD = 3); TCE & alcohol expo: average measured TCE in exhaled air = 63 µg/L (SD = 12)	Binary Choice Task (Visual); Pursuit Rotor; Recording of heart rate, sinus arrhythmia, breathing rate; Questionnaire (15 items on subjective feelings)	K-sample trend test; two-tailed Wilcoxon test	Pilot study: no systematic effect of exposure on test perform. Alcohol group had higher heart rate than TCE group, and TCE & alcohol group; minimal effect of mental load on heart rate; sinus arrhythmia suppressed as mental load increased with higher suppression in exposed groups (all 3) compared to controls (differences possibly due to existing group differences); Final Study: pursuit-rotor task "somewhat impaired by exposure condition"; authors acknowledge possibility of sequence effects; no significant difference between conditions on questionnaire responses; performing mental tasks resulted in higher heart rate in the TCE+alcohol condition than in Alcohol alone condition; Mental load suppressed sinus arrhythmia, especially in TCE+alcohol condition; Conclusion: TCE and alcohol together impair mental capacity more than each one alone

Table D.2.2. Epidemiological Studies: Neurological Effects of Trichloroethylene/Mixed Solvents					
Reference	**Study Population**	**Exposure Assessment & Biomarkers**	**Tests used**	**Statistics**	**Results**
Albers et al., 1999	30 Railroad workers with toxic encephalopathy; involved in litigation; long-term exposure to solvents (*n* = 20 yrs.; range = 10−29 yrs.); Historical controls matched by gender, age, & body mass	Most common solvents included: trichloroethylene, trichloroethane, perchloroethylene; respirator not typically used	Neurologic exams (cranial nerves, motor function, alternate motion range, subjective sensory function, Romberg test, reflexes), occupational history, medical history, sensory and motor nerve conduction studies (NCS)	Log transformations of amplitude data; Mann-Whitney U Test for NCS; t test; simple linear regression and stepwise regression for dose-response	3 workers met clinical polyneuropathy criteria; NCS values not influenced by exposure duration or job title; no significant difference in NCS between presence or absence of polyneuropathy symptoms, disability status, severity or type of encephalopathy, or prior polyneuropathy diagnosis
Antti-Poika, 1982	87 patients (painters, paint & furniture factory workers, carpet & laundry workers) diagnosed 3−9 yrs. prior with chronic solvent exposure (mean age 38.6 yrs.) Control: 29 patients with occupational asthma	Mean duration of exposure 10.4 yrs; solvents: trichloroethylene, perchloroethylene, solvent mixture; based on patients' and/or employers' reports; 9 worksites visited for environmental measures; biological measures at 1 worksite; exposure classified as low, moderate, or high	Interview, Neurologic exam, EEG, electroneuromyographs, psychological examination (intellectual, short-term memory, sensory & motor functions)	Correlation coefficients for prognosis & factors influencing diagnosis	Reported symptoms: fatigue, headaches, memory disturbances, pain, numbness, paresthesias; 1st exam: 87 patients with objective and subjective neurological signs, 61 with psychological disturbance, 58 abnormal EEG, 25 clinical abnormalities, 57 PNS symptoms; 69 patients had neurophysiological or psychological disturbances identified by neurologist in only 4 patients; 2nd exam: 42 with clinical neurological signs, ; 21 patients deteriorated, 23 improved, 43 same; poor correlation between prognosis of examinations; no significant correlation between prognosis and age, sex, exposure duration & level, alcohol use, or other diseases

Aratani et al., 1993	437 exposed workers from various industries (not specified); 394 males, 43 females & 1,030 male clerical workers as controls; age range: 16−72	Exposed to Thinner, G/5100, TCE, xylene, toluene, methylchloride, gasoline	Vibrometer (VPT); Urinary Metabolites	Spearman correlation	Positive correlations between age and VPT 7; between job experience and VPT; Urinary metabolites not significantly correlated with VPT; no dose-effect for subjective symptoms & neurological signs
Binaschi & Cantu, 1982	35 patients with occupational exposure to organic solvents; Industry not specified; no controls	Occupational history provided by patients; Descriptions of jobs and conditions provided by employer; Workplace observations; Some available measurements of solvents in air; 9 patients exposed to trichloroethylene; 11 exposed to toluene and xylene; 15 exposed to mixtures of solvents; all exposures described to be under TLV-TWA, but short exposure might have exceeded ACGIF limit for short time	Examination of provoked and spontaneous vestibular symptoms; Pure tone threshold measurement; EEG; psychiatric interviews and psychiatric history; Prevalence of 37 psychiatric symptoms	Not stated	All patients had subjective symptoms (fatigue, psychic disturbances, dizziness, vegetative symptoms, vertigo); Vestibular system affected in most cases, with lesions in nucleo-reticular substance & brain stem; EEG change with diffuse & focal slowing; 71 % of patients had mild neurasthenic symptoms (fatigue, emotional instability, memory & concentration difficulties)
Bowler et al., 1991	67 former microelectronics workers exposed to multiple organic solvents; Controls (n = 157) were recruited from the same region; 67 pairs were matched on the basis of age, sex, ethnicity, educational level, sex, & number of children	Self-report & work history from microelectronics workers. Exposures and risks were estimated. Solvents include TCE, TCA, benzene, toluene, methylene chloride, n-hexane	California Neuropsychological Screening Battery	t test for matched pairs; Wilcoxon Signed Rank test	Exposed workers performed significantly worse on tests of attention, verbal ability, memory, visuospatial, visuomotor speed, cognitive flexibility, psychomotor speed, & reaction time; no significant differences in mental status, visual recall, learning, & tactile function

Colvin et al., 1993	Final sample: 67 workers (43 exposed; 24 unexposed) in a paint manufacturing plant employed there for at least 5 yrs.; all black males; exclusion criteria: encephalopathy, head injury with 24 + hr. unconsciousness, psychotropic medication, alcohol/drug dependence history, epilepsy, mental illness	Chronic exposure was assessed through: self-reported detailed work history for each worker; past & current industrial hygiene measurements of solvent levels in air; "total cumulative expo" in the factory and "average lifetime exposures" were calculated; visitations to establish areas with 'homogeneous exposure"; All exposures below the ACGIH limit. Solvents include MEK, benzene, TCE, MIBK, toluene, butyl acetate, xylene, cellosolve acetate, isophorone, and white spirits	Work & personal history interview; brief neurological evaluation, WHO Neurobehavioral Core Test Battery (all tests except POMS); Computer-administered tests: Reaction time, Fingertapping, Continuous Performance Test, Switching attention, Pattern Recognition Test, Pattern Memory; UNISA Neuropsychological Assessment Procedure: Four word memory test, Paragraph memory, Geometric Shape drawing; symptom and health questionnaires	Division into exposed and unexposed; Student's t test; Multiple linear regression	Exposed group performed worse than unexposed on 27 out of 33 test results; only significant difference was on latency times of two switching attention tests; no difference in subjects' symptom reporting between groups when questions analyzed separately or analyzed as a group; Average lifetime exposure was a significant predictor for: Continuous performance latency time, Switching attention latency time, Mean reaction time, Pattern Memory; fine visuomotor tracking speed significantly associated with cumulative exposure; effects of exposure concluded to be "relatively mild" and subclinical

Daniell et al., 1999	89 retired male workers (62−74 yrs. old) with prior long-term exposure to solvents including 67 retired painters & 22 aerospace manufacturing workers; Controls: 126 retired carpenters with minimal solvent exposure	Chronic occupational exposure; Structured clinical interview about past and present exposure to solvents; Cumulative Exposure Index (CEI) was constructed. Solvents not specified.	Psychiatric interview; questionnaires; physical exam; blood cell counts, chemistry panel, blood lead levels, Neuropsychological: BDI, verbal fluency test, WAIS-R: Vocabulary, Similarities, Block Design, Digit Span, Digit Symbol; Wisconsin Card Sorting; verbal aphasia screening test, Trails A & B, Fingertapping; WMS-R: logical memory & visual subtests; Rey Auditory Verbal Learning; Benton Visual Retention test; d2 test; Stroop; Grooved pegboard; simple reaction time	Odds ratio, logarithmic transformation of non-Gaussian data, standardization of test scores, ANCOVA, Multiple Linear regression; Kruskal Wallis test for differences in blood lead concentration	CEI was similar for painters and aerospace workers; Painters reported greater alcohol use than carpenters; painters also had lower scores on WAIS-R Vocabulary subtest; Controlling for age, education, alcohol use, and vocabulary score, painters performed worse on motor, memory, and reasoning ability tests; painters reported more symptoms of depression and neurological symptoms; painters more likely to have more abnormal test scores (odds ratio: 3.1) as did aerospace workers (odds ratio: 5.6); no dose effect with increasing exposure & neuropsychological tests

Donoghue et al., 1995	16 patients diagnosed with organic-solvent-induced toxic encephalopathy with various occupations compared to age-stratified normal groups (*n* = 38); average age: 43 yrs. (range = 31−58); Exclusion criteria: diabetes mellitus, ocular disease impairing vision, visual acuity with existing refractive correction of less than 4/6, abnormal direct ophthalmoscopic exam	Average exposure duration was 19 yrs. (range = 5−36 yrs.); Solvents include TCE, MEK, toluene, thinners, unidentified hydrocarbons	Visual acuity measured with a 4-m optotype chart; Contrast sensitivity measured with Vistech VCTS 6500 chart; monocular thresholds, pupil diameter	Chi square test	6 participants (37.5%) with abnormal contrast sensitivity; 2 of the 6 (33%) had monocular abnormalities; abnormalities occurred at all tested spatial frequencies; significant difference between groups at 3 cpd, 6 cpd, 12 cpd frequencies
Elofsson et al., 1980	Epidemiologic study of car or industrial spray painters (male) exposed long-term to low levels of organic solvents (*n* = 80); 2 groups of matched controls; 80 non-exposed male industrial workers in each control group	Long term, low level expo to multiple solvents; Assessed by interviews, on-the-job measurements, and a 1955 workshop model; Blood analysis: mean values were within normal limits for both groups; Exposed group had significantly higher values for alkaline phosphates, hemoglobin, hematocrit, & erythrocytes; early exposure TLVs in Sweden were significantly lower; solvents include TCE, TCA, methylene chloride, and others	Self-administered psychiatric questionnaires, Eysenck's Personality Inventory, psychosocial structured interview, Comprehensive Psychopathological Rating Scale; Visual Evoked Responses; EEG; Electroneurography; Vibration Sense Threshold estimations; Neurological exam	Calculation of z values; Pearson correlation; Multiple Regression Analysis	Significant differences between controls and exposed in symptoms of neurasthenic syndrome, in reaction time, manual dexterity, perceptual speed, & short-term memory; No significant differences on verbal, spatial, and reasoning ability; Some differences on EEG, VER, ophthalmologic, & CT

Gregersen, 1988	Workers exposed to organic solvents (paint, lacquer, photogravure, & polyester boat industries); Controls: warehousemen electricians; 1st follow-up 5.5 yrs. after initial evaluation (59 exposed, 30 unexposed); 2nd follow-up: 10.6 years after initial evaluation (53 exposed, 30 unexposed controls)	1st followup: data about working conditions, materials and exposure in prior 5 years used for exposure index; 2nd Followup: 9 questions asking about exposure to solvents in the prior 5 yrs.; TCE, toluene, styrene, white spirits	1st followup: structured interviews on occupational, social, medical history; clinical exam, neurological exam; 2nd followup: mailed questionnaire (49 follow-up issues to 1st followup)	Wilcoxon-Mann-Whittney tests; Kruskal-Wallis test; Chi-square; Spearman Rank Partial Correlation Coefficient	More acute neurotoxic symptoms in exposed group at both followups, but fewer symptoms at second follow-up than at 1st follow-up; at both followups exposed participants had more encephalopathy symptoms, especially memory & concentration; no encephalopathy symptoms in control group; symptoms and signs of peripheral, sensory, & motor neuropathy significantly worse in participants still exposed; Exposure index showed dose-effect with memory and concentration; Both follow-ups: improvement in acute symptoms; aggravation in CNS; more symptoms of peripheral nervous system & social consequences
Juntunen et al., 1980	37 patients with suspected organic solvent poisoning (mean age = 40.1 yrs.); selection based on pneumoencephalography ; no controls	Patients were exposed to: Carbon disulphide (*n* = 6), trichloroethylene (5), styrene (1), thinner (2), toluene (1), methanol (1), and carbon tetrachloride (2), mixtures (19); Exposure was assessed by patients' and employers' reports and measurements of air concentrations when available	Neurologic examination, pneumoencephalographic exam (PEG), EEG, tests assessing intelligence, memory and learning, motor function, and personality	Descriptive Statistics	Clinical neurological findings of slight psychoorganic alterations, cerebellar dysfunction, & peripheral neuropathy; 63 % had indication of brain atrophy; 23 of the 28 patients examined with electroneuromyography showed signs of peripheral neuropathy; 94 % had personality changes, 80 % had psychomotor deficits, 69% had impaired memory, and 57 % had intelligence findings; No dose-effect found

Juntunen et al., 1982	80 (41 women, 39 men) Finnish patients diagnosed 3−9 yrs. prior with chronic solvent exposure (mean age = 38.6 yrs.); 31 had slight neurological signs; no controls	Assessed by patients' occupational history, employers' workplace description, observations and data collected at workplace, environmental measurements, biological tests; TCE, PCE, or mixed solvent exposures	Neurologic examination; EEG & ENMG; tests of intellectual function, memory, learning, personality & psychomotor performance	Chi-square, Maxwell-Stuart, Correlation & multiple linear regression analyses	Significant correlations between prognosis of disturbances in gait ($p < 0.05$) & station and length of follow-up, duration & level of exposure & multiplying the two; no gender effects; Common subjective symptoms; headaches, fatigue, & memory problems; Impairment in fine motor skills, gait, & cerebellar functions; Subjective symptoms decreased during followup, but clinical signs increased
Laslo-Baker et al., 2004	32 mothers with occupational exposure to organic solvents during pregnancy and their children (3−9 yrs. of age); included if exposure started in 1st trimester and lasted for at least 8 weeks of pregnancy (32 mother-child pairs); Controls: 32 unexposed control mothers matched on age, child age, child sex, SES, & reported cigarette use and their children (32 mother-child pairs)	Exposure information collected at 3 times: 1) during pregnancy, 2) when contacted for study participation later in pregnancy, 3) at time of assessment; Information collected included types of solvent, types of setting, duration of exposure during pregnancy, use of protection, symptoms, ventilation; Solvents include toluene (*n* = 12 women), xylene (10), ethanol (7), acetone (6), methanol (5), TCE (3), etc. (a total of 78 solvents were reported).	Children: Wechsler Preschool and Primary Scale of Intelligence, WISC, Preschool Language Scale, Clinical Evaluations of Language Fundamentals, Beery-Buktenica Developmental test of Visuo-Motor Integration, Grooved Pegboard Test, Child Behavior Checklist (Parent Version), Connor's Rating Scale-Revised (Parent Version), Behavioral Style Questionnaire; Mothers: WASI	Power analysis, Multiple linear regression	Verbal IQ was lower (104) in children exposed in utero vs unexposed children controls (110); Children did not differ between groups in birth weight, gestational age, or developmental milestones; Children in the exposed group had significantly lower VIQ (108) and Full IQ (108) than controls (VIQ = 116 and Full IQ = 114; No significant difference in PIQ; Performance on expressive language, total language, & receptive language was significantly worse in children from exposed group

Lee et al., 1998	40 Korean female shoe factory workers employed there for at least 5 yrs.; cases with head injury, neurological or psychological disorder, or hearing or visual impairment were excluded; Controls: 28 (housekeepers); no in-plant controls available	4 workers wore passive personal air samplers for a full 8 hr. shift; Detected solvents: toluene, methyl ethyl ketone, *n*-hexane, *c*-hexane, cyclohexane, dichloroethylene, trichloroethylene, benzene, and xylene; In frame-making – air concentration of solvents was 0.46−0.71; In adhesive process – solvent air concentrations were 1.83−2.39; three exposure indices were calculated: current exposures, exposure duration (years), and Cumulative Exposure Estimate (CEE)(years x average exposures)	Questionnaire; Neurobehavioral Core Test Battery (includes: POMS, Simple Reaction Time, Santa Ana Dexterity test, Digit Span, Benton Visual Retention Test, Pursuit aiming motor steadiness test); POMS was excluded because of cultural inapplicability	MANOVA for tests with 2 outcomes; ANOVA for tests with 1 outcome; education was adjusted in analyses	Significant differences between groups based on exposure index; Differences in performance between controls and participants on Santa Ana were found only in the CEE (participants performed worse); CEE is a more sensitive measure of exposure to organic solvents
Lindstrom, 1973	168 male workers with suspected occupational exposure to solvents Group I with solvent poisoning (*n* = 42); Group II with solvent exposure, undergoing mandatory periodic health check (*n* = 126); Control-50 healthy non-exposed male volunteers working in a viscose factory; Group IV 50 male workers with carbon disulfide poisoning	44 exposed to TCE, 8 to tetrachloroethylene, 26 to toluene, 25 to toluene and xylene, 44 to thinners, 21 to "miscellaneous"; Solvent-exposed group had an average of 6 yrs. of expo; CS_2 group had average of 9 yrs. of exposure.	WAIS: Similarities, Picture Completion, Digit Symbol; Bourdon-Wiersma vigilance test, Santa Ana, Rorschach Inkblot test, Mira test	Student's t test	The solvent-exposed group and CS_2 group had significantly worse "psychological performances" than controls; Greatest differences in sensorimotor speed and psychomotor function; solvent-exposed and CS_2 groups had deteriorated visual accuracy

Lindstrom, 1980	56 male workers diagnosed with occupational disease caused by solvents; Controls: 98 styrene-exposed workers; 43 non-exposed construction workers	Chronic " excessive" exposure: Mean duration of exposure = 9.1 yrs (SD = 8.3).; Exposed to; halogenated and aromatic hydrocarbons, paint solvents, alcohols, and aliphatic hydrocarbons (TCE *n* = 14); Individual exposure levels estimated as time-weighted averages, based on information provided by subjects, employer, or workplace measurements, were categorized as low (3 patients), intermediate (26 patients), and high (27 patients)	WAIS subtests: Similarities, Digit Span, Digit Symbol, Picture Completion, Block Design; WMS subtests: Visual Reproduction; Benton Visual Retention test; Symmetry Drawing; Santa Ana Dexterity test; Mira test	Factor analysis; Student's t test; Multivariate Discriminant analysis	Significant decline in visuomotor performance and freedom from distractibility (attention) in the solvent-exposed participants; significant relationship between duration of solvent exposure & visuomotor performance; solvent exposure level was not significant; psychological test performance of styrene-exposed control was only slightly different from non-exposed controls
Lindstrom et al., 1982	86 Patients with prior diagnosis of solvent intoxication (mean age 38.6 yrs.); 40 male, 46 female; 52 exposed to mixed solvents; 21 exposed to TCE or PCE; 13 exposed to both; results at follow-up compared to those at initial diagnosis	Mean duration of exposure 10.4 yrs; solvents: trichloroethylene, perchloroethylene, solvent mixture; based on patients' and/or employers' reports	Intellectual Function: from WAIS – Similarities, Block Design, Picture Completion; Short Term Memory: from WMS – Digit Span, Logical Memory, Visual Reproduction; Benton Visual Retention test; Sensory & Motor Functions: Bourdon Wiersma Vigilance Test, Symmetry Drawing, Santa Ana Dexterity test, Mira test	Frequency distributions, Student's t test for paired data, stepwise linear regression	All patients grouped together regardless of types of past solvent exposure; on follow-up, significant learning effects for Similarities when compared to results at initial diagnosis; group mean for intellectual functioning increased; no significant change in memory test results; group means for sensory and motor tasks were lower; prognosis was better for longer follow-up and younger age and poorer for users of medicines with neurological effects

Marshall et al., 1997	All singleton births in 1983−1986 in 188 New York State counties (total number not specified); 473 CNS-defect births & 3,305 musculoskeletal-defect births; Controls: 12,436 normal births; Exclusion criteria: Trisomy 13, 18, or 21, birth weight of less than 1,000 g, sole diagnosis of hydrocephaly or microencephalopathy, hip subluxation	Information on inactive waste sites was examined, including: air vapor, air particulates, groundwater exposure via wells, and groundwater exposure. via basements; exposure was categorized as "high," "medium". "low", or unknown based on probability of exposure; proximity to waste sites was also considered; Most common solvents: TCE, toluene, xylenes, tetrachloroethene, 1-1-1 trichloroethane; Most common metals found: lead, mercury, cadmium, chromium, arsenic, & nickel		Odds Ratios (OR), Fisher's exact test, Chi-square, unconditional logistic regression	13 CNS cases & 351 controls with potential exposures; crude OR: 0.98; When controlling for mother's education, prenatal care, and exposure to a TRI facility, OR was 0.84; CNS and solvents OR = 0.8; CNS and metals OR = 1.0, musculoskeletal defects and solvents OR = 0.9, musculoskeletal defects and pesticides OR = 0.8; higher risk for CNS defects when living close to solvent-emitting facilities
McCarthy & Jones, 1983	384 industrial workers with solvent poisoning; 103 operated degreasing baths, 62 maintained degreasing baths, 37 used TCE in portable form, 37 misc; no controls	Individuals poisoned with trichloroethylene, perchloroethylene, & methylchloroform were examined retrospectively; Medical record review; 288 exposed to TCE, 44 to perchloroethylene, 52 to 1,1.1-trichloroethane	Symptoms reported in occupational/medical records from industrial poisoning incidents; data from 1961 to 1980 on demographics, occupation, work process, type of industry, if incident caused fatality		17 fatality cases, with 10 in confined spaces; Most common symptoms include effects on CNS; Gastrointestinal & Respiratory symptoms; no strong evidence for cardiac & hepatic toxicity; no change in affected number of workers in 1961 to 1980; greatest effect due to narcotic properties

Mergler et al., 1991	54 matched pairs ; Matching on the basis of age, sex, ethnicity, educational level, sex, & number of children taken from180 former microelectronics workers exposed to multiple organic solvents and control population of 157 recruited from the same region	Average duration of employment - 6.1 yrs. (range: 1−15 yrs.); information about products used and chemical make-up from employer; chemicals: chlorofluorocarbons, chlorinated hydrocarbons, glycol ethers, isopropanol, acetone, toluene, xylene, & ethyl alcohol	Sociodemographic questionnaire; Monocular examination of visual function: Far visual acuity using a Snellen chart, near visual acuity using a National Optical Visual Chart, color vision using Lanthony D-15, near contrast sensitivity using Vistech grating charts	Signed-rank Wilcoxon test; Mann-Whitney; Chi-square test for matched pairs; Multiple Regression; Stepwise regression	Significant difference in near contrast sensitivity: 75% of exposed workers with poorer contrast sensitivity at most frequencies than the matched controls (no difference in results based on smoking, alcohol use, and near visual acuity loss); Significant differences on near visual acuity, color vision, and rates of acquired dyschromatopsia for one eye only; No difference between groups in near or far visual acuity
Morrow et al., 1989	22 male patients with exposure to multiple organic solvents; 4 involved in litigation; Exclusion: neurologic or psychiatric disorder prior to assessment, alcohol consumption more than 2 drinks/day; Average yrs. education 12 (range: 10−16 yrs.); average age 38 yrs. (range: 27−61); compared to responses of WWII prisoner of war (POW) population with post-traumatic stress disorder (PTSD)	Exposure assessed with questionnaire (duration, type of solvents, weeks since last exposure, cases of excessive exposure); Average exposure duration = 7.3 yrs. (range: 2 months−19 yrs.); average weeks since last exposure was 19.8 (range: 1−84 wks.); 28% had at least one instance of excessive exposure	Exposure questionnaire, Group form of the MMPI	Stepwise multiple regression	All profiles valid; 90% with at least 2 elevated scales above T score of 70 (clinically significant); Highest elevations on scales 1, 2, 3, and 8; only 1 case within normal limits; when compared to a group of non-psychiatric patients, exposed patients had more elevations, although both groups have physical complaints; When compared with WWII POW (1/2 diagnosed with PTSD) with similar SES & education, both groups have similar profiles; no age effects found; significant positive correlation between scale 8 & duration of exposure; no significant difference based on time since last exposure or on experiencing excessive exposure

Morrow et al., 1992	9 men and 3 women occupationally exposed to multiple organic solvents with CNS complaints; all met criteria for mild toxic encephalopathy; exposed group average age was 47 yrs.; Controls: 19 (healthy male volunteers); 26 psychiatric controls (male patients with chronic schizophrenia) average age unexposed controls: 34 yrs.; average age schizophrenic patients.: 36 yrs.	Exposure assessed with occupational and environmental exposure questionnaire; mean duration of expo = 3 yrs (range = <1 day−30 yrs.); average time between last exposure and assessment was 2 yrs. (range ; 2 months−10 yrs.); solvents toluene, TCE	Auditory event-related potentials under the oddball paradigm: counting & choice reaction time tasks	Repeated measures ANOVA	Exposed patients had significant delays in N250 and P300 compared to normal controls and in P300 compared to psychiatric controls; Exposed patients had higher amplitudes for N100, P200, and N250; no difference in P300 amplitude between groups; for the exposed group, P300 positively correlated with exposure duration; findings indicate that solvent exposure affects neural networks
Seppäläinen & Antti-Poika, 1983	87 patients with solvent poisoning (40 male & 47 female) with occupational exposure to solvents; Follow-up 3−9 yrs. after initial diagnosis; Mean age at diagnosis 38.6 (range: 20−59 yrs.); no control population	Chronic exposure with average. duration of 10.7 yrs. (range:1−33); patients were exposed to TCE (*n* = 21), perchloroethylene (*n* = 12), mixtures of solvents (*n* = 53), mixtures and TCE or Perc. (*n* = 13); Exposure of 54 patients stopped after diagnosis, 33 continued to be exposed; at follow-up, only 5 working with potential of some exposure	EEG using 10/20 system with 25−30 min. of recording, 3 min. hyperventilation & intermittent photic stimulation; ENMG	Chi-square, Hypergeometric distribution, McNemar test	Significantly more ENMG abnormalities at follow-up than at initial diagnosis; Most common finding: slight polyneuropathy; 43% showed improved ENMG, 33% had deteriorated, and 18 pts. with similar ENMG findings (6 normal at both exams); at follow-up, slow-wave abnormalities decreased & paroxysmal abnormalities increased; 41 with improved EEG, 28 with similar EEG (19 had normal EEG at diagnosis), & 18 with deteriorated EEG; EEG pattern of change compared to external head injuries

Shlomo et al., 2002	Male industrial workers; Mercury exposure group (*n* = 40); average age 49.7 (± 6.4) yrs; chlorinated hydrocarbons (CHs) exposure group (*n* = 37) average age 46.0 (± 4.73); Controls, unexposed (*n* = 36) average age 49.8 (± 5.8), matched by age; (industries not specified)	Interview and record review; Urine samples collected at end of work shift prior to testing and tested for mercury & trichloroacetic acid (TCAA); chlorinated hydrocarbons: TCE (*n* = 7), perchloroethylene (PCE) (*n* = 8), trichloroethane (TCA) (*n* = 22); Mean duration of CH exposure 15.8 (± 7.2) yrs.; Mean duration of mercury exposure 15.5 (± 6.4) yrs; Air sampling: mercury: 0.008 mg/m^3 (TLV = 0.025); TCE: 98 ppm (TLV = 350); PCE: 12.7ppm (TLV = 25); trichloroethane: 14.4 ppm (TLV = 200); Blood levels: mercury (B-hg) 0.5 gr% (±0.3); TCAA urine levels: 1−80 % of Biologic Exposure Index (BEI); CH urine levels: 0.11−0.2 of BEI	Medical history, Neurological tests assessing cranial nerves and cerebellar function; Otoscopy, review of archival data from pure-tone audiometric tests; Auditory brain stem responses (ABR)	Student's t test, proportions test	Significant differences between exposed and controls: 33.8% of CH exposed workers with abnormal IPL I-III; 18 % of controls; Authors suggest ABRs are sensitive for detecting subclinical CNS effects of CH & mercury

Till at al., 2001	The children of mothers who had contacted a Canadian pregnancy risk counseling program during pregnancy & reported occupational exposure to solvents (*n* = 33); children age range: 3−7; Mothers' occupations: lab technicians, factory workers, graphic designers, artists, and dry cleaning; Controls: 28 matched on age, gender, parental SES, and ethnicity; children of mothers exposed to non-teratogenic agents	Structured questionnaire about exposure; Method: weight assigned to each exposure Parameter (length of exposure, frequency of exposure, symptoms); sum of scores for each parameter used as exposure index; median split used to categorize in low (*n* = 19) and high (*n* = 14) exposures; solvents include benzene, toluene, methane, ethane, TCE, methyl chloride, etc	NEPSY: Visual Attention, Statue, Tower, Body Part Naming, Verbal Fluency, Speeded Naming, Visuomotor Precision, Imitating Hand Positions, Block Construction, Design Copying, Arrows; Peabody Picture Vocabulary Test; WRAVMA Pegboard test; Child Behavior Checklist (Parent form); Continuous Performance Test	Mantel Haenszel test, t test, ANCOVA, Hierarchical multiple linear regression	Lower composite neurobehavioral scores as exposure increased after adjusting for demographics in: Receptive language, expressive language, graphomotor ability; Significantly more exposed children rated with mild-severe problems; No significant difference between groups in attention, visuo-spatial ability, & fine-motor skills; Mean difference on broad- and narrow-band scales of Child Behavior Checklist scores not significant
Till et al., 2001 in Teratology, issue 64	Children of mothers who had contacted a Canadian pregnancy risk counseling program during pregnancy & reported occupational exposure to solvents (*n* = 32); children age range: 3−7; Mothers' occupations: lab technicians, factory workers, graphic designers, artists, and dry cleaning; Controls: 27 matched on age, gender, parental SES, and ethnicity; children of mothers exposed to non-teratogenic agents	Structured questionnaire about exposure; Method: weight assigned to each exposure parameter (length of exposure, frequency of exposure, symptoms); sum of scores for each parameter used as exposure index; median split used to categorize in low (*n* = 19) and high (*n* = 14) exposures; solvents include benzene, toluene, methane, ethane, TCE, methyl chloride, etc	Minimalist test to assess color vision; Cardiff Cards to assess visual acuity	Independent samples t tests, Mantel Haenszel Chi test; Wilcoxon-Mann-Whitney test; Kruskal-Wallis Chi square	Significantly higher number of errors on red-green and blue-yellow discrimination in exposed children compared to controls; exposed children had poorer visual acuity than controls; No significant dose-response relationship between exposure index and color discrimination and visual acuity.

Till et al., 2005	21 infants (9 male, 12 female)of mothers who contacted a Canadian pregnancy risk counseling program & reported occupational exposure to solvents (occupations: factory, lab., dry cleaning; Controls: 27 age-matched infants (17 male, 10 female) of mothers contacted the program due to exposure during pregnancy to non-teratogenic substances)	Structured questionnaire about exposure; Method: weight assigned to each exposure parameter (length of exposure, frequency of exposure, symptoms); sum of scores for each parameter used as exposure index; median split used to categorize in low and high exposures; exposure groups: 1) aliphatic &/or aromatic hydrocarbons (n = 9), 2) alcohols (n = 3), 3) multiple solvents (n = 6), 4) PCE, (n = 3); mean duration of exposure during pregnancy 27.2 wks. (SD7.93, range = 12−40); solvents include benzene, toluene, methane, ethane, TCE, methyl chloride, etc	1st visit: Sweep visual evoked potentials (VEP) to assess contrast sensitivity and grating acuity; 2nd visit (2 wks. after 1st): Transient VEPs to assess chromatic & achromatic mechanisms; ophthalmological exam, physical & neurological exam; testers masked to exposure status of infant	Median split; Multiple Linear Regression; Chi-square, t test, Mann-Whitney U test, MANCOVA, Pearson correlation, Logistic Regression	Significant decline of contrast sensitivity in low and intermediate spatial frequencies in exposed infants when compared with controls; Significant effect of exposure level on grating acuity, 26.3% of exposed (but 0% of controls) with abnormal VEP to red-green onset stimulus; No differences between groups in latency & amplitude of chromatic & achromatic response
Valic et al., 1997	138 occupationally exposed & 100 unexposed controls; Exclusion criteria: congenital color vision loss, severe ocular disease, significant vision impairment, tainted glasses or contact lenses, diabetes mellitus, neurological disease, prior severe head or eye injuries, alcohol abuse, medication impairing color vision	Solvents: TCE, PCE, toluene, xylene; Historical data on: duration of exposure protective equipment use, subjective evaluation of exposure, non-occupational solvent exposure, solvent-related symptoms at work, alcohol & smoking, drug intake; Mean urinary levels of trichloroacetic acid: 1.55 (±1.75) mg/L	Lanthony D15	Polytomous logistic regression	Significant effect of age in exposed group; With alcohol of <250g/week no significant correlation between color confusion and solvent exposure; Significant interaction between solvent exposure & alcohol intake; Color Confusion Index significantly higher in exposed group with alcohol use of >250g/wk

Windham et al., 2006	Children born in 1994 in San Francisco Bay Area with Autism Spectrum Disorders (ASDs)(*n* = 284) and controls (*n* = 657), matched on basis of gender and month of birth	Birth addresses were geocoded & linked to hazardous air pollutant (HAP) database; Exposure levels assigned for 19 chemicals; chemicals were grouped based on mechanistic & structural properties; Summary index scores were calculated; risk of ASD calculated in upper quartiles of groups or individual chemical concentrations; Adjustment for demographic factors	Archival data	Pearson correlation, Logistic Regression	Elevated adjusted odds ratios for ASD (by 50%) in top quartile of chlorinated solvents, but not for aromatic solvents; AOR for TCE in 4^{th} quartile = 1.47; lessened when adjusted for metals; correlation between hydrocarbon and metals exposures; when adjusted, increased risk for metals (in 3rd quartile = 1.95; in 4th quartile = 1.7). Contributing compounds: mercury, cadmium, nickel, TCE, vinyl chloride; Results interpreted to suggest relationship between autism and estimated metal and solvent concentrations in air around place of birth residence

Epidemiological Studies: Controlled Exposure Studies; Neurological Effects of Trichloroethylene/Mixed Solvents

Levy et al., 1981	9 participants (8 males & 1 female) recruited through newspaper ad; 8 hrs. fasting before testing; no control	Experiment 1: alcohol consumption (3 doses)- blood alcohol levels were measured with breath analyzer pre (multiple baselines) and post test (multiple) Experiment 2: Chloral hydrate administered orally over 2 min. in either 500 mg or 1,500 mg dose; multiple baseline SPEM tests and multiple posttests after exposure; No control dose administered	Smooth pursuit eye movement (SPEM) tests of following a sinusoidally oscillated target at 0.4 Hz; eye movements were recorded through electrodes at each eye	t tests; ANOVA	Experiment 1: pre-alcohol all subjects had intact SPEM; no significant effect for 1.5 mL/kg of alcohol; significant decline in SPEM at 2.0 and 3.0 mL/kg alcohol; significant dose-effect; Experiment 2: at 500 mg. chloral hydrate, no significant change in pursuit was noted ; at 1,500 mg chloral hydrate, qualitative disruptions in pursuit in all participants (4); at 500 mg participants observed to be drowsy; When number reading was added SPEM impairment was 'attenuated' in both alcohol and chloral hydrate conditions
Stopps & McLaughlin, 1967	Chamber study using 2 healthy male volunteers exposed to Freon-113; 1 volunteer exposed to TCE; No	Exposure booth was constructed; TCE in air: TCE concentrations: 100, 200, 300, 400 ppm (1965 TLV: 100 ppm for 8 hr.	Crawford Small Parts Dexterity Test, Necker Cube Test, Card Sorting, Card	Descriptive statistics for air measurement plots by % of TCE	No TCE effect at 100 ppm, but test performance deteriorated with increase of TCE concentration; No effect of Freon-113 on psychomotor

	control	exposure) in ascending & descending order; total time in chamber: 2.75 hrs; Freon-113 concentrations: 1,500, 2,500, 3,500, 4,500 ppm (1965 TLV: 1,000 ppm for 8 hr. exposure), duration 1.5 hrs.; TCE: 1) reduction of weight of compound during exposure was calculated, 2) continuous air sampling in the chamber; Freon-113 in air: 1) and 2) same; 3) gas chromatography on air captured in bottles sealed in the chamber; no control dose given	Sorting with an Auxiliary Task, Dial Display (TCE participant only); Short Employment Test-Clerical (Freon-113 participants only)	change in groups	function at 1,500 ppm – deterioration at 2,500 ppm, as concentration increased, performance deteriorated

Table D.2.3 Literature Review of studies of TCE and domains assessed with neurobehavioral/neurological methods.

Authors	Year	Study Type	Participants No. (N=exposed C=non-exposed)	Dura-tion	Psycho-motor/RT	Visuo-motor	Cogni-tive	Mem-ory & Learn-ing	Mood & Person-ality	Symp-toms †	Sen-sory ††	Respi-ratory	Dose Effect √√ Urinary Metabolites √	TCE Levels
ATSDR	**2003**	E	N=116, C=177	**C**	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	**A**	ne	ne	0 → 23 ppb in dg water
Barret et al.	**1984**	O	N= 188	C	*ne*	*ne*	*ne*	*ne*	*ne*	**H, D**	**T, N, V**	*ne*	√	150 ppm
Barret et al.	**1987**	O	N=104, C=52	C	*ne*	*ne*	*ne*	*ne*	√	**H, D, S, I**	**T, N**	*ne*	√	*ne*
Barrett, et al.	**1982**	O	N=11, C=2	C	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	**T**	*ne*	√	*ne*
Burg, et al.	**1995**	E	N=4,281	C	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	**A, N**	√	√	*ne*
Burg & Gist	**1999**	E	N=3915	C	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	**A, N**	√	√√	4 gps: 2 - 75000 ppb
El Ghawabi et al.	**1973**	O	N=30, C=30	C	*ne*	*ne*	*ne*	*ne*	*ne*	**H, S**	(-)	*ne*	√	165 ppm
Feldman et al.	**1988**	E	N=21, C=27	C	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	**T**	*ne*	*ne*	*ne*
Feldman et al.	**1992**	O	N=18, C=30	A,C	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	**T, N**	*ne*	*ne*	*ne*
Gamberale, et al.	**1976**	C	N=15	A	√	*ne*	√	(-)	*ne*	*ne*	*ne*	*ne*	*ne*	540 - 1080 mg^3
Gash et al.	**2007**	O	N=30	C	√	*ne*	*ne*	*ne*	*ne*	**M, N**		*ne*	*ne*	*ne*
Grandjean et al.	**1955**	O	N=80	C	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	**N**	*ne*	√, √√	6 - 1120 ppm
Gun, et al.	**1978**	O	N=8, C=8	C	√	*ne*	√	*ne*	*ne*	*ne*	**N**	*ne*	*ne*	3 - 418 ppm
Hirsch, et al.	**1996**	E	N=106	C	*ne*	*ne*	*ne*	*ne*	*ne*	**H**	*ne*	*ne*	*ne*	0 - 2441 ppb
Kilburn & Thornton	**1996**	E	N=237, C=264	C	√	*ne*	√	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*
Kilburn & Warshaw	**1993**	E	N=544, C=181	C	√	√	√	√	√	**M**	**T, N**	*ne*	*ne*	6 - 500 ppb
Kilburn	**2002a**	E	N=236, C=228	C	*ne*	*ne*	√	*ne*	*ne*	**M**	**B**	*ne*	*ne*	6 - 500 ppb
Kilburn	**2002b**	E	N=236, C=58	C	(-)	*ne*	*ne*	*ne*	(-)	*ne*	*ne*	*ne*	*ne*	0.2 - 1000 ppb
Konietzko, et al.	**1975**	C	N=20	A	*ne*	*ne*	*ne*	*ne*	*ne*	**M**	**N**	*ne*	√	953 ppm
Kylin, et al. 1967	**1967**	C	N=12	A	√	*ne*	*ne*	*ne*	*ne*	*ne*	**N**	*ne*	*ne*	1000 ppm
Landrigan, et al.	**1987**	O	Residents & 12 W	A,C	*ne*	*ne*	√	*ne*	*ne*	**H, D**	*ne*	*ne*	√√	≥ 183,000 ppb
Liu, et al.	**1988**	O	N=103, C=111	C	*ne*	*ne*	*ne*	√	*ne*	**D, N**	**N**	*ne*	√√	1 - 100 ppm
Mhiri et al.	**2004**	O	N=23, C=23	A	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	**T**	*ne*	√, √√	*ne*
Nagaya et al.	**1990**	O	N=84, C=83	C	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	**N**	*ne*	√	22 ppm
Rasmussen & Sabroe	**1986**	O	N=240, C=350	C	*ne*	*ne*	*ne*		√	**H,D, I, M**	*ne*	*ne*	*ne*	*ne*

Rasmussen et al.	**1993**	O	N=96	C	*ne*	*ne*	√	*ne*	*ne*	*ne*	*ne*	*ne*	√√	*ne*
Rasmussen et al.	**1993**	O	N=96	C	*ne*	√	√	*ne*	*ne*	*ne*	*ne*	*ne*	√√	*ne*
Rasmussen et al.	**1993**	O	N=99	C	√	*ne*	*ne*	*ne*	*ne*	*ne*	**N**	*ne*	√√	*ne*
Reif et al.	**2003**	E	N=143	C	√	√	*ne*	*ne*	√	**M**	**M**	*ne*	√√	5 -15 ppb
Ruijten, et al.	**1991**	O	N=31, C=28	C	√	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	17 - 70 ppm
Smith	**1970**	O	N=130, C=63	C	*ne*	*ne*	*ne*	*ne*	*ne*	**H, D**	**N**	*ne*	√, √√	*ne*
Stewart et al	**1970**	C	N=13	A	*ne*	*ne*	√	*ne*	*ne*	**H**	*ne*	*ne*	√	100 - 202 ppm
Triebig, et al.	**1976**	C	N=7, C=7	A	*ne*	*ne*	√	√	√	(-)	*ne*	*ne*	√, √√	0 - 100 ppm
Triebig, et al.	**1977**	C	N=7, C=7	A	*ne*	*ne*	√	√	√	**M**	(-)	*ne*	√, √√	0 - 100 ppm
Triebig, et al.	**1977**	O	N=8	A,C	*ne*	√	√	√	*ne*	*ne*	*ne*	*ne*	√	50 ppm
Triebig, et al.	**1982**	O	N=24, C=24	C	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	**N**	*ne*	√, √√	5 - 70 ppm
Triebig, et al.	**1983**	O	N=66, C=66	C	*ne*	*ne*	*ne*	*ne*	*ne*	**N, H**	**N**	*ne*	√	10 - 600 mg/m3
Troster & Ruff	**1990**	O	N=3, C=60	A	√	√	√	√	√	*ne*	**N**	*ne*	*ne*	*ne*
Vernon & Ferguson	**1969**	C	N=8	A	√	√	*ne*	*ne*	*ne*	*ne*	**N**	*ne*	√√	0 - 1000 ppm
Windemuller & Ettema	**1987**	C	N=39	A	√	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	200 ppm
Winneke	**1982**	O	Not reported	*ne*	(-)	(-)	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	*ne*	50 ppm

√ = positive findings (-) = findings not significant *ne* = not examined or reported

† **H** = Headaches; **D** = Dizziness; **I** = Insomnia; **S** = Sex Probls; **M**=Mood; **N**=Neurological

†† **A** = Audition; **B** = Balance; **V** = Vision; **T** = Trigeminal nerve; **N** = Other Neurological

Study: **C** = Chamber, **E** = Environmental, **O** = Occupational **Duration**: **A** = Acute, **C** = Chronic

D.2. Central Nervous Toxicity in Animal Studies Following TCE Exposure

In vivo studies in animals and *in vitro* models have convincingly demonstrated that TCE produces functional and physiological neurological changes. Overall, these effects collectively indicate that TCE has CNS depressant-like effects at lower exposures and causes anesthetic-like effects at high exposures. Studies of TCE toxicity in animals have generally not evaluated whether or not adverse effects seen acutely persist following exposure or whether there are permanent effects of exposure. Exceptions to the focus on acute impairment while under TCE intoxication include studies of hearing impairment and histopathological investigations focused primarily on specific neurochemical pathways, hippocampal development, and demyelination. These persistent TCE effects are discussed initially followed by the results of studies that examined the acute effects of this agent. Summary tables for all the animal studies are at the end of this section.

D.2.1 Alterations in Nerve Conduction

There is little evidence that TCE disrupts trigeminal nerve function in animal studies. Two studies demonstrated TCE produces morphological changes in the trigeminal nerve at a dose of 2,500 mg/kg-day for 10 weeks (Barret et al., 1991, 1992). However, dichloroacetylene, a degradation product formed during the volatilization of TCE was found to produce more severe morphological changes in the trigeminal nerve and at a lower dose of 17 mg/kg-day (Barret et al., 1991,1992). Only one study (Albee et al., 2006) has evaluated the effects of TCE on trigeminal nerve function, and a subchronic inhalation exposure did not result in any significant functional changes. A summary of these studies is provided in Table D.2.1.

Barret et al. (1991, 1992) conducted two studies evaluating the effects of both TCE and dichloroacetylene on trigeminal nerve fiber diameter and internodal length as well as several markers for fiber myelination. Female Sprague Dawley rats (n = 7/group) were dosed with 2,500 mg/kg TCE or 17 mg/kg-day dichloroacetylene by gavage for 5 days/week for 10 weeks. These doses were selected based upon the ratio of the LD_{50}s for these two agents. Two days after administration of the last dose, a morphometric approach was used to study the diameter of teased fibers from the trigeminal nerve. The fibers were classified as Class A or Class B and evaluated for internode length and fiber diameter. TCE-dosed animals only exhibited changes in the smaller Class A fibers where internode length increased marginally (<2%) and fiber diameter increased by 6%. Conversely, dichloroacetylene-treated rats exhibited significant and more

robust decreases in internode length and fiber diameter in both fiber classes A and B. Internode length decreased 8% in Class A fibers and 4% in Class B fibers. Fiber diameter decreased 10% in Class A fibers and 6% in Class B fibers. Biochemical data are presented for fatty acid composition from total lipid extractions from the trigeminal nerve. These two studies identify a clear effect of dichloroacetylene on trigeminal nerve fibers, but the effect by TCE is quite limited.

Albee et al. (2006) evaluated the effects of a subchronic inhalation TCE exposure in Fischer 344 rats (10/sex/group). Rats were exposed to 0, 250, 800, and 2,500 ppm TCE for 6 hours/day, 5 days/week for 13 weeks. At the eleventh week of exposure, rats were surgically implanted with epidural electrodes over the somatosensory and cerebellar regions, and TSEPs were collected 2−3 days following the last exposure. TSEPs were generated using subcutaneous needle electrodes to stimulate the vibrissal pad (area above the nose). The resulting TSEP was measured with electrode previously implanted over the somatosensory region. The TCE exposures were adequate to produce permanent auditory impairment even though TSEPs were unaffected. While TCE appears to be negative in disrupting the trigeminal nerve, the TCE breakdown product, dichloroacetylene, does impair trigeminal nerve function.

Albee et al. (1997) reported that dichloroacetylene disrupted trigeminal nerve somatosensory evoked potentials in Fischer 344 male rats. The subjects were exposed to a mixture of 300 ppm dichloroacetylene, 900 ppm acetylene, and 170 ppm TCE for a single 2.25-hour period. This dichloroacetylene was generated by decomposing TCE in the presence of potassium hydroxide and stabilizing with acetylene. A second treatment group was exposed to a 175-ppm TCE/1,030-ppm acetylene mix with no potassium hydroxide present. Therefore, no dichloroacetylene was present in the second treatment group, providing an opportunity to determine the effects on the trigeminal nerve somatosensory evoked potential in the absence of dichloroacetylene. Evoked potentials from the dichloroacetylene/TCE/acetylene-exposed rats were about 17% smaller measured between peaks I and II and 0.13 msec slower in comparison to the pre-exposure measurements. Neither latency nor amplitude of this potential changed significantly between the pre-exposure and post-exposure test in the air-exposed animals (control). The dichloroacetylene-mediated evoked potential changes persisted at least until day 4 post exposure. No changes in evoked potentials were observed in the 175-ppm TCE/1,030-ppm acetylene mix group. It is noteworthy that dichloroacetylene treatment produced broader evidence of toxicity as witnessed by a persistent drop in body weight among subjects over the 7-day post exposure measuring period. In light of the differences observed between the effects of TCE and dichloroacetylene on the trigeminal nerve, it would be instructive to calculate the dose

of TCE that would be necessary to produce comparable tissue levels of dichloroacetylene produced in the Albee et al. (1997) study.

Kulig (1987) also measured peripheral (caudal nerve) nerve conduction time in male Wistar rats and failed to show an effect of TCE with exposures as high as 1,500 ppm for 16 hours/day, 5 days/week for 18 weeks.

D.2.2 Auditory Effects

D.2.2.1 Inhalation

The ability of trichloroethylene (TCE) to disrupt auditory function and produce inner ear histopathology abnormalities has been demonstrated in several studies using a variety of test methods. Two different laboratories have identified NOAELs for auditory function of 1,600 ppm following inhalation exposure for 12 hr/day for 13 weeks in Long Evans rats (n = 6−10) (Rebert et al., 1991) and 1,500 ppm in Wistar-derived rats (n = 12) exposed by inhalation for 18 hr/day, 5 days/week for 3 weeks (Jaspers et al., 1993). The LOAELs identified in these and similar studies are 2,500−4,000 ppm TCE for periods of exposure ranging from 4 hr/day for 5 days to 12 hr/day for 13 weeks (e.g. Muijser et al., 2000; Rebert et al., 1995, 1993; Crofton et al., 1994; Crofton and Zhao, 1997; Fechter et al., 1998; Boyes et al., 2000; Albee et al., 2006). Rebert et al. (1993) estimated acute blood TCE levels associated with permanent hearing impairment at 125 μg/mL by methods that probably underestimated blood TCE values (rats were anaesthetized using 60% CO_2). A summary of these studies is presented in Table D.2.2.

Rebert et al. (1991) evaluated auditory function in male Long Evans rats (n = 10) and F344 rats (n = 4−5) by measuring brainstem auditory-evoked responses (BAERs) following stimulation with 4, 8, and 16 kHz sounds. The Long-Evans rats were exposed to 0, 1,600, or 3,200 ppm TCE, 12 hour/day for 12 weeks and the F344 rats were exposed to 0, 2,000, or 3,200 ppm TCE, 12 hours/day for 3 weeks. BAERs were measured every 3 weeks during the exposure and then for an additional 6 weeks following the end of exposure. For the F344 rats, both TCE exposure (2,000 and 3,200 ppm) significantly decreased BAER amplitudes at all frequencies tested. In comparison, Long Evans rats exposed to 3,200 ppm TCE also had significantly decreased BAER amplitude, but exposure to 1,600 ppm did not significantly affect BAERs at any stimulus frequency. These data suggest a LOAEL at 2,000 ppm for the F344 rats and a NOAEL at 1,600 ppm for the Long Evans rats. In subsequent studies, Rebert et al. (1993, 1995)

again demonstrated TCE significantly decreases BAER amplitudes and significantly increases the latency of the initial peak (identified as P1).

Jaspers et al. (1993) exposed Wistar-derived WAG-Rii/MBL rats (n = 12) to 0, 1,500 and 3,000 ppm TCE exposure for 18 hr/day, 5 days/week for 3 weeks. Auditory function for each frequency was assessed by reflex modification (recording the decibel threshold required to generate a startle response from the rat). Three tones (5, 20, and 35 kHz) were used to test auditory function. The startle measurements were made prior to exposure and at 1, 3, 5, and 6 weeks after exposure. A selective impairment of auditory threshold for animals exposed to 3,000 ppm TCE was observed at all post-exposure times at 20 kHz only. No significant effects were noted in rats exposed to 1,500 ppm TCE. This auditory impairment was persistent up through 6 weeks after exposure, which was the last time point presented. There was no impairment of hearing at either 5 or 25 kHz for animals exposed to 1,500 or 3,000 ppm TCE. This study indicates TCE selectively produces a persistent mid-frequency hearing loss and identifies a NOAEL of 1,500 ppm. Similarly, Crofton et al. (1994) exposed male Long Evans rats (n = 7−8) to 3,500 ppm TCE, 8 hours/day for 5 days. Auditory thresholds were determined by reflex modification audiometry 5−8 weeks after exposure. TCE produced a selective impairment of auditory threshold for mid frequency tones, 8 and 16 kHz.

Muijser et al. (2000) evaluated the ability of TCE to potentiate the damaging effect of noise on hearing. Wistar rats (n = 8 per group) were exposed by inhalation to 0 or 3,000 ppm TCE alone for 18 hr/day, 5 days/week for 3 weeks (no noise) or in conjunction with 95-dB broad band noise. The duration of noise exposure is not specified, but presumably was also 18 hr/day, 5 days/week for 3 weeks. Pure tone auditory thresholds were determined using reflex modification audiometry 1 and 2 weeks following the exposures. Significant losses in auditory sensitivity were observed for rats exposed to noise alone at 8, 16, and 20 kHz, for rats exposed to TCE alone at 4, 8, 16, and 20 kHz and for combined exposure subjects at 4, 8, 16, 20, and 24 kHz. The loss of hearing sensitivity at 4 kHz is particularly striking for the combined exposure rats, suggesting a potentiation effect at this frequency. Impairment on this auditory test suggests toxicity at the level of the cochlea or brainstem.

Fechter et al. (1998) exposed Long Evans rats inhalationally to 0 or 4,000 ppm TCE 6 hours/day for 5 days. Three weeks later auditory thresholds were assessed by reflex modification audiometry (n = 12), and then 5−7 weeks later, cochlear function was assessed by measuring compound action potentials (CAPs) and the cochlear microphonic response (n = 3−10). Cochlear histopathology was assessed at 5−7 weeks (n = 4) using light microscopy.

Reflex modification thresholds were significantly elevated at 8 and 18 kHz, as were CAP thresholds. The growth of the N1 evoked potential was reduced in the TCE group, and they failed to show normal N1 amplitudes even at supra-threshold tone levels. There was no effect on the sound level required to elicit a cochlear microphonic response of 1 μV. Histological data suggest that TCE produces a loss of spiral ganglion cells.

Albee et al. (2006) exposed male and female F344 rats to TCE at 250, 800, or 2,500 ppm for 6 hours/day, 5 days/week, for 13 weeks. At 2,500 ppm TCE, mild frequency-specific hearing deficits were observed, including elevated tone-pip auditory brainstem response thresholds. Focal loss of hair cells in the upper basal turn of the cochlea was observed in 2,500 ppm-exposed rats; this was apparently based upon midmodiolar sections, which lack power in quantification of hair cell death. Except for the cochleas of 2,500 ppm-exposed rats, no treatment-related lesions were noted during the neuro-histopathologic examination. The NOAEL for this study was 800 ppm based on ototoxicity at 2,500 ppm

The relationship between dose and duration of exposure with respect to producing permanent auditory impairment was presented in Crofton and Zhao (1997) and again in Boyes et al. (2000). The LOAELs identified in Long Evans rats (n = 10−12) were 6,000 ppm for a 1-day exposure, 3,200 ppm per day for both the 1- and 4-week exposures, and 2,400 ppm per day for the 13-week exposure. It was estimated from these data that the LOAEL for a 2-year long exposure would be 2,100 ppm. Auditory thresholds were determined for a 16-kHz tone 3−5 weeks after exposure using reflex modification audiometry. Results replicated previous findings of a hearing loss at 16 kHz for all exposure durations. One other conclusion reached by this study is that TCE concentration and not concentration × duration of exposure is a better predictor of auditory toxicity. That is, the notion that total exposure represented by the function, concentration (C) × time (t), or Haber's law, is not supported. Therefore, higher exposure concentrations for short durations are more likely to produce auditory impairment than are lower concentrations for more protracted durations when total dosage is equated. Thus, consideration needs to be given not only to total C × t, but also to peak TCE concentration.

Crofton and Zhao (1997) also presented a benchmark dose for which the calculated dose of TCE would yield a 15-dB loss in auditory threshold. This benchmark response was selected because a 15-dB threshold shift represents a significant loss in threshold sensitivity for humans. The benchmark concentrations for a 15-dB threshold shift are 5,223 ppm for 1 day, 2,108 ppm for 5 days, 1,418 ppm for 20 days and 1,707 ppm for 65 days of exposure. While more sensitive test methods might be used and other definitions of a benchmark effect chosen with a strong

rationale, these data provide useful guidance for exposure concentrations that do yield hearing loss in rats.

These data demonstrate that the ototoxicity of TCE was less than that predicted by a strict concentration × time relationship. These data also demonstrate that simple models of extrapolation (i.e., C × t = k, Haber's Law) overestimate the potency of TCE when extrapolating from short-duration to longer-duration exposures. Furthermore, these data suggest that, relative to ambient or occupational exposures, the ototoxicity of TCE in the rat is a high-concentration effect; however, the selection of a 15-dB threshold for detecting auditory impairment along with tests at a single auditory frequency may not capture the most sensitive reliable measure of hearing impairment.

With the exception of a single study performed in the Hartley guinea pig (n = 9−10; Yamamura et al., 1983), there are no data in other laboratory animals related to TCE-induced ototoxicity. Yamamura et al. (1983) exposed Hartley guinea pigs to TCE at doses of 6,000, 12,000, and 17,000 ppm for 4 hr/day for 5 days and failed to show an acute impairment of auditory function. However, despite the negative finding in this study, it should be considered that auditory testing was performed in the middle of a laboratory and not in an audiometric sound attenuating chamber. The influence of extraneous and uncontrolled noise on cochlear electrophysiology is marked and assesses auditory detection thresholds in such an environment unrealistic. Although the study has deficiencies, it is important to note that the guinea pig has been reported to be far less sensitive than the rat to the effects of ototoxic aromatic hydrocarbons such as toluene.

It may be helpful to recognize that the effects of TCE on auditory function in rats are quite comparable to the effects of styrene (e.g. Pryor et al., 1987; Crofton et al., 1994; Campo et al., 2006), toluene (e.g. Pryor et al., 1983; Campo et al., 1999) ethylbenzene (e.g. Cappaert et al., 1999, 2000; Fechter et al., 2007), and *p*-xylene (e.g. Pryor et al., 1987; Gagnaire et al., 2001)**.** All of these aromatic hydrocarbons produce reliable impairment at the peripheral auditory apparatus (inner ear), and this impairment is associated with death of sensory receptor cells, the outer hair cells. In comparing potency of these various agents to produce hearing loss, it appears that TCE is approximately equipotent to toluene and less potent than, in order, ethylbenzene, p-xylene, and styrene. Occupational epidemiological studies do appear to identify auditory impairments in workers who are exposed to styrene (Sliwinska-Kowalska et al., 1999; Morioka et al., 2000; Morata et al., 2002) and those exposed to toluene (Abbate et al., 1993; Morata et al., 1997), particularly when noise is also present.

D.2.2.2 Oral and Injection Studies

No experiments were identified in which auditory function was assessed following TCE administration by either oral or injection routes.

D.2.3 Vestibular System Studies

The effect of TCE on vestibular function was evaluated by either 1) promoting nystagmus (vestibular system dysfunction) and comparing the level of effort required to achieve nystagmus in the presence and absence of TCE or 2) using an elevated beam apparatus and measuring the balance. Overall, it was found that TCE disrupts vestibular function as presented below. Summary of these studies is found in Table D.2.3.

Tham et al. (1979, 1984) demonstrated disruption in the stimulated vestibular system in rabbits and Sprague Dawley rats during iv infusion with TCE. It is difficult to determine the dosage of TCE necessary to yield acute impairment of vestibular function since testing was performed under continuing infusion of a lipid emulsion containing TCE, and therefore, blood TCE levels were increasing during the course of the study. Tham et al. (1979), for example, infused TCE at doses of 1−5 mg/kg/min reaching arterial blood concentrations as high as 100 ppm. They noted increasing numbers of rabbits experiencing positional nystagmus as blood TCE levels increased. The most sensitive rabbit showed nystagmus at a blood TCE concentration of about 25 ppm. Similarly, the Sprague Dawley rats also experienced increased nystagmus with a threshold effect level of 120 ppm as measured in arterial blood (Tham et al., 1984). Animals demonstrated a complete recovery in vestibular function when evaluated for nystagmus within 5−10 minutes after the IV infusion was stopped.

Niklasson et al. (1993) showed acute impairment of vestibular function in male and female pigmented rats during acute inhalation exposure to TCE (2,700−7,200 ppm) and to trichloroethane (500−2,000 ppm). Both of these agents were able to promote nystagmus during optokinetic stimulation in a dose related manner. While there were no tests performed to assess persistence of these effects, Tham et al. (1979, 1984) did find complete recovery of vestibular function in rabbits (n = 19) and female Sprague-Dawley rats (n = 11) within minutes of terminating a direct arterial infusion with TCE solution.

The finding that trichloroethylene can yield transient abnormalities in vestibular function is not unique. Similar impairments have been shown for toluene, styrene, along with trichloroethane (Niklasson et al., 1993) and by Tham et al. (1984) for a broad range of aromatic

hydrocarbons. The concentration of TCE in blood at which effects were observed for TCE (0.9 mM/L) was quite close to that observed for most of these other vestibulo-active solvents.

D.2.4 Visual Effects

Changes in visual function have also been demonstrated in animal studies following acute (Boyes et al., 2003, 2005) and subchronic exposure (Blain et al., 1994). Summary of all TCE studies evaluating visual effects in animals can be found in Table D.2.3. In these studies, the effect of TCE on visual-evoked responses to patterns (Boyes et al., 2003, 2005; Rebert et al., 1991) or a flash stimulus (Rebert et al., 1991; Blain et al., 1994) were evaluated. Overall, the studies demonstrated that exposure to TCE results in significant changes in the visual evoked response, which is reversible once TCE exposure is stopped. Only one study (Rebert et al., 1991) did not demonstrate changes in visual system function with a subchronic TCE exposure, but visual testing was conducted 10 hours after each exposure.

Boyes et al. (2003, 2005) found significant reduction in the visual evoked potential acutely while Long Evans male rats were being exposed to TCE concentrations of 500, 1,000, 2,000, 3,000, 4,000, and 5,000 ppm for intervals ranging from 4 to 0.5 hr, respectively. In both instances, the degree of effect correlated more with brain TCE concentrations than with duration of exposure.

Boyes et al. (2003) exposed adult, male Long-Evans rats to TCE in a head-only exposure chamber while pattern onset/offset visual evoked potentials (VEPs) were recorded. Exposure conditions were designed to provide C × t products of 0 ppm/h (0 ppm for 4 h) or 4,000 ppm/h created through four exposure scenarios: 1,000 ppm for 4 h; 2,000 ppm for 2 h; 3,000 ppm for 1.3 h; or 4,000 ppm for 1h (n = 9−10/concentration). Blood TCE concentrations were assessed by GC with ECD, and brain TCE concentrations were estimated using a PBPK model. The amplitude of the VEP frequency double component (F2) was decreased significantly ($p < 0.05$) by exposure. The mean amplitude (+/- SEM in μV) of the F2 component in the control and treatment groups measured 4.4 +/- 0.5 (0 ppm/4 h), 3.1 +/- 0.5 (1,000 ppm/4 h), 3.1 +/- 0.4 (2,000 ppm/2 h), 2.3 +/- 0.3 (3,000 ppm/1.3 h), and 1.9 +/- 0.4 (4,000 ppm/1 h). A PBPK model was used to estimate the concentrations of TCE in the brain achieved during each exposure condition. The F2 amplitude of the VEP decreased monotonically as a function of the estimated peak brain concentration but was not related to the area under the curve (AUC) of the brain TCE concentration. These results indicate that an estimate of the brain TCE concentration at the time of VEP testing predicted the effects of TCE across exposure concentrations and duration.

In a follow-up study, Boyes et al. (2005) exposed Long Evans male rats (n = 8−10/concentration) to TCE exposures of 500 ppm for 4 hr, 1,000 ppm for 4 hr, 2,000 ppm for 2 hr, 3,000 ppm for 1.3 hr, 4,000 ppm for 1 hr and 5,000 ppm for 0.8 hr. VEP recordings were made at multiple time points, and their amplitudes were adjusted in proportion to baseline VEP data for each subject. VEP amplitudes were depressed by TCE exposure during the course of TCE exposure. The degree of VEP depression showed a high correlation with the estimated brain TCE concentration for all levels of atmospheric TCE exposure.

This transient effect of TCE on the peripheral visual system has also been reported by Blain (1994) in which New Zealand albino rabbits were exposed by inhalation to 350 and 700 ppm TCE 4 hrs/day, 4 days/week for 12 weeks. Electroretinograms (ERGs) and oscillatory potentials (OPs) were recorded weekly under mesopic conditions. Recordings from the 350 and 700 ppm exposed groups showed a significant increase in the amplitude of the a- and b-waves (ERG). The increase in the a-wave was dose related increasing 30% at the low dose and 84% in the high dose. For the b-wave, the lower exposure dose yielded a larger change from baseline (52%) than did the high dose (33%). The amplitude of the OPs was significantly decreased at 350 ppm (57%) and increased at 700 ppm (117%). The decrease in the OP shown in the low dose group appears to be approximately 25% from 9−12 weeks of exposure. These electroretinal changes were reversed to the baseline value within 6 weeks after the inhalation stopped.

Rebert et al. (1991) evaluated visual evoked potentials (flash evoked potentials and pattern reversal evoked potentials) in male Long Evans rats that received 1,600 or 3,200 ppm TCE for 3 weeks 12 hours/day. No significant changes in flash evoked potential measurements were reported following this exposure paradigm. Limited shifts in pattern reversal visual evoked potentials were reported during subchronic exposure, namely a reduction in the N1-P1 response amplitude that reached statistical significance following 8, 11, and 14 weeks of exposure. The drop in response amplitude ranged from approximately 20% after 8 weeks to nearly 50% at week 14. However, this potential recovered completely during the recovery period.

D.2.5 Cognitive function

There have been a number of reports (e.g. Kjellstrand et al.,1980; Kulig, 1987; Kishi et al., 1993) showing alteration in performance in learning tasks such as a change in speed to complete the task, but little evidence that learning and memory function are themselves impaired by exposure. Table D.2.4 presents the study summaries for animal studies evaluating cognitive effects following TCE exposure. Such data are important in efforts to evaluate the functional

significance of decreases in myelinated fibers in the hippocampus reported by Isaacson et al. (1990) and disruption of long-term potentiation discovered through *in vitro* testing (Ohta et al., 2001) since the hippocampus has been closely tied to memory formation.

Kjellstrand et al. (1980) exposed Mongolian gerbils (*n* = 12/sex**)** to 900 ppm TCE by inhalation for 9 months. Inhalation was continuous except for 1−2 hr/week for cage cleaning. Spatial memory was tested using the radial arm maze task. In this task, the gerbils had to visit each arm of the maze and remember which arm was visited and unvisited in selecting an arm to visit. The gerbils received training and testing in a radial arm maze starting after 2 months of TCE exposure. There was no effect of TCE on learning or performance on the radial arm maze task.

Kishi et al. (1993) acutely exposed Wistar rats to TCE at concentrations of 250, 500, 1,000, 2,000, and 4,000 ppm for 4 hours. Rats were tested on an active (light) signaled shock avoidance operant response. Rats exposed to 250 ppm TCE showed a significant decrease both in the total number of lever presses and in avoidance responses at 140 minutes of exposure compared with controls. The rats did not recover their pre-exposure performance until 140 minutes after the exhaustion of TCE vapor. Exposures in the range 250 to 2,000 ppm TCE for 4 hours produced concentration related decreases in the avoidance response rate. No apparent acceleration of the reaction time was seen during exposure to 1,000 or 2,000 ppm TCE. The latency to a light signal was somewhat prolonged during the exposure to 2,000 to 4,000 ppm TCE. It is estimated that there was depression of the central nervous system with slight performance decrements and the corresponding blood concentration was 40 micrograms/mL during exposure. Depression of the central nervous system with anesthetic performance decrements was produced by a blood TCE concentration of about 100 micrograms/mL. In general, they observed dose related reductions in total number of lever presses, but these changes may be more indicative of impaired motor performance than of cognitive impairment. In any event, recovery occurred rapidly once TCE exposure ceased.

Isaacson et al. (1990) studied the effects of oral TCE exposure in weanling rats at exposure doses of 5.5 mg/day for 4 weeks, followed by an additional 2 weeks of exposure at 8.5 mg/day. No significant changes were observed in locomotor activity in comparison to the control animals. This group actually reported improved performance on a Morris swim test of spatial learning as reflected in a decrease in latency to find the platform from 14 sec in control subjects to 12 sec in the lower dose TCE group to a latency of 9 sec in the higher TCE group. The high dose TCE group differed significantly from the control and low TCE dose groups while

these latter two groups did not differ significantly from each other. This improvement relative to the control subjects occurred despite a loss in hippocampal myelination, which approached 8% and was shown to be significant using Duncan's multiple range test.

Likewise, Umezu et al. (1997) exposed ICR strain male mice acutely to doses of TCE ranging from 62.5−1,000 mg/kg depending upon the task. They reported a depressed rate of operant responding in a conditioned avoidance task that reached significance with ip injections of 1,000 mg/kg. Increased responding during the signaled avoidance period at lower doses (250 and 500 mg/kg) suggests an impairment in ability to inhibit responding or failure to attend to the signal. However, all testing was performed under TCE intoxication.

D.2.6 Psychomotor Effects

Changes in psychomotor activity such as loss of righting reflex, functional observational battery changes, and locomotor activity have been demonstrated in animals following exposure to TCE. Summaries for some of these studies can be found below and are presented in detail in Table D.2.5.

D.2.6.1 Loss of righting reflex

Kishi et al. (1993) evaluated the activity and performance of male Wistar rats in a series of tasks following an acute 4-hr exposure to 250, 500, 1,000, 2,000, and 4,000 ppm. They reported disruption in performance at the highest test levels with CNS depression and anesthetic performance decrements. Blood TCE concentrations were about 100 µg/mL in Wistar rats (such blood TCE concentrations were obtained at inhalation exposure levels of 2,000 ppm).

Umezu et al. (1997) studied disruption of the righting reflex following acute injection of 250, 500, 1,000, 2,000, 4000, and 5,000 mg/kg TCE in male ICR mice. At 2,000 mg/kg, loss of righting reflex (LORR) was observed in only 2/10 animals injected. At 4,000 mg/kg – 9/10 animals experienced LORR, and 100% of the animals experienced LORR at 5,000 mg/kg. Shih et al. (2001) reported impaired righting reflexes at exposure doses of 5,000 mg/kg in male Mf1 mice although lower exposure doses were not included. They showed, in addition, that pretreatment prior to TCE with DMSO or disulfiram (which is a CYP2E1 inhibitor) in DMSO could delay loss of the righting reflex in a dose related manner. By contrast, the alcohol dehydrogenase inhibitor, 4-metylpyradine did not delay loss of the righting reflex that resulted from 5,000 mg/kg TCE. These data suggest that the anesthetic properties of TCE involve its oxidation via CYP2E1 to an active metabolite, a finding that is consistent with the anesthetic properties of chloral hydrate.

D.2.6.2 Functional Observational Battery (FOB) and Locomotor Activity Studies

D.2.6.2.1 FOB and locomotor activity studies with TCE

A number of papers have measured locomotor activity and used functional observational batteries (FOBs) in order to obtain a more fine grained analysis of the motor behaviors that are impaired by TCE exposure. While exposure to TCE has been shown repeatedly to yield impairments in neuromuscular function acutely, there is very little evidence that the effects persist beyond termination of exposure.

One of the most extensive evaluations of TCE on innate neurobehavior was conducted by Moser et al. (1995, 2003) using functional observational battery (FOB) testing procedures. Moser et al. (1995) evaluated the effects of acute and subacute (14-day) oral gavage administration of TCE in adult female Fischer 344 rats. Testing was performed both 4 hr post TCE administration and 24 hr after TCE exposure, and a comparison of these two time points along with comparison between the first day and the last day of exposure provides insight into the persistence of effects observed. Various outcome measures were grouped into five domains: autonomic, activity, excitability, neuromuscular, and sensorimotor. Examples of tests included in each of these groupings are as follows: Autonomic—lacrimation, salivation, palpebral closure, pupil response, urination, and defecation; Activity—rearing, motor activity counts home cage position. Excitability—ease of removal, handling reactivity, arousal, clonic, and tonic movements; and Neuromuscular—gait score, righting reflex, fore and hindlimb grip strength, and landing foot splay. Sensorimotor-tail-pinch response, click response, touch response, and approach response. Scoring was performed on a 4-point scale ranging from "1" (normal) to "4" (rare occurrence for control subjects). In the acute exposure, the exposure doses utilized were 150, 500, 1,500, and 5,000 mg/kg TCE in corn oil. These doses represent 3, 10, 30, and 56% of the limit dose. For the 14-day subacute exposure, the doses used were 50, 150, 500, and 1,500 mg/kg. Such doses represent 1, 3, 10, and 30% of the limit dose for TCE.

The main finding for acute TCE administration is that a significant reduction in activity level occurred after the highest dose of TCE (5,000 mg/kg) only. This effect showed substantial recovery 24 hr after exposure though residual decrements in activity were noted. Neuromuscular function as reflected in the gait score was also severely affected only at 5,000 mg/kg dose and only at the 4-hr test period. Sensorimotor function reflected in response to a sudden click, was abnormal at both 1,500 and 5,000 mg/kg with a slight difference observed at 1,500 mg/kg and a robust difference apparent at 5,000 mg/kg. Additional effects noted, but not shown quantitatively were abnormal home-cage posture, increased landing foot splay, impaired righting

and decreased fore and hind limb grip strength. It is uncertain at which doses such effects were observed.

With the exception of sensorimotor function, these same categories were also disrupted in the subacute TCE administration portion of the study. The lack of effect of TCE on sensorimotor function with repeated TCE dosing might reflect either habituation, tolerance, or an unreliable measurement at one of the time points. Given the absence of effect at a range of exposure doses, a true dose-response relationship cannot be developed from these data.

In the subacute study, there are no clearly reliable dose-related differences observed between treated and control subjects. Rearing, a contributor to the activity domain, was elevated in the 500-mg/kg dose group, but was normal in the 1,500-mg/kg group. The neuromuscular domain was noted as significantly affected at 15 days, but it is not clear which subtest was abnormal. It appears that the limited group differences may be random among subjects unrelated to exposure condition.

In a follow-up study, Moser et al. (2003) treated female Fischer 344 rats with TCE by oral gavage for periods of 10 days at doses of 0, 40, 200, 800, and 1,200 mg/kg/day, and testing was undertaken either 4 hr following the first or 10^{th} dose as well as 24 hr after these two time points. The authors identified several significant effects produced by TCE administration including a decrease in motor activity, tail pinch responsiveness, reactivity to handling, hind limb grip strength, and body weight. Rats administered TCE also showed significantly more piloerection, higher gait scores, lethality, body weight loss, and lacrimation compared to controls. Only effects observed 4 hours after the 10^{th} exposure dose were presented by the authors, and no quantitative information of these measurements is provided.

Albee et al. (2006) exposed male and female Fischer 344 rats to 250, 800, and 2,500 ppm TCE for 6 hr/day, 5 days/week for 13 weeks. FOB was performed 4 days prior to exposure and then monthly. Auditory impairments found by others (e.g., Muijser et al., 2000; Rebert et al., 1995; Crofton et al., 1994; Crofton and Zhao, 1997; Fechter et al., 1998; Boyes et al., 2000) were replicated at the highest exposure dose, but treatment related differences in grip strength or landing foot splay were not demonstrated. The authors report slight increases in handling reactivity among female rats and slightly more activity than in controls at an intermediate time point, but apparently did not conduct systematic statistical analyses of these observations. In any event, there were no statistically significant effects on activity or reactivity by the end of exposure

Kulig (1987) also failed to show significant effects of TCE inhalation exposure on markers of motor behavior. Wistar rats exposed to 500, 1,000, and 1,500 ppm for 16 hr/day, 5 days/week for 18 weeks failed to show changes in spontaneous activity, grip strength, or coordinated hind limb movement. Measurements were made every three weeks during the exposure period and occurred between 45 min and 180 min following the previous TCE inhalation exposure. This study establishes a NOAEL of 1,500 ppm TCE with an exposure duration of 16 hr/day.

D.2.6.2.2 Acute and subacute oral exposure to dichloroacetic acid on FOB

Moser et al. (1999) conducted a series of experiments on dichloroacetic acid (DCA) ranging from acute to chronic exposures. The exposure doses used in the acute experiment were 100, 300, 1,000, and 2,000 mg/kg. In the repeated exposure studies (8 week−24 months), doses varied between 16 and 1,000 mg/kg/day. The authors showed pronounced neuromuscular changes in Long Evans and F344 rats dosed orally with the TCE metabolite, dichloroacetic acid (DCA), over a period ranging from 9 weeks to 24 months at different exposure doses. Using a multitude of exposure protocols which most commonly entailed daily exposures to DCA either by gavage or drinking water the authors identify effects that were "mostly limited" to the neuromuscular domain. These included disorders of gait, grip strength, foot splay and righting reflex that are dose and duration dependent. Data on gait abnormality and grip strength are presented in greatest detail. In adults exposed to DCA by gavage, gait scores were "somewhat abnormal" at the 7 week test in both the adult Long Evans rats receiving 300 and those receiving 1,000 mg/kg-day. There was no adverse effect in the rats receiving 100 mg/kg-day. In the chronic study, which entailed intake of DCA via drinking water yielding an estimated daily dose of 137 and 235 mg/kg-day "moderately to severely abnormal" gait was observed within 2 months of exposure and dosing was either reduced or discontinued because of the severity of toxicity. For the higher DCA dose, gait scores remained "severely abnormal" at the 24 month test time even though the DCA had been discontinued at the 6 month test time. Hindlimb grip strength was reduced to about ½ the control value in both exposure doses and remained reduced throughout the 24 months of testing even though DCA administration ceased at 6 months for the 235 mg/kg-day group. Forelimb grip strength showed a smaller and apparently reversible effect among DCA treated rats.

D.2.6.3 Locomotor activity

Wolff and Siegmund (1978) administered 182 mg/kg TCE (i.p.) in AB mice and observed a decrease in spontaneous locomotor activity. In this study, AB mice were injected

with TCE 30 minutes prior to testing for spontaneous activity at one of 4 time points during a 24 hr/day (0600, 1200, 1800, and 2400 hours). Marked decreases (estimated 60−80% lower than control mice) in locomotor activity were reported in 15 min test periods. The reduction in locomotion was particularly profound at all time intervals save for the onset of light (0600). Nevertheless, even at this early morning time point, activity was markedly reduced from control levels (60% lower than controls as approximated from a graph.

Moser et al. (1995, 2003) included locomotor activity as one of their measures of neurobehavioral effects of TCE given by gavage over a 10−14 day period. In the 1995 paper, female Fischer 344 rats were dosed either acutely with 150, 500, 1,500 or 5,000mg/kg TCE or for 14 days with 50, 150, 500 or 1,500 mg/kg. In terms of the locomotor effects, they report that acute exposure produced impaired locomotor scores only at 5,000 mg/kg while in the subacute study, locomotion was impaired at the 500 mg/kg dose, but not at the 1,500 mg/kg dose. In the Moser (2003) study, it appears that 200 mg/kg TCE may actually have increased locomotor activity while the higher test doses (800 and 1,200 mg/kg) decreased activity in a dose related manner. What is common to both studies, however, is a depression in motor activity that occurs acutely following TCE administration and which may speak to the anesthetic if not central nervous system depressive effects of this solvent.

There are also a number of reports (Waseem et al., 2001; Fredriksson et al., 1993; Kulig, 1987) that failed to demonstrate impairment of motor activity or ability following TCE exposure. Waseem et al. (2001) failed to show effects of TCE given in the drinking water of Wistar rats over the course of a 90 day trial. While nominal solvent levels were 350, 700, and 1,400 ppm in the water, no estimate is provided of daily TCE intake or of the stability of the TCE solution over time. However, assuming a daily water intake of 25 mL/day and body weight of 330 g, these exposures would be estimated to be approximately 26, 52, and 105 mg/kg. These doses are far lower than those studied by Moser and colleagues.

Fredriksson et al. (1993) studied the effects of TCE given by oral gavage to male NMRI mice at doses of 50 and 290 mg/kg/day from postnatal day 10−16 on locomotion assessed either on the day following exposure or at age 60 days. They found no significant effect of TCE on locomotor activity and no consistent effects on other motor behaviors (e.g. rearing).

Waseem et al. (2001) studied locomotor activity in Wistar rats exposed for up to 180 days to 376 ppm TCE by inhalation for 4 h/day, 5 days/week and acutely intoxicated with TCE. Here the authors report seemingly inconsistent effects of TCE on locomotion. After 30 days of exposure, the treated rats show an increase in locomotor activity relative to control subjects.

However, after 60 days of exposure they note a significant *increase* in distance traveled found among experimental subjects, but a decrease in horizontal activity in this experimental group. Moreover, the control subjects vary substantially in horizontal counts among the different time periods. No differences between the treatment groups are found after 180 days of exposure. It is difficult to understand the apparent discrepancy in results reported at 60 days of exposure.

D.2.7 Sleep and Mood Disorders

D.2.7.1 Effects on Mood: Laboratory animal findings

It is difficult to obtain comparable data of emotionality in laboratory studies. However, Moser et al. (2003) and Albee et al. (2006) both report increases in handling reactivity among rats exposed to TCE. In the Moser study, female Fischer 344 rats received TCE by oral gavage for periods of 10 days at doses of 0, 40, 200, 800, and 1,200 mg/kg-day while Albee et al. (2006) exposed Fischer 344 rats to TCE by inhalation at exposure doses of 250, 800, and 2,500 ppm for 6 hr/day, 5 days/week for 13 weeks.

D.2.7.2 Sleep Disturbances

Arito et al. (1994) exposed male Wistar rats to 50, 100, and 300 ppm TCE for 8 hour/day, 5 days/week for 6 weeks and measured electroencephalographic (EEG) responses. EEG responses were used as a measure to determine the number of awake (wakefulness hours) and sleep hours. Exposure to all the TCE levels significantly decreased amount of time spent in wakefulness (W) during the exposure period. Some carry over was observed in the 22 hr post exposure period with significant decreases in wakefulness seen at 100 ppm TCE. Significant changes in wakefulness-sleep elicited by the long-term exposure appeared at lower exposure levels. These data seem to identify a low dose of TCE that has anesthetic properties and established a LOAEL of 50 ppm for sleep changes.

D.2.8 Mechanistic Studies

D.2.8.1 Dopaminergic Neurons

In two separate animal studies, subchronic administration of TCE has resulted in a decrease of DA cells in both rats and mice. Although the mechanism for DA neurons resulting from TCE exposure is not elucidated, disruption of DA-containing neurons has been extensively studied with respect to Parkinson's Disease and parkinsonism. In addition to Parkinson's Disease, significant study of MPTP and of high-dose manganese toxicity provides strong evidence for extrapyramidal motor dysfunction accompanying loss of dopamine neurons in the

substantia nigra. These databases may provide useful comparisons to the highly limited database with regard to TCE and dopamine neuron effects. The studies are presented in Table D.2.6.

Gash et al. (2007) assessed the effects of subchronic TCE administration on dopaminergic neurons in the central nervous system. Fischer 344 male rats were orally administered by gavage 1,000 mg/kg TCE in olive oil, 5 days/week for 6 weeks. Degenerative changes in DA containing neurons in the substantia nigra were reported as indexed by a 45% decrease in the number of tyrosine hydroxylase positive cells. Additionally, there was a decrease in the ratio of 3,4-dihydroxyphenylacetic acid (DOPAC), a metabolite of DA, to DA levels in the striatum. This shift in ratio, on the order of 35%, was significant by Students t test, suggesting a decrease in release and utilization of this neurotransmitter. While it is possible that long-term adaptation might occur with regard to release rates for DA, the loss of DA cells in the substantia nigra is viewed as a permanent toxic effect. The exposure level used in this study was limited to one high dose and more confidence in the outcome will depend upon replication and development of a dose-response relationship. If the results are replicated, they might be important in understanding mechanisms by which TCE produces neurotoxicity in the central nervous system. The functional significance of such cellular loss has not yet been determined through behavioral testing.

Guehl (1999) also reported persistent effects of TCE exposure on DA neurons. In this study, OF1 male mice (n = 10) were injected ip daily for 5 days/week for 4 weeks with TCE (400 mg/kg/day). Following a 7 day period when the subjects did not receive TCE, the mice were euthanized and tyrosine hydroxylase immunoreactivity was used to measure neuronal death in the substantia nigra pars compacta. Treated mice presented significant dopaminergic neuronal death (50%) in comparison with control mice based upon total cell counts conducted by an examiner blinded as to treatment group in six samples per subject. The statistical comparison appears to be by Students t test (only means, standard deviations, and a probability of $p < 0.001$ are reported). While this study appears to be consistent with that of Gash et al. (2007) there are some limitations of this study. Specifically, no photomicrographs are provided to assess adequacy of the histopathological material. Additionally, no dose response data are available to characterize dose-response relationships or identify either a benchmark dose or NOAEL. Behavioral assessment aimed at determining functional significance was not determined.

The importance of these two studies suggesting death of dopaminergic neurons following TCE exposure may be addressable by human health studies because they suggest the potential for TCE to produce a parkinsonian syndrome.

D.2.8.2 GABA and Glutamatergic neurons

Disruption of GABAergic and glutamatergic neurons by toxicants can represent serious impairment as GABA serves as a key inhibitory neurotransmitter while glutamate is equally important as an excitatory neurotoxicant. Moreover, elevations in glutamatergic release have been identified as an important process by which more general neurotoxicity can occur through a process identified as excitotoxicity. The data with regard to TCE exposure and alteration in GABA and glutamate function is limited. The studies are presented in Table D.2.7.

Briving et al. (1986) conducted a chronic inhalation exposure in Mongolian gerbils to 50 and 150 ppm TCE continuously for 12 months and reported the changes in amino acids levels in the hippocampus and cerebellar vermis and on high affinity uptake of GABA and glutamate in those same structures. A dose related elevation of glutamine in the hippocampus of approximately 20% at 150 ppm was reported, but no other reliable changes in amino acids in either of these two structures. With regard to high affinity uptake of glutamate and GABA, there were no differences in the hippocampal uptake between control and treated gerbils although in the cerebellar vermis there was a dose related elevation in the high affinity uptake for both of these neurotransmitter. Glutamate uptake was increased about 50% at 50 ppm and 100% at 150 ppm. The corresponding increases for GABA were 69% and 74%. Since control tissue uptake is identified as being 100% rather than as an absolute rate, the ability to assess quality of the control data is limited. It is unclear if this finding in cerebellar vermis is also present in other brain tissues and should be studied further. If these findings are reliable, the changes in high affinity uptake in cerebellum for GABA and glutamate might represent alterations that could have functional outcomes. For example, alteration in GABA release and reuptake from the cerebellum might be consistent with acute alteration in vestibular function described below. However, there are presently no compelling data to support such a relationship.

The change in hippocampal glutamine levels is not readily interpretable. What is not clear from this paper is whether the alterations observed were acute effects observable only while subjects were intoxicated with TCE or whether they would persist once TCE had been removed from the neural tissue. This study used inhalation doses that were at least 1 order of magnitude lower than those required to produce auditory impairment.

A study by Shih et al. (2001) provides indirect evidence in male Mf1 mice that TCE exposure by injection might alter GABAergic function. The mice were injected ip with 250, 500, 1,000 and 2,000 mg/kg TCE in corn oil and the effect of these treatments on susceptibility to seizure induced by a variety of drugs was observed. Shih et al. report that doses of TCE as low as 250 mg/kg could reduce signs of seizure induced by picrotoxin, bicuculline, and pentylenetetrazol. These drugs are all GABAergic antagonists. TCE treatment had a more limited effect on seizure threshold induced by non-GABAergic convulsant drugs such as strychnine (glycine receptor antagonist), 4-aminopyridine (alcohol dehydrogenase inhibitor) and N-methyl-d-aspartate (glutamatergic agonist) than was observed with the GABAergic antagonists. While these data suggest the possibility that TCE could act at least acutely on GABAergic neurons, there are no direct measurements of such an effect. Moreover, there is no obvious relationship between these findings and those of Briving et al. (1986) with regard to increased high affinity uptake of glutamate and GABA in cerebellum. Beyond that fact, this study does not provide information regarding persistent effects of TCE on either seizure susceptibility or GABAergic function as all measurements were made acutely shortly following a single injection of TCE.

D.2.8.3 Demyelination following TCE exposure

Because of its anesthetic properties and lipophilicity, it is hypothesized that TCE may disrupt the lipid-rich sheaths that cover many central and peripheral nerves. This issue has also been studied both in specific cranial nerves known to be targets of TCE neurotoxicity (namely the trigeminal nerve) and in the central nervous system including the cerebral cortex, hippocampus and cerebellum in particular. For peripheral and cranial nerves, there are limited nerve conduction velocity studies that are relevant as a functional measure. For central pathways, the most common outcomes studied include histological endpoints and lipid profiles.

A significant difficulty in assessing these studies concerns the permanence or persistence of effect. There is a very large literature unrelated to TCE, which demonstrates the potential for repair of the myelin sheath and at least partial if not full recovery of function. In the studies where nerve myelin markers are assessed, it is not possible to determine if the effects are transient or persistent.

There are two published manuscripts (Isaacson and Taylor, 1989; Isaacson et al., 1990) that document selective hippocampal histopathology when Sprague Dawley rats are exposed to TCE within a developmental model. Both of these studies employed oral TCE administration

via the drinking water. In Isaacson and Taylor, (1989), a combined prenatal and neonatal exposure was used while Isaacson's et al. (1990) report focused on a neonatal exposure. In addition, Ohta et al. (2001) presented evidence of altered hippocampal function in an *in vitro* preparation following acute *in vivo* TCE intoxication. The latter most manuscript details a shift in long term potentiation elicited by tetanic shocks to hippocampal slices *in vitro*. In the two developmental studies the exposure doses are expressed in terms of the concentration of TCE placed in the drinking water and the total daily dose is then estimated based upon average water intake by the subjects. However, since the subjects' body weight is not provided, it is not possible to estimate dosage on a mg/kg body weight basis.

Isaacson and Taylor (1989) examined the development of the hippocampus in neonatal rats that were exposed in utero and in the preweaning period to TCE via their dam. TCE was added to the drinking water of the dam and daily maternal doses are estimated based upon water intake of the dam as being 4 and 8.1 mg/day. Based upon body weight norms for 70 day old female Sprague Dawley rats, which would predict body weights of about 250 g at that age, such a dose might approach 16−32 mg/kg/day initially during pregnancy. Even if these assumptions hold true, it is not possible to determine how much TCE was received by the pups although the authors do provide an estimate of fetal exposure expressed as μg/mL of TCE, trichloroethanol, and trichloroacetic acid. The authors reported a 40% decline in myelinated fibers in the CA1 region of the hippocampus of the weanling rats. There was no effect of TCE treatment on myelination in several other brain regions including the internal capsule, optic tract or fornix and this effect appears to be restricted to the CA1 region of the hippocampus at the tested exposures.

In a second manuscript by that group (Isaacson et al., 1990), weanling rats were exposed to TCE via their drinking water at doses of 5.5 mg/day for 4 weeks or 5.5 mg/day for 4 weeks, a 2 week period with no TCE and then a final 2 weeks of exposure to 8.5 mg/day TCE. Spatial learning was studied using the Morris water maze and hippocampal myelination was examined histologically starting 1 day post exposure. The authors report that the subjects receiving a total of 6 weeks exposure to TCE showed *better* performance in the Morris swim test ($p < .05$) than did controls while the 4 week exposed subjects performed at the same level as did controls. Despite this apparent improvement in performance, histological examination of the hippocampus demonstrated a dose dependent relationship with hippocampal myelin being significantly reduced in the TCE exposed groups while normal myelin patterns were found in the internal capsule, optic tract and fornix. The authors did not evaluate the signs of gross toxicity in treated animals such as growth rate, which might have influenced hippocampal development.

Ohta et al. (2001) administered 300 or 1,000 mg/kg TCE, i.p., to male ddY mice. Twenty-four hours after TCE administration, the mice were sacrificed and hippocampal sections were prepared from the excised brains and long term potentiation was measured in the slices. A dose related reduction in the population spike was observed following a tetanic stimulation relative to the size of the population spike elicited in the TCE mice prior to tetany. The spike amplitude was reduced 14% in the 300 mg/kg TCE group and 26% in the 1,000 mg/kg group. Precisely how such a shift in excitability of hippocampal CA1 neurons relates to altered hippocampal function is not certain, but it does demonstrate that injection with 300 mg/kg TCE can have lingering consequences on the hippocampus at least 24 hr following ip administration.

A critical area for future study is the potential that TCE might have to produce demyelination in the central nervous system. While it is realistic to imagine that an anesthetic and lipophilic agent such as TCE might interact with lipid membranes and produce alterations, for example, in membrane fluidity at least at anesthetic levels, the data collected by Kyrklund and colleagues suggest that low doses of TCE (50 and 150 ppm chronically for 12 months, 320 ppm for 90 days, 510 ppm 8 hr/day for 5 months) might alter fatty acid metabolism in Sprague Dawley rats and Mongolian gerbils. Because they have not included high doses in their studies and because the low doses produce only sporadic significant effects and these tend to be of very small magnitude (5−10%) it is not certain that they are truly observing events with biological significance or whether they are observing random effects. A key problem in determining whether the effects under study are spurious or are due to ongoing exposure is that the magnitude and direction of the effect does not grow larger as exposure continues. It could be hypothesized that the alterations in fatty acid metabolism could be an underlying mechanism for demyelination. However, there is not enough evidence to determine if the changes in the lipid profiles lead to demyelination or if the observed effects are purely due to chance. Similarly, the size of statistically significant effects (5−12%) is generally modest. A broad dose response analysis or the addition of a positive control group that is treated with an agent well-known to produce central demyelination would be important in order to characterize the potency of TCE as an agent that disrupts central nervous system lipid profiles.

Kyrklund and colleagues (e.g. 1986) have generally evaluated the hippocampus, cerebral cortex, cerebellum, and in some instances brainstem in adult gerbil. It is not apparent that one brain region is more vulnerable to the effects of TCE than is another region. While this group does not report significant changes in levels of cholesterol, neutral and acidic phospholipids or total lipid phospholipids, they do suggest a shift in lipid profiles between treated and untreated subjects. Similarly, inhalation exposure to trichloroethane at 1,200 ppm for 30 days (Kyrklund

and Haglid, 1991) leads to sporadic changes in fatty acid profiles in Sprague Dawley rats. However, these changes are small and are not always in the same direction as the changes observed following trichloroethylene exposure In the case of trichloroethane, a NOAEL of 320 ppm for 30 days 24 hr/day was observed and no other doses were evaluated (Kyrklund et al., 1988).

D.2.7 Summary Tables

Table D.2.1 Summary of mammalian *in vivo* trigeminal nerve studies

Reference	Exposure route	Species/strain/ sex/number	Dose level/ Exposure duration	NOAEL; LOAEL a	Effects
Barret et al., 1991	Direct Gastric Administration	Rat, Sprague-Dawley, female, 21	0, 2.5 g/kg, acute administration	LOAEL: 2.5 g/kg	Morphometric analysis was used for analyzing the trigeminal nerve. Increase in external and internal fiber diameter as well as myelin thickness was observed in the trigeminal nerve after TCE treatment.
Barret et al., 1992	Direct Gastric Administration	Rat, Sprague-Dawley, female, 18	0, 2.5 g/kg; 1 dose/day, 5 days/wk, 10 wks	LOAEL: 2.5 g/kg	Trigeminal nerve analyzed using morphometric analysis. Increased internode length and fiber diameter in class A fibers of the trigeminal nerve observed with TCE treatment. Changes in fatty acid composition also noted.
Albee et al., 2006	Inhalation	Rat, Fischer 344, male and female, 10/sex/group	0, 250, 800, 2,500 ppm	NOAEL: 2,500 ppm	No effect on trigeminal nerve function was noted at any exposure level

a NOAEL (No Observed Adverse Affect Level), LOAEL (Lowest Observed Adverse Affect Level)

Table D.2.2 Summary of mammalian *in vivo* otoxicity studies

Reference	Exposure route	Species/strain/ sex/number	Dose level/ Exposure duration	NOAEL; LOAEL a	Effects
Rebert et al., 1991	Inhalation	Rat, Long Evans, male, 10/group	Long Evans: 0, 1,600, 3,200 ppm; 12 hr/day, 12 weeks	Long Evans: NOAEL: 1,600 ppm; LOAEL: 3,200 ppm	BAERs were measured. Significant decreases in BAER amplitude and an increase in latency of appearance of the initial peak (P1).
		Rat, F344, male, 4−5/group	F344: 0, 2000, 3200 ppm; 12 hr/day, 3 weeks	F344: LOAEL: 2,000 ppm	
Rebert et al., 1993		Rat, Long Evans, male, 9/group	0, 2,500, 3,000, 3,500 ppm; 8 hr/day, 5 days	NOAEL: 2,500 ppm LOAEL: 3,000 ppm	Brainstem auditory evoked responses (BAERs) were measured 1−2 weeks post-exposure to assess auditory function. Significant decreases in BAERs were noted with TCE exposure.
Rebert et al., 1995		Rat, Long Evans, male, 9/group	0, 2,800 ppm; 8 hr/day, 5 days	LOAEL: 2,800 ppm	BAER measured 2−14 days post-exposure at a 16 kHz tone. Hearing loss ranged from 55−85 dB.
Crofton et al., 1994		Rat, Long Evans, male, 7−8/group	0, 3,500 ppm TCE; 8 hr/day, 5 days	LOAEL: 3,500 ppm	BAER measured and auditory thresholds determined 5−8 weeks post-exposure. Selective impairment of auditory function for mid-frequency tones (8 and 16 kHz)
Crofton and Zhao, 1997; Boyes et al., 2000	Inhalation	Rat, Long Evans, male, 9−12/group	0, 4,000, 6,000, 8,000 ppm; 6 hours	NOAEL: 6,000 ppm LOAEL: 8,000 ppm	Auditory thresholds as measured by BAERs for the 16 kHz tone increased with TCE exposure.
		Rat, Long Evans, male, 8−10/group	0, 1,600, 2,400, 3,200 ppm; 6 hr/day, 5 days	NOAEL: 2,400 ppm LOAEL: 3,200 ppm	
		Rat, Long Evans, male, 8−10/group	0, 800, 1,600, 2,400, 3,200 ppm; 6 hr/day, 5 days/wk, 4 weeks	NOAEL: 2,400 ppm LOAEL: 3,200 ppm	
		Rat, Long Evans, male, 8−10/group	0, 800, 1,600, 2,400, 3,200 ppm; 6 hr/day, 5 days/wk, 13 weeks	NOAEL: 1,600 ppm LOAEL: 2,400 ppm	

Fechter et al., 1998	Inhalation	Rat, Long Evans, male, 12/group	0, 4,000 ppm; 6 hr/day, 5 days	LOAEL: 4,000 ppm	Cochlear function measured 5−7 weeks after exposure. Loss of spiral ganglion cells noted. Auditory function was significantly decreased as measured by compound action potentials.
Jaspers et al., 1993	Inhalation	Rat, Wistar derived WAG-Rii/MBL, male, 12/group	0, 1,500, 3,000 ppm; 18 hr/day, 5 days/week, 3 wks	LOAEL: 1,500 ppm	Auditory function assessed repeatedly 1−5 weeks post-exposure for 5, 20, and 35 kHz tones; No effect at 5 or 35 kHz; Decreased auditory sensitivity at 20 kHz
Muijser et al., 2000	Inhalation	Rat, Wistar derived WAG-Rii/MBL, male, 8	0, 3,000 ppm	LOAEL: 3,000 ppm	Auditory sensitivity decreased with TCE exposure at 4, 8, 16, and 20 kHz tones
Albee et al., 2006	Inhalation	Rat, Fischer 344, male and female, 10/sex/group	0, 250, 800, 2,500 ppm	NOAEL: 800 ppm LOAEL: 2,500 ppm	Mild frequency specific hearing deficits; Focal loss of hair cells and cochlear lesions.
Yamamura et al., 1983	Inhalation	Guinea Pig, albino Hartley, male, 7−10/group	0, 6,000, 12,000, 17,000 ppm; 4 hr/day, 5 days	NOAEL: 17,000 ppm	No change in auditory sensitivity at any exposure level as measured by cochlear action potentials and microphonics.

a NOAEL (No Observed Adverse Affect Level), LOAEL (Lowest Observed Adverse Affect Level)

Table D.2.3 Summary of mammalian sensory studies – vestibular and visual systems

Reference	Exposure route	Species/strain/ sex/number	Dose level/ Exposure duration	NOAEL; LOAEL a	Effects
Vestibular System Studies					
Tham et al., 1979	Intravenous	Rabbit, strain unknown, sex unspecified, 19	1−5 mg/kg /min	---	Positional nystagmus developed once blood levels reached 30 ppm
Tham et al., 1984	Intravenous	Rat, Sprague-Dawley, female, 11	80 ug/kg/min	---	Excitatory effects on the vestibule-oculomotor reflex. Threshold effect at blood [TCE] of 120 ppm or 0.9 mM/L.
Niklasson et al., 1993	Inhalation	Rat, strain unknown, male and female, 28	0, 2,700, 4,200, 6,000, 7,200 ppm; 1 hour	LOAEL: 2,700 ppm	Increased ability to produce nystagmus.
Umezu et al., 1997	Intraperitoneal	Mouse, ICR, male, 116	0, 250, 500, 1,000 mg/kg, single dose and evaluated 30 min post-administration	NOAEL: 250 mg/kg LOAEL: 500 mg/kg	Decreased equilibrium and coordination as measured by the Bridge test (staying time on an elevated balance beam).
Visual System Studies					
Rebert et al., 1991	Inhalation	Rat, Long Evans, male, 10/group	0, 1,600, 3,200 ppm; 12 hr/day, 12 weeks	NOAEL: 3,200 ppm	No effect on visual function as measured by visual evoked potential changes.
		Rat, F344, male, 4−5/group	0, 2,000, 3,200 ppm; 12 hr/day, 3 weeks	NOAEL: 3,200 ppm	
Boyes et al., 2003	Inhalation	Rat, Long Evans, male, 9−10/group	0 ppm, 4 hours; 1,000 ppm, 4 hours; 2,000 ppm, 2 hours; 3,000 ppm, 1.3 hours 4,000 ppm, 1 hour	LOAEL: 1,000 ppm, 4 hours	Visual function significantly affected as measured by decreased amplitude (F2) in Fourier-transformed visual evoked potentials
Boyes et al., 2005	Inhalation	Rat, Long Evans, male, 8−10/group	0 ppm, 4 hours; 500 ppm, 4 hours; 1,000 ppm, 4 hours; 2,000 ppm, 2 hours; 3,000 ppm, 1.3 hours 4,000 ppm, 1 hour; 5,000 ppm, 0.8 hour	LOAEL: 500 ppm, 4 hours	Visual function significantly affected as measured by decreased amplitude (F2) in Fourier-transformed visual evoked potentials.
Blain et al., 1994	Inhalation	Rabbit, New Zealand albino, male, 6−8/group	0, 350, 700 ppm; 4 hour/day, 4 days/wk, 12 wks	LOAEL: 350 ppm	Significant effects noted in visual function as measured by electroretinogram (ERG) and oscillatory potentials (OP) immediately after exposure. No differences in ERG or OP measurements were noted at 6 weeks post-TCE exposure.

a NOAEL (No Observed Adverse Affect Level), LOAEL (Lowest Observed Adverse Affect Level)

Table D.2.4 Summary of mammalian cognition studies

Reference	Exposure route	Species/strain/ sex/number	Dose level/ Exposure duration	NOAEL; LOAEL a	Effects
Kjellstrand et al., 1980	Inhalation	Gerbil, Mongolian, males and females, 12/sex/dose	0, 320 ppm; 9 months, continuous (24 hr/day) except 1−2 hr/wk for cage cleaning	NOAEL: 320 ppm	No significant effect on spatial memory (radial arm maze)
Kulig et al., 1987	Inhalation	Rat, Wistar, male, 8/dose	0, 500, 1,000, 1,500 ppm; 16 hrs/day, 5 days/wk, 18 weeks	NOAEL: 500 ppm LOAEL: 1,000 ppm	Increased latency time in the two-choice visual discrimination task (cognitive disruption and/or motor activity related effect)
Isaacson et al., 1990	Oral, drinking water	Rat, Sprague Dawley, male, 12/dose	1)0 mg/kg/day, 8 wks 2) 5.5 mg/day (47mg/kg/day[b]), 4 wks + 0 mg/kg/day, 4 wks 3) 5.5 mg/day, 4 wks (47 mg/kg/day[b]) + 0 mg/kg/day, 2 wks + 8.5 mg/day (24 mg/kg/day[b]), 2 weeks	NOAEL: 5.5 mg/day, 4 weeks – spatial learning LOAEL: 5.5 mg/day – hippocampal demyelination	Decreased latency to find platform in the Morris water maze (Group #3); Hippocampal demyelination observed in all TCE treated groups.
Kishi et al., 1993	Inhalation	Rats, Wistar, male, number not specified	0, 250,500, 1,000, 2,000, 4,000 ppm, 4 hours	LOAEL: 250 ppm	Decreased lever presses and avoidance responses in a shock avoidance task
Umezu et al., 1997	Intraperitoneal	Mouse, ICR, male, 6 exposed to all treatments	0, 125, 250, 500, 1,000 mg/kg, single dose and evaluated 30 min post-administration	NOAEL: 500 mg/kg LOAEL: 1,000mg/kg	Decreased response rate in an operant response – cognitive task.
Ohta et al., 2001	Intraperitoneal	Mouse, ddY, male, 5/group	0, 300, 1,000 mg/kg, sacrificed 24 hours after injection	LOAEL: 300 mg/kg	Decreased response (LTP response) to tetanic stimulation in the hippocampus.
Oshiro et al., 2004	Inhalation	Rat, Long Evans, male, 24	0, 1,600, 2,400 ppm; 6 hr/day, 5 days/wk, 4 weeks	NOAEL: 2,400 ppm	No change in reaction time in signal detection task and when challenged with amphetamine, no change in response from control.

a NOAEL (No Observed Adverse Affect Level), LOAEL (Lowest Observed Adverse Affect Level)
b mg/kg/day conversion estimated from average male Sprague-Dawley rat body weight from ages 21−49 days (118 g) for the 5.5 mg dosing period and ages 63−78 days (354 g) for the 8.5 mg dosing period.

Table D.2.5 Summary of mammalian psychomotor function, locomotor activity, and reaction time studies

Reference	Exposure route	Species/strain/ sex/number	Dose level/ Exposure duration	NOAEL; LOAEL a	Effects
Savolainen et al., 1977	Inhalation	Rat, Sprague Dawley, male, 10	0, 200 ppm; 6 hr/day, 4 days	LOAEL: 200 ppm	Increased frequency of preening, rearing, and ambulation. Increased preening time.
Wolff and Siegmund, 1978	Intraperitoneal	Mouse, AB, male, 144	0, 182 mg/kg, tested 30 minutes after injection	LOAEL: 182 mg/kg	Decreased spontaneous motor activity.
Kulig et al., 1987	Inhalation	Rat, Wistar, male, 8/dose	0, 500, 1,000, 1,500 ppm; 16 hrs/day, 5 days/wk, 18 weeks	NOAEL: 1,500 ppm	No change in spontaneous activity, grip strength or hindlimb movement.
Motohashi and Miyazaki, 1990	Intraperitoneal	Rat, Wistar, male, 44	0, 1.2 g/kg, tested 30 minutes after injection	LOAEL: 1.2 g/kg	Increased incidence of rats slipping in the inclined plane test.
			0, 1.2 g/kg/day, 3 days	LOAEL: 1.2 g/kg	Decreased spontaneous motor activity.
Fredericksson et al., 1993	Oral	Mouse, NMRI, male, 12 (3−4 litters)	0, 50, 290 mg/kg/day, at days 10−16	---	Decreased rearing; No evidence of dose-response.
Moser et al., 1995	Oral	Rat, Fischer 344, female, 8/dose	0, 150, 500, 1,500, 5,000 mg/kg, 1 dose	NOAEL: 500 mg/kg LOAEL: 1,500 mg/kg	Decreased motor activity; Neuro-muscular and sensorimotor impairment
			0, 50, 150, 500, 1,500 mg/kg/day, 14 days	NOAEL: 150 mg/kg/day LOAEL: 500 mg/kg/day	Increased rearing activity
Bushnell, 1997	Inhalation	Rat, Long Evans, male, 12	0, 400, 800, 1,200, 1,600, 2,000, 2,400 ppm, 1 hour/test day, 4 consecutive test days, 2 weeks	NOAEL: 800 ppm LOAEL: 1,200 ppm	Decreased sensitivity and increased response time in the signal detection task.
Umezu et al., 1997	Intraperitoneal	Mouse, ICR, male, 6 exposed to all treatments	0, 2,000, 4,000, 5,000 mg/kg – loss of righting reflex measure	LOAEL: 2,000 mg/kg – loss of righting reflex	Loss of righting reflex, decreased operant responses, increased punished responding.

			0, 62.5, 125, 250, 500, 1,000 mg/kg, single dose and evaluated 30 min post-administration	NOAEL: 500 mg/kg LOAEL: 1,000 mg/kg – operant behavior NOAEL: 125 mg/kg LOAEL: 250 mg/kg – punished responding	
Bushnell and Oshiro, 2000	Inhalation	Rat, Long Evans, male, 32	0, 2,000, 2,400 ppm; 70 min/day, 9 days	LOAEL: 2,000 ppm	Decreased performance on the signal detection task. Increased response time and decreased response rate.
Nunes et al., 2001	Oral	Rat, Sprague Dawley, male, 10/group	0, 2,000 mg/kg/day, 7 days	LOAEL: 2,000 mg/kg/day	Increased foot splay. No change in any other functional observational battery (FOB) parameter (e.g. piloerection, activity, reactivity to handling)
Waseem et al., 2001	Oral	Rat, Wistar, male, 8/group	0, 350, 700, 1,400 ppm in drinking water for 90 days	NOAEL: 1,400 ppm	No significant effect on spontaneous locomotor activity
	Inhalation	Rat, Wistar, male, 6/group	0, 376 ppm for up to 180 days	LOAEL: 376 ppm	Changes in locomotor activity but not consistent when measured over the 180-day period.
Moser et al., 2003	Oral	Rat, Fischer 344, female, 10/group	0, 40, 200, 800, 1,200 mg/kg/day, 10 days	---	Decreased motor activity; Decreased sensitivity; Increased abnormality in gait; Adverse changes in several FOB parameters.
Albee et al., 2006	Inhalation	Rat, Fischer 344, male and female, 10/sex/group	0, 250, 800, 2,500 ppm	NOAEL: 2,500 ppm	No change in any FOB measured parameter.

a NOAEL (No Observed Adverse Affect Level), LOAEL (Lowest Observed Adverse Affect Level)

Table D.2.6 Summary of mammalian *in vivo* dopamine neuronal studies

Reference	Exposure route	Species/strain/ sex/number	Dose level/ Exposure duration	NOAEL; LOAEL a	Effects
Guehl et al., 1999	Intraperitoneal Administration	Mouse, OF1, male, 10	0, 400 mg/kg	LOAEL: 400 mg/kg	Significant dopaminergic neuronal death in substantia nigra.
Gash et al., 2007	Oral	Rat, Fischer 344, male, 17/group	0, 1,000 mg/kg	LOAEL: 1,000 mg/kg	Degeneration of dopamine-containing neurons in substantia nigra.

a NOAEL (No Observed Adverse Affect Level), LOAEL (Lowest Observed Adverse Affect Level)

Table D.2.7 Summary of neurochemical effects with TCE exposure

Reference	Exposure route	Species/strain/ sex/number	Dose level/ Exposure duration	NOAEL; LOAEL a	Effects
In Vivo Studies					
Shih et al., 2001	Intraperitoneal	Mouse, Mf1, male, 6/group	0, 250 500, 1,000, 2,000 mg/kg, 15 minutes; followed by tail infusion of PTZ (5 mg/mL), picrotoxin (0.8 mg/mL), bicuculline (0.06 mg/mL), strychnine (0.05 mg/mL), 4-AP (2 mg/mL), or NMDA (8 mg/mL)	---	Increased threshold for seizure appearance with TCE pretreatment for all convulsants. Effects strongest on the $GABA_A$ antagonists, PTZ, picrotoxin, and bicuculline suggesting $GABA_A$ receptor involvement. NMDA and glycine Rc involvement also suggested.

Briving et al., 1986	Inhalation	Gerbils, Mongolian, male and female, 6/group	0, 50, 150 ppm, continuous, 24 hr/day, 12 months	NOAEL: 50 ppm; LOAEL: 150 ppm for glutamate levels in hippocampus NOAEL: 150 ppm for glutamate and GABA uptake in hippocampus LOAEL: 50 ppm for glutamate and GABA uptake in cerebellar vermis	Increased glutamate levels in the hippocampus. Increased glutamate and GABA uptake in the cerebellar vermis.
Subramoniam et al., 1989	Oral	Rat, Wistar, female,	0, 1,000 mg/kg, 2 or 20 hours 0, 1,000 mg/kg/day, 5 days/week, 1 year	---	PI and PIP2 decreased by 24 and 17% at 2 hr; PI and PIP2 increased by 22 and 38% at 20 hrs. PI, PIP, and PIP2 reduced by 52,23, and 45% in 1 year study.
Kjellstrand et al., 1987	Inhalation	Mouse, NMRI, male	0, 150, 300 ppm, 24 hr/day, 4 or 24 days	LOAEL: 150 ppm, 4 and 24 days	Sciatic nerve regeneration was inhibited in both mice and rats.
		Rat, Sprague Dawley, female	0, 300 ppm, 24 hr/day, 4 or 24 days	NOAEL: 300 ppm, 4 days LOAEL: 300 ppm, 24 days	
Haglid et al., 1981	Inhalation	Gerbil, Mogolian, male and female, 6−7/group	0, 60, 320 ppm, 24 hr/day, 7 days/week, 3 months	LOAEL: 60 ppm, brain protein changes NOAEL: 60 ppm; LOAEL: 320 ppm, brain DNA changes	1) Decreases in total brain soluble protein whereas increase in S100 protein. 2) Elevated DNA in cerebellar vermis and sensory motor cortex

a NOAEL (No Observed Adverse Affect Level), LOAEL (Lowest Observed Adverse Affect Level)

Table D.2.8 Summary of *in vitro* ion channel effects with TCE exposure

Reference	Cellular System	Neuronal Channel/ Receptor	Concentrations	Effects
In Vitro Studies				
Shafer et al., 2005	PC12 cells	Voltage Sensitive Calcium Channels (VSCC)	0, 500, 1,000, 1,500, 2,000 uM	Shift of VSCC activation to a more hyperpolarizing potential. Inhibition of VSCCs at a holding potential of -70 mV.
Beckstead et al., 2000	Xenopus oocytes	Human recombinant Glycine receptor $\alpha 1$, $GABA_A$ receptors, $\alpha 1\beta 1$, $\alpha 1\beta 2\gamma 2L$	0, 390 uM	50% potentiation of the $GABA_A$ receptors; 100% potentiation of the glycine receptor
Lopreato et al., 2003	Xenopus oocytes	Human recombinant serotonin 3A receptor	???	Potentiation of serotonin receptor function.
Krasowski and Harrison, 2000	Human embryonic kidney 293 cells	Human recombinant Glycine receptor $\alpha 1$, $GABA_A$ receptors $\alpha 2\beta 1$	Not provided	Potentiation of glycine receptor function with an EC_{50} of 0.65 ± 0.05 mM. Potentiation of $GABA_A$ receptor function with an EC_{50} of 0.85 ± 0.2

Table D.2.9 Summary of mammalian *in vivo* developmental neurotoxicity studies – oral exposures

Reference	Species/strain/ sex/number	Dose level/ Exposure duration	Route/vehicle	NOAEL; LOAEL a	Effects
Fredriksson et al., 1993	Mouse, NMRI, male pups, 12 pups from 3−4 different litters/group	0, 50, or 290 mg/kg-day PND 10−16	Gavage in a 20% fat emulsion prepared from egg lecithin and peanut oil	Dev. LOAEL: 50 mg/kg-day	Rearing activity sig. ↓ at both dose levels on PND 60
George et al., 1986	Rat, F334, male and female, 20 pairs/ treatment group, 40 controls/sex	0, 0.15, 0.30 or 0.60% microencapsulated TCE Breeders exposed 1 wk pre-mating, then for 13 wk; pregnant ♀s throughout pregnancy (i.e., 18 wk total)	Dietary	LOAEL: 0.15%	Open field testing in pups: a sig. dose-related trend toward ↑ time required for male and female pups to cross the first grid in the test devise

Isaacson & Taylor, 1989	Rat, Sprague-Dawley, females, 6 dams/group	0, 312, or 625 mg/L. (0, 4.0, or 8.1 mg/day) b Dams (and pups) exposed from 14 days prior to mating until end of lactation.	Drinking water	Dev. LOAEL: 312 mg/L c	Sig. ↓ myelinated fibers in the stratum lacunosum-moleculare of pups. Reduction in myelin in the hippocampus.
Noland-Gerbec et al., 1986	Rat, Sprague-Dawley, females, 9−11 dams/ group	0, 312 mg/L (Avg. total intake of dams: 825 mg TCE over 61 days.) b Dams (and pups) exposed from 14 days prior to mating until end of lactation.	Drinking water	Dev. LOEL: 312 mg/L c	Sig. ↓ uptake of ^{3}H-2-DG in whole brains and cerebella (no effect in hippocampus) of exposed pups at 7, 11, and 16 days, but returned to control levels by 21 days.
Taylor et al., 1985	Rat, Sprague-Dawley, females, no. dams/group not reported	0, 312, 625, and 1,250 mg/L Dams (and pups) exposed from 14 days prior to mating until end of lactation.	Drinking water	Dev. LOAEL: 312 mg/L c	Exploratory behavior sig. ↑ in 60- and 90-day old male rats at all treatment levels. Locomotor activity was higher in rats from dams exposed to 1,250 ppm TCE.

a NOAEL (No Observed Adverse Affect Level), LOAEL (Lowest Observed Adverse Affect Level), and LOEL (Lowest Observed Effect Level) are based upon reported study findings.
b Dose conversions provided by study author(s).

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