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ScienceDirect
Neurotoxicology and Teratology 30 (2008) 167–174
NEUROTOXICOLOGY AND TERATOLOGY
www.elsevier.com/locate/neutera

Characterization of the effects of inhaled perchloroethylene on sustained attention in rats performing a visual signal detection task ☆

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Received 12 July 2007; received in revised form 6 December 2007; accepted 5 January 2008
Available online 12 January 2008

Abstract

The aliphatic hydrocarbon perchloroethylene (PCE) has been associated with neurobehavioral dysfunction including reduced attention in humans. The current study sought to assess the effects of inhaled PCE on sustained attention in rats performing a visual signal detection task (SDT). Due to its similarities in physiological effect to toluene and trichloroethylene (TCE), two other commonly used volatile organic compounds (VOCs) known to reduce attention in rats, we hypothesized (1) that acute inhalation of PCE (0, 500, 1000, 1500 ppm) would disrupt performance of the SDT in rats; (2) that impaired accuracy would result from changes in attention to the visual signal; and (3) that these acute effects would diminish upon repetition of exposure. PCE impaired performance of the sustained attention task as evidenced by reduced accuracy [*P*(correct): 500 to 1500 ppm], elevated response time [RT: 1000 and 1500 ppm] and reduced number of trials completed [1500 ppm]. These effects were concentration-related and either increased (RT and trial completions) or remained constant [*P*(correct)] across the 60-min test session. The PCE-induced reduction in accuracy was primarily due to an increase in false alarms, a pattern consistent with reduced attention to the signal. A repeat of the exposures resulted in smaller effects on these performance measures. Thus, like toluene and TCE, inhaled PCE acutely impaired sustained attention in rats, and its potency weakened upon repetition of the exposure.
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Keywords: Attention; Organic solvent; Rat; Signal detection; Tolerance; Perchloroethylene; Tetrachloroethylene

1. Introduction

Perchloroethylene (PCE) is an aliphatic, halogenated hydrocarbon used commercially in dry cleaning, textile processing, and metal cleaning operations. Due to its wide variety of uses and prevalence in air and in ground water near industrial sites, exposure can occur through inhalation as well as through ingestion from contaminated water sources [1]. PCE and other volatile organic compounds (VOCs) primarily affect the central nervous system due to their high lipophilicity. Thus, information regarding the neurotoxicity of PCE is important to risk assessors and agencies regulating this and other VOCs.

Occupational and epidemiological studies in humans exposed chronically to relatively low levels of PCE have shown impairments in neurobehavioral function. In addition to deficits in visual [21,42] and motor [4,25,30,31,45] functions, cognitive processes such as memory, attention and vigilance were also commonly affected in these studies [4,23,25,30].

Humans exposed acutely to PCE also showed deficits in sensory, cognitive and motor functions. Human volunteers exposed to 50 ppm PCE via inhalation 4 h/day for four consecutive days showed increased visually evoked potential (VEP) latencies, but not brainstem auditory evoked potential latencies, when compared to a group exposed to 10 ppm (an odor-control condition) [3]. Using the same exposure scenario, volunteers exposed to 50 ppm showed significant deficits in a vigilance task and impaired eye–hand coordination compared to subjects exposed to 10 ppm [5]. In another study, male

☆ This manuscript has been reviewed by the National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency and approved for publication. Approval does not signify that the contents necessarily reflect the policies of the Agency nor does mention of trade names or commercial products constitute endorsement or recommendation for use.

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0892-0362/$ - see front matter. Published by Elsevier Inc.
doi:10.1016/j.ntt.2008.01.002

volunteers were exposed to 100 ppm for 7 h day for 1 or 5 consecutive days [45]. Twenty-five percent of subjects reported subjective symptoms on the first day including headache, dizziness, sleepiness and speech difficulty. A few of these volunteers also showed a reduced score on a modified Romberg test, which tested for balance, 3 h after exposures began.

Acute and subchronic studies in animals exposed to PCE have demonstrated impairments similar to those reported in the human acute and chronic studies. Flash-evoked potentials, somatosensory-evoked potentials, and EEGs were changed in rats exposed to 800 ppm PCE for 6 h day for 4 days [33]. Motor activity was increased in mice inhaling 1000 ppm PCE for 1 h and then decreased when exposures continued for 3 h [32]. Rats given 500 mg/kg PCE by oral gavage showed lower locomotor activity and rearing when tested 1 h after treatment in an open-field test; when dosing was repeated, similar effects were seen in animals tested 3 days after receiving 50 mg/kg PCE for 8 weeks [22]. Response rates of rats trained on a schedule-controlled operant task (FR40) were reduced immediately following administration of 480 mg/kg PCE by gavage [49]. Response rates were also reduced in mice tested on a schedule-controlled operant task (FR20) 30 min after receiving 1000 mg/kg PCE, IP [47].

More recently, PCE, toluene and trichloroethylene (TCE), all commonly used VOCs, were shown to inhibit neuronal nicotinic acetylcholine receptors (nAChRs) in both human and rat cells *in vitro* [7,8]. These same VOCs inhibited voltage-sensitive Ca^{2+} channels (VSCCs), which regulate neuronal functions including neurotransmitter release [43]. These effects were immediate, reversible, and occurred in a concentration-dependent manner.

In addition to inhibiting nAChRs and VSCCs, VOCs disrupt other neurotransmitter systems including NMDA, GABA and glycine (see [20] for review). Disruptions in these systems can impair cognitive processes such as attention in rats [16,28,34,39,46]. Although PCE disrupts both nAChRs and VSCCs *in vitro*, we know of no animal studies that have investigated the effects of PCE on sustained attention. The current study sought to characterize the effects of inhaled PCE in rats trained to perform a visual signal detection task (SDT). The SDT measures sustained attention in rats and humans [12,13] and is sensitive to the effects of cholinergic and adrenergic drugs [16]. Because inhalation of toluene and TCE [11,14,17] impair performance of the SDT, we hypothesized that PCE would also disrupt performance of the SDT.

Additionally, the potencies of toluene and TCE in disrupting SDT performance are known to change with repeated exposures. Previous work showed that behavioral adaptation (tolerance) to these compounds developed within a week of daily hour-long exposures [15,37]. This adaptation is thought to be driven by a loss of reinforcement due to intoxication [15,36,37,44,48]. Therefore, this study also sought to determine whether animals would show signs of tolerance during a second acute exposure to PCE. A shift in the concentration–effect function during the second determination would indicate whether tolerance or sensitivity had developed in these animals.

This experiment was designed to answer three questions about the acute behavioral effects of PCE. First, does PCE affect behavior in the SDT and, if so, what aspects of performance are affected? Three primary dependent variables were examined to address this question: accuracy, defined as *P*(correct), the proportion of correct choices; response time, defined as the time taken by the rat to make its choice; and number of trials completed in the session. Second, if accuracy is reduced, what is the source of the errors? This question was addressed by dissociating *P*(correct) into hits (reflecting accuracy on signal trials) and false alarms (reflecting errors on trials lacking a signal). Third, do rats develop tolerance to the acute effects of PCE? Two concentration–effect functions (CEFs) were determined sequentially in each rat to evaluate this question, using the three primary dependent variables used for the first question.

2. Methods

2.1. Subjects

Twelve male Long–Evans rats (Charles River, Portage, MI) were housed individually in suspended polycarbonate cages on heat-treated pine shavings in a housing facility fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) according to NIH guidelines. This animal research protocol was reviewed and approved by the NHEERL Institutional Animal Care and Use Committee which ensures conformance with the 1996 NRC "Guide for the Care and Use of Laboratory Animals", the Animal Welfare Act and Public Health Service Policy on the Humane Care and Use of Laboratory Animals. Lighting followed a light:dark 12 h:12 h (lights on at 0600: lights off at 1800) photoperiod; all behavioral testing occurred in the light phase of the cycle. Each animal was maintained at 350±10 g body weight by scheduled home cage feeding (rat chow, Ralston Purina, St. Louis, MO) after daily test sessions [2]. Tap water was available *ad libitum* in the home cage. Rats were 3.5 months old at the start of training and 7 months old at the beginning of the PCE exposures.

2.2. Apparatus — operant behavior

Four 32.9-L operant-inhalation chambers were constructed as previously described [11,14,18]. Briefly, each chamber was made of stainless steel and glass for the assessment of operant performance of rats inhaling controlled concentrations of solvent vapors. The front wall of each of these chambers contained two retractable omnidirectional response levers; a food cup with a hinged, clear plastic door, centered between the levers; a house light; a signal light; and a 5-cm cone loudspeaker. The house and signal lights were mounted 15 cm above the floor of the chamber: the signal light was centered above the food cup, between the house light and the loudspeaker. Background white noise of 65 dB(A) was generated in each chamber. Experimenter access and rat placement into the chamber was accomplished by removal of a transparent, red-tinted rear panel.