

**AROUSALS AND/OR WAKE PATTERNS ASSOCIATED WITH PHEROMONES
ADMINISTERED IN THE
AMBIENT ENVIRONMENT DURING SLEEP**

EXECUTIVE LEADERSHIP

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ABSTRACT

This study is about an important scientific discovery: Humans may possess a true sixth sense. Perhaps a primal secret for thousands of years, the pheromone-dependent sixth sense seems to be a recent development in the scientific continuum. The researcher became aware of a growing body of research that indicated the possibility of interrupting sleep for the purpose of fire detection-awareness. The problem was not knowing if this was possible. No research had been performed to determine this. The purpose of this evaluative research was to determine if an ambient exposure to pheromones could cause awakenings in a defined group. To determine this, the following research questions were used: (a) Will bio-measurements confirm an ambient airborne exposure of pheromones? (b) Will pheromones cause arousals in sleeping subjects? (c) Will pheromones cause awakenings in sleeping subjects? To answer these questions, the researchers administered a pheromone called PH 15 and a placebo to sleep subjects in an approved study. This was performed in a sleep center utilizing a number of bio-measurements. The pheromone and placebo were nebulized into a room where ten males and five females slept. These two agents were administered during stage 2, stage 3-4, and REM sleep. All of the subjects were pre-screened to determine if they possessed a vomeronasal organ. The sleep records were scored by the standard Rechtschaffen and Kales system. EKG and cardiac frequency confirmed that the PH 15 did cause arousals (.020 overall Chi-square significance) in sleeping subjects and that the placebo responses were insignificant (Chi-square .796). There was also an insignificant number of awakenings experienced during the study. These findings were followed up with a t-test for paired samples to determine the magnitude of difference between the two. The t-test produced a .003 2-tailed significant P value. That P value confirmed the significant difference in the two fields. Knowing that the difference between arousals and awakenings is in the degree of sleep interruption, the research indicated that PH 15 had the potential of disrupting sleep patterns to the point of waking a sleeping subject. From these findings, the researchers produced fourteen recommendations that support additional research, education, product development, and marketing of pheromone-based fire detection-awareness products.

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INTRODUCTION

In an earlier paper, the researcher evaluated the presence of olfactory fire protection (Lynch, 1997). Failing to verify its existence and being concerned about the number of fire deaths that occur during the night, the researcher became aware of a growing body of knowledge in which research indicates the possibility of chemically interrupting sleep for the purpose of fire detection and awareness. The problem is that it is not known whether an ambient exposure to a human pheromone (known as PH 15) can awaken a defined group of sleeping subjects. This evaluative research study was approved by the Western Institutional Review Board to determine if human pheromones administered in the ambient environment can awaken subjects in the various stages of sleep. The following research questions will be used to determine this: (a) Will bio-measurements confirm an ambient airborne exposure of pheromones? (b) Will pheromones cause arousals in sleeping subjects? (c) Will pheromones cause awakenings in sleeping subjects?

BACKGROUND AND SIGNIFICANCE

The headline stated that the "Police officer rescues man sleeping in burning house" (Jones, 2001). Events such as this indicate that people do not smell while they sleep. In an earlier paper, the investigator examined olfaction and sensitivity to smoke odor during sleep. That study was entitled *Nocturnal Olfactory Response to Smoke Odor* and can be referenced in entirety at the following electronic address: http://www.usfa.fema.gov/nfa/tr_97jl.htm. Lynch verified that overall responsiveness to olfactory stimuli presented in sleep was low. Only two of ten subjects awoke from an ambient exposure to wood smoke odor (Lynch, 1997). That finding produced a number of recommendations. Of these, recommendation three led to this project. Recommendation three is restated below:

Recommendation 3.

Additional sleep studies should be performed to identify odors that are likely to arouse us from sleep. If specific odors can be identified, products that liberate that odor during fires can be incorporated into the manufacture of common building materials and home furnishings. Consequently, an incipient fire would therefore provide notice of its existence by production of chemically manipulated fire products. This concept is very similar to the industrial process of adding a chemical odorant known as methyl mercaptan to natural gas for the purpose of providing early detection (Lynch, 1997).

Man has relied on the electrical circuitry and sensors of an inexpensive disposable device (and its essential power supply) to protect him from fires while he sleeps. There continue to be attempts to improve home detectors. For example, the possibility of pairing carbon monoxide and carbon dioxide sensors in one detector to increase the detection system's ability to discriminate between fire and nuisance sources is being discussed (Milke, 1999). Detector design has evolved; however, there also continue to be application, compliance and maintenance barriers associated with the use of smoke detectors. The absence or non-functioning of smoke detectors is clearly a contributing factor in the number of fire deaths occurring in this country

(Ahrens, 1998). "In that regard, the fire death experience in the city of Irondale, Alabama, is a serious issue and is consistent with that reported in the national data" (Dwight Graves, personal communication, June 6, 1999). See the "Fire Facts" section of appendix A to review the national data. Smoke detectors have been credited with saving many lives, but (as with all active processes) the operational status of the detector seems to depend on the occupant's attitude. Unfortunately, this apathetic attitude has contributed and will continue to contribute to the number of fire deaths. Consider for a moment that reliance on the detector is the problem. Maybe, just maybe, static fire protection is the answer! The paradigm of reliance on visual and audible cues (alarms) for fire detection may be in jeopardy. Could it be that a safe agent of olfaction has been identified that will reliably arouse a sleeping human? Is a sixth sense monitoring and regulating bodily functions; and, if present, can it be used as a pathway for fire protection? This paper will explore these intriguing concepts.

A recent discovery has suggested a sixth sense exists in humans. Touted as one in which remarkable advancements in medicine and safety are attainable, the vomeronasal organ may be that sixth sense and the key to sensual fire protection during sleep. This study will examine a specific sleep-disrupting compound (known as a pheromone) that has been described as naturally occurring, safe, fast acting, and localized in its effect on the body. The ability to detect a fire during sleep without the aid of smoke detectors is an astounding concept and somewhat visionary. Utilized differently, the incorporation of a pheromone delivery system within a multi-sensor smoke detector may be the right fire protection combination. The addition of a pheromone delivery system could create the first "smart" detector on the market. The local application of such a product would be a significant life saving development in the City of Irondale.

Any examination of a sixth sense and this compound necessitates a review of sleep, the sense of smell, and related studies.

Sleep

"Sleep is a normal, easily reversible, recurrent, and spontaneous state of decreased and less efficient responsiveness to external stimulations" (Goetz, 1991, p. 298). Research has indicated that a number of basic states of sleep exist. These states are known as waking, REM (rapid eye movement), and NREM (nonrapid eye movement). REM sleep and NREM sleep are controlled from separated groups of brain cells, or neurons, located in the brain stem--the hindmost part of the brain that regulates basic survival functions (Pollak, 1996). Specifically, the control of NREM sleep likely resides in widely ranging circuits from the area around the solitary track in the medulla through the dorsal raph'e to the basal forebrain area (Hauri, 1992). The responsible groups of brain cells or neurons (all located in the brain stem area) communicate with each other with chemical messengers known as serotonin and norepinephrine (Pollak, 1996).

NREM is further characterized as having four distinctive stages which a person normally moves through in a preset order or rhythm. Stage 1 of NREM can be thought of as the boundary between wakefulness and sleep, while stage 2 is the first (lightest) bonafide level of sleep. Stages 3 and 4 represent the most remote levels of responsiveness. A person in stage 4 sleep is very hard to arouse by any outside stimuli. Specific stages of sleep have been defined through

the presence of certain electroencephalogram (EEG) patterns that occur during specific behavior sleep periods. The typical sleep pattern is represented by the following model: Conscious-NREM Stage 1, 2, 3, 4, 3, 2, REM, NREM 2, 3, 4, 3, 2, REM, etc. (Hauri, 1992). The pattern takes approximately 70-90 minutes to be completed and is repeated throughout the night (Goetz, 1991). Dreaming occurs in REM, and it is the easiest state of sleep in which to be aroused (Pollack, 1996). "During wakefulness, the EEG is characterized by low-voltage fast activity consisting of a mix of alpha (8 to 13 Hz) and beta (>13 Hz) frequencies" (Monti & Monti, 1999, p. 2). Although alpha rhythm is blocked when the eyes are open, it is very discernible when a person is conscious with his or her eyes closed. Alpha intrusions are considered brief superimpositions of EEG alpha activity (arousals) during a stage of sleep (Pegram, 1997). Drug abuse can cause an inordinate amount of sleep spindles and/or alpha intrusions during NREM sleep (Russell Laney, personal communication, May 9, 1996). As reported earlier,

Stage 1 of non-REM sleep is a transitional stage between wakefulness and sleep during which the predominant alpha rhythm disappears, giving way to the slow theta (4 to 7 Hz) frequencies. Tonic electromyography (EMG) activity decreases and the eyes move in a slow rolling pattern. Stage 2 is characterized by a background theta rhythm and episodic appearances of sleep spindles (i.e., brief bursts of 12- to 14-Hz activity) and K complexes (i.e., a high amplitude, slow frequency electronegative wave followed by an electropositive wave) (Monti & Monti, 1999, p. 2).

Sleep spindles are naturally occurring and are the brain's electrical sleep signature. K-complexes or sharp biphasic waves lasting 0.5 seconds also occur naturally or can be induced by external stimulation. Muscle tone remains diminished and eye movements are rare in stage 2 sleep. Most sleep studies are performed in stage 2 (NREM) sleep because humans spend 50 percent of their time in light sleep. Sleep is normally defined as a state in which there is a limited amount of alpha rhythm (Pegram, 1997). Stage 3 and 4 are also NREM stages of sleep

Stage 3 and stage 4 are defined as epochs of sleep consisting of greater than 20 percent and 50 percent, respectively, of high amplitude activity in the delta band (0.5-3.00 Hz). Muscle tone is nearly atonic, and eye movements are absent. REM sleep is characterized by a low-amplitude, mixed-frequency EEG, rapid eye movement, and absence of muscle tone (Monti & Monti, 1999, p. 2).

The lower the bandwidth of voltage being emitted from the brain, the deeper the sleep. Sleep centers utilize polysomnography machines to monitor patients during their study. The tracings obtained on a polysomnogram (tracing) represent electrical activity within the cerebral cortex (EEG), voltages generated by muscle fibers (EMG), voltage shifts caused by the movements of the eyes (EOG), voltages generated by the heart (ECG), nasal and air flow, breathing effort (measured at chest and abdomen), and oximetry. Considering that humans average sleeping one third of their lives, which amounts to 219,000 hours by the age of 75, sleep is a very important issue (V. Pegram, personal communication, January 15, 2001).

Smell

While studies of the anatomy and physiology of olfaction have not been finalized, the most acceptable model of olfaction depends on the concept of odoriferous molecules attaching to olfactory receptor sites. The size and shape of both the odor molecules and the receptor sites are essential elements in currently adopted theories and descriptions of the mechanics of olfaction (See appendix B for an illustration of the olfactory system). Molecules of an odor-emitting substance chemically interact at receptor sites within specialized structures of the nasal cavity. It is currently believed that olfactory receptors are regions of specialized molecular architecture located on cilia-like fibers called olfactory hairs.

Olfactory hairs are extensions or branches of the olfactory sensing cells. The hairs, which are actually made of microfilaments, are dispersed over the surface of the olfactory sensing region of the nasal cavity. While the size of the olfactory region of the nasal cavity is small (about the size of a dime), its surface area is comparatively large because of the many olfactory hairs coating the surface or epithelium of the olfactory cleft. It is estimated that humans have between 10 and 40 million olfactory receptors. The olfactory hairs are surrounded by a thick, brown-colored mucus and are partially covered and partially exposed.

Odoriferous molecules must be trapped by the mucus so that they can travel to chemoreceptor sites on the olfactory hairs. The interaction between the odor molecules and the chemoreceptors of the olfactory hairs requires a mutual attraction, originating from small electrostatic forces. The shape, size, and polarity or nonpolarity of molecules causing odor are important factors in the creation of a smell stimulus. From the olfactory hairs in the membrane structure, the odor molecules travel through the cribriform plate and into the olfactory tract, which leads directly to the hypothalamus in the brain. The olfactory hairs extend from the olfactory knobs, which are unexposed sensory cell endings completely covered by brown mucus. Five to eight hairs extend from each knob; electron micrographs show that the hairs are actually dendrites extending from the cell body into the external environment, while the axons of the cells carry nerve impulses toward the brain. The olfactory tract connects these nerves directly to the hypothalamus region of the brain, which is associated with basic instinctual responses including flight-or-fight cues, food intake, and sexual curiosity and drive. This direct link to the brain cause a rapid and powerful response in animals to odor stimuli (Piotrowski, 1996, pp. 1603-1607).

There are a number of conditions that lead to a loss of smell.

Natural Loss of Smell

Due to their fragile nature, olfactory nerves regenerate in a twenty-eight-day cycle; nevertheless, about 1 percent of the sites die each year due to damage and general wear. The loss in the ability to smell (anosmia), the state of hyposmia (which is a decrease of the smell function), and dysosmia (an altered sense of smell) can all manifest themselves in numerous

ways (Piotrowski, 1996). The common medical problems associated with the loss of smell are smoking habits, nasal polyps, allergic rhinitis, viral and bacterial infections, head injuries, and complications of nasal surgery and brain tumors (Larson, 1996). There is an overall weakening of our ability to smell as we get older (Petraglia, 1991). In 1957, Clarke and Dewhurst reported that thirty percent of a defined group of people over the age of sixty-five were unable to smell propane gas (Stevens, Cain, and Weinstein, 1987).

Occupational Loss of Smell

A pilot study performed by Dr. Alan Hirsch of the Smell and Taste Treatment and Research Foundation indicates that forty-eight percent of a group of Chicago firefighters could not tell natural gas or smoke odors from those such as perfume and bubble gum. Hirsch said, "The longer on the job, the more likely the firefighters were to have lost their sense of smell" (Hirsch, 2000, p. 20). Firefighters use breathing masks to protect themselves from toxic chemicals released during fires. But the sense of smell of those who reported using masks was not better than in those who did not. The general population was also considered. Alarmingly, this study went on to suggest that ninety percent of fire survivors were found to have elevated blood cyanide levels, indicating that they were exposed to substantial levels of olfactotoxins. "With nearly two million fires in the United States each year, the extent of olfactory damage could be epidemic" (Hirsch, 2000, p. 20).

The Olfactory Studies and Sleep

Intrinsically, the most valuable work in the area of olfactory responses during sleep was published by Micheal J. Kahn and Pietro Badia. In 1983, Kahn studied sleep response to the stimulus of a smoke odor, heat sensations, and auditory alarms. Twenty-four college-aged males were divided into two groups and exposed to smoke alarm sounds of different intensities. By test design, both groups were exposed to heat and smoke odor. Kahn found that sleeping subjects exposed to higher signal-to-noise ratios responded more quickly than those who were not. Kahn also attempted to address a hypothesis concerning the time required for a sleeping adult to respond to a smoke odor. Unfortunately, he reported that "comparing smoke alarm and sleeping human proficiency in detecting a smoke presentation could not be tested meaningfully" (Kahn, 1983, p. 51). He finished his presentation by calling for additional research in this area. In 1991, Pietro Badia evaluated the effects of fragrances on the quality of a person's sleep. In his discussion, he also indicated the need for additional inquiries into the perplexing topic of odor research during sleep.

In 1989, Pietro Badia, Nancy Wesenstern, William Lammers, Joel Culpepper, and John Harsh wrote a report entitled "Responsiveness to Olfactory Stimuli Present in Sleep." The results of their study showed that although the overall responsiveness to olfactory stimuli presented in sleep was low, statistically significant differences in responsiveness to odors were found for micro switch closures, EEG, EMG, and heart rate. The condition of micro switch closure involved the physical manipulation of an electrical switch attached to the patient. Ten patients were presented a peppermint and a non-fragrance air supply via a modified oxygen mask

during sleep. Polysomnograph machines recorded the biomeasurements listed above to assist the researchers in detecting a psychophysiological response. The patients were presented the fragrance multiple times during the night so that the related dependent variables were repeatedly assessed during the test period. The number of times a patient responded to the condition divided by the opportunities a patient had to respond resulted in a percentage of response variable. These percentages of responses were determined to be statistically significant (Sign test $=p<0.05$) for the overall group. The methodology for reporting these before and after observations was the non-parametric Sign or paired-samples t-test. All fragrance presentations occurred in stage 2 sleep. Awakenings were noted and evaluated separately to determine their rate of occurrence. Sign tests failed to reveal any significant awakening occurrences (Sign test $=p>0.05$). Although multiple trials were presented on each of the ten patients, only three awakenings occurred during the study.

In "Olfactory Arousal Thresholds During Sleep," Mary A. Carskadon, et al. (n.d.) examined the various stages of sleep and found that the arousal threshold is lower in stage 2 and REM than it is in stage 4 sleep. They used oil of peppermint and pyridine (an unpleasant stimulus) as odorants in the test. The two odors were presented by nasal cannula to the sleeping subjects. Arousals were accessed during Stage 2, 4, and REM sleep. Six healthy subjects between 20 and 25 years of age (3 male and 3 female) were selected for the test. The sex of the subject did not affect the results. "Behavioral and EEG arousals to the olfactory stimuli occurred significantly more frequently in stage 2 sleep than in REM sleep or stage 4. The arousal frequency in stage 4 was significantly lower than in stage 2 or REM" (Carskadon, et al., n.d., p. 147).

Finally, the research project of Fire Chief Joe Lynch (1997) accessed the sense of smell during sleep to learn whether a sleeping adult could detect the odors of water, smoke, or citrus. These odors were first introduced to conscious subjects to screen them for olfactory response. The subjects went to sleep, and a compressor pump nebulized three different odorants through an elaborate delivery system into the sleep rooms. EKG, EEG, EMG, and EOG biomeasurements were monitored for response to the stimuli. The following research questions were identified for use: (a) Could a defined group of conscious adults detect the presence of the smell of smoke odor? (b) Would the smell of smoke odor awaken a defined group of sleeping adults? (c) Would the smells of water, smoke, or citrus odors cause arousals in a defined group of sleeping adults? The results revealed that although a significant number of subjects responded to the stimuli, only two of the ten subjects awoke to smoke odor. None of the subjects awoke to the citrus odor (Lynch, 1997). Perhaps the presentation of the smoke odor (an identified threat) to these two subjects represented conditioning or meaningful stimulus, whereas the citrus odor did not. Meaningful stimulus can be light noises (a child's cry), smells (a burning smell), or sounds (a door knob turning) that have some significance and therefore produce awakenings. This contrasts to the equivalent in non-meaningful stimuli (the sound of a car passing by) that produces no awakenings (V. Pegram, personal communication, January 15, 2001). This concept was explored by Perrin, Garcia-Larrea, Manguiere, and Bastuji (1999) in a study that suggested the sleeping brain is able to detect and categorize some particular aspects of stimulus significance. While Voss and Harsh (1998) called this higher level processing, Harsh, Voss, Hull, Schrepfer, and Badia (1994) defined the concept as stimulus deviance and task relevance in sleepiness and sleep. The origins of these theorems date back to the fundamental tests of

Williams, Hammack, Daly, Dement, and Lubin reported in 1962. They stated that the "EKG stage of sleep was not an invariant indicator of the responsiveness of the organism" (Williams, Hammack, Daly, Dement & Lubin, 1962, p. 278). Bremer and Brain reported the alleged superiority of an auditory stimulus of personal significance compared with an auditory stimulus lacking special importance to the sleeper. The arousal response can follow all sensory stimulation during sleep and does not depend on the degree of novelty introduced into the stimulus (Oswald, Taylor, & Treisman, 1960).

Though the concept of meaningful stimulus deserves more attention, the research clearly indicates that sleeping people (statistically) cannot rely on the sense of smell to alert them to the presence of a fire.

Is There a Sixth Sense?

People have known for centuries that animals communicate with biochemical cues understood by others of their own species. Baby marmosets and grass carp, blue crabs and ants release pheromones to mark the boundaries of their territory, as a warning to enemies, as recognition signs, as enticements to love, as status symbols, and for many other purposes. Queen bees use pheromones to inhibit the sexual maturity of female workers and to make the drones swarm ("Chemical Messengers," 1995, p.1).

The understanding of this principle has led to the marketing of the Feliway[®] pheromone spray by Abbott Laboratories. This product uses feline facial pheromones to prevent urinary marking and to comfort a cat in an unknown or stressful environment ("Synthetic Hormones," 2000). "While entire brigades of researchers are focusing on animal pheromones, little has been known until today about the chemical agents of human attraction" ("Chemical Messengers," 1995, p.1).

Consider this story: The March 12, 1998, volume of *Bioworld Today* reported that ovulation in women can be manipulated by airborne (natural-occurring) odorless chemicals (Leff, 1998). In fact, according to investigator Martha McClintock, "The entire menstrual cycle is subject to being regulated by the influence of other women being present" (Weiss, 1997, p.1A). At least one drug manufacturer has realized the potential effectiveness of these chemicals and has patented approximately 1000 of them (Goldman, 1999). Pherin Corporation's product development centers on the functioning of the human vomeronasal organ (VNO), which is found in the nose. The company's pharmaceutical compounds (called vomeropherins) are designed to be used topically within the nasal passage where they trigger a nerve impulse to the hypothalamus, the control center in the brain that acts as the link between the endocrine and nervous systems, regulating a host of physiological functions ("Pherin: A Nose," 1996). According to Pherin's corporate literature, the company has compounds in its product pipeline and partnerships that target premenstrual syndrome, acute anxiety disorders, appetite stimulation, modulation of endocrine function, depression, appetite suppression, and sexual motivation (Pherin Pharmaceuticals, 1999). The components of the endocrine system are the thyroid, adrenal, and pituitary glands, the ovaries, the testis, and the Island of Langerhans in the pancreas.

"By controlling the endocrine system, a physician may be able to treat male sex offenders, women and men that need hormone therapy, women who desire birth control, men with prostate cancer, and anyone with breast cancer" (David Moran, personal communication, January 5, 2001). Conceptually, the use of the human VNO organ as an effective route of drug administration has evolved from theory to application with the Janssen Pharmaceutica (a subsidiary of Johnson and Johnson Development Corporation) agreement covering pheromone compounds for the treatment of a broad range of anxiety disorders (McCarthy, 1999) and the partnership of Pherin Pharmaceuticals and the N.V. Organon (a subsidiary of the Dutch-based chemical corporation Akzo Nobel) to develop compounds focusing on premenstrual syndrome (McCarthy, 1997). "Unlike traditional drugs, vomeropherins (pheromones) do not need to enter the systemic circulation in order to exert their therapeutic effects. Instead, when administered via a nasal spray, vomeropherins stimulate the VNO directly, which triggers in the hypothalamus. Locally administered vomeropherins thus do not need to cross the biological barriers that are associated with systemic absorption and distribution. In addition, because only minute quantities of vomeropherins likely will be required to induce a biological response, both production costs and the potential for adverse side effects are minimized" (Pherin Pharmaceuticals, 1999a, p. 1). Clearly, this route of drug administration offers numerous advantages over the traditional internal routes.

The Human Vomeronasal Organ

In most mammals, the VNO is a blind ending tubular structure located close to the base of the nasal septum and separated from the olfactory epithelium by a large field of nonsensory respiratory epithelium. "This tube is lined by tall, narrow cells" (Kodis, Moran, & Houy, 1998, p. 57). "The VNO contains cells not found anywhere else in the body that give the human VNO its unique chemosensory properties" (Kodis, Moran, & Houy, 1998, p. 53). Where studied in mammals, the central axonal processes of VNO receptor cells collect to form the vomeronasal nerve that projects to the accessory olfactory bulb. These axons of the bipolar VNO chemosensory neurons are tiny (0.2 μ m in diameter) and unmyelinated (not have a myelin sheath on the nerve). They are often accompanied on their journey to the brain by large fibers of the nervus terminalis, whose bipolar neurons--also derived from the medial olfactory placode--have relatively large cell bodies in the submucosal plexus of the nasal septum. Both the somata and axons of many terminalis neurons are immunoreactive for LHRH (leutenizing hormone releasing hormone) and seem to provide direct input to similar cells in the basal forebrain, medial preoptic nucleus, and anterior portions of the hypothalamus--brain regions that regulate neuroendocrine function (Berliner, Jennings-White, Monti-Bloch, 1998). The VNO controls vital regulatory and behavioral functions, such as the hormonal system, the fight-or-flight response, anxiety, fear and aggression, sexual motivation, heart rate and blood pressure, body temperature, appetite, sugar and fat metabolism, and water and electrolyte balance (Pherin Pharmaceutical, 1999). By affecting regulatory control of the hypothalamus, it is possible to modulate autonomic, psychophysiological, and hormonal responses (Berliner, et al., 1997). The cerebral cortex of the brain gives us our reasoning and thinking abilities, while the most primitive part of the brain (the hypothalamus) directs what we do on a subconscious level (Kodis, Moran, & Houy, 1998). "The hypothalamus, which sits just beneath the thalamus and above the pituitary gland, makes up only 0.3 percent of the total weight of the brain, but it is the structure that controls our basic human

drives" (Kodis, Moran, & Houy, 1998, p. 73). "Our VNO is about a thousand times more sensitive than our sense of smell. The VNO reacts as quick as lightning to any breath of a pheromone. We respond to 30 picograms of pheromone, and that is thirty millionths of a billionth of a milligram" (Louis Monti-Bloch, personal communication, October 15, 1999). While most medicine in pill form is prescribed in milligram quantities, a vomeropherin works with a fraction of that amount. "If you compare a picogram to a gram, it's like the length of a pencil eraser compared to the length from here to the moon. Also significant is the speed at which vomeropherins travel to the brain: One ten-thousandth of a second is all it takes for the molecule to activate the hypothalamus" (Kodis, Moran, & Houy, 1998, p. 160). A study performed by Dr. Monti-Bloch used single VNO cells that had been harvested from research volunteers and cultivated in a petri dish. The single VNO cells fired in reaction to the pheromones but showed no response to odors. "This study showed that the VNO contains neurons that jumped to life in the presence of a pheromonal stimulant, even when separated from their homebase VNO" (Kodis, Moran, & Houy, 1998, p. 62).

Human Discovery

The vomeronasal organ was discovered in 1703 by a Dutch military surgeon named Ruych who was examining a young soldier with a facial wound that left open the lateral walls of the nose (Doty, 1995). Thought once to be vestigial, the vomeronasal organ is called Jacobson's organ. "Jacobson, for whom the organ is named, observed it in animals but not in humans, and published his findings in 1811" (Doty, 1995, p. 1793). Described as a small chemosensory organ, the VNO serves as a receptor of naturally emitted human pheromones. The typical VNO (see appendix C for an illustration of the vomeronasal system) is a tube that runs in an anteroposterior direction beneath the surface of the nasal mucosa. There is one on each side of the nasal septum. Although the VNO is not evident by superficial inspection, the vomeronasal pits (the opening into the organ) are clearly visible (Doty, 1995). The pits range in size from .2 mm to 2 mm in diameter ("Chemical Messengers," 1995). It is impossible to observe the smallest VNO pits without microscopic assistance (Doty, 1995). "Recent studies show that most (if not all) adult humans have a pair of VNO's in the nose. The VNO produces a definite electrophysiological response to chemostimulation by specific stimulatory substances" (Doty, 1995, p. 816). "The vomeronasal and terminalis nerves connect the VNO to the hypothalamus region of the brain. That is the region of midbrain that regulates the most important processes in the organism" ("Chemical Messengers," 1995, p. 3). "The consensus of investigations, into the connectivity of the VNO to the brain can be thus summarized: (a) the vomeronasal nerve (VN) exists; (b) it travels across the nasal septum to connect with the accessory olfactory bulb; and (c) the VN nerve is accompanied by large ganglionic elements of the terminal nerve" (Doty, 1995, p. 812).

Characteristics of Pheromones

The term pheromone was introduced in 1959 by German chemist Adolph Butenandt to define substances secreted by an individual and producing behavior effects in conspecifics. In mammals, the effect of pheromones seems to be mediated through the vomeronasal system (Berliner, et al., 1997). Electrophysiological recordings from the human VNO have revealed a

distinct response to naturally occurring compounds derived from adult human skin (Doty, 1995). This is plausible because the skin is the largest and most complex organ of the human body. Crowded together in a single square centimeter are, on the average, over six million cells, 5000 sensory bodies, 100 sweat and 15 sebaceous glands, as well as 200 pain points, 10 to 25 pressure points, 12 cold and 2 warm points. Four meters of nerve fibers and one meter of blood vessels guarantee interconnection and supply. The armpits are the most important pheromone factories ("Chemical Messengers," 1996). The glands that are thought to emit pheromones are located in the torso of the body (Shapiro, 1999).

"We began to lose our awareness of pheromones when we started to wear cloths and bathe" (Bishop, 1996, p. 9). Napoleon Bonaparte was to the point: "Don't wash any longer, I'm coming back soon." He wrote this in a dispatch from his camp to Empress Josephine. The brilliant strategist obviously possessed an infallible sense of how the nose plays a key role in love and sex ("Chemical Messengers," 1996). Vomeroopherins are chemosensory substances whose effect is mediated through the vomeronasal organ (Taylor, 1994). Pheromones are species specific. Gender specificity has also been identified for a significant number of vomeroopherins (Berliner, et al., 1997). This should not be surprising. New research is uncovering startling, even life-threatening, differences that show that physicians should start prescribing drugs based on gender. Even common drugs such as aspirin affect women differently from men. A recent vaccine has been developed for genital herpes that appears to protect women only (Haney, 2000). Why are these differences emerging now? A possible explanation is "that it was not until the early 1990's that the Federal Drug Administration forced drug manufacturers to allow women of child-bearing age into drug studies" ("Prescriptions Must," 1999, p. 7A).

Pheromones are external chemical messengers, which are secreted to the outside by an individual and received by a second individual of the same species in which they induce a behavioral reaction ("Chemical Messengers," 1996). Dr. Clive Jennings-White, Ph.D., suggests that "mood, sexual interest, anger, and rage are but a few of the emotions that are believed to be pheromone sensitive. This may explain behaviors such as 'mob-mentality' in which people unexpectedly exhibit aggressive behaviors in a group that they normally would not alone" (Shapiro, 1999). "Pheromones are not aphrodisiacs but rather subtle communicators that provide information and not instant, flat-out lust" (Kodis, Moran, & Houy, 1998, p. 92).

Pheromones are safe. Initial toxicology tests in laboratory animals, utilizing oral and inhalation administration routes at dosages ranging from 100,000 to 1 million times the projected human dose, have not demonstrated evidence of toxicity (Berliner, et al., 1997). Vomeroopherins are not readily absorbed in vital organs or other tissues, are readily excreted in feces and urine, and should offer a substantial safety factor compared to standard drug therapy. Seventy-five percent of the dose was excreted within 48 hours. Among the observations for one class of vomeroopherins were reduction of cardiac and respiratory rate, increase in body temperature, increase in the electrical conductance of the skin (galvanic skin response), and an increase in alpha rhythm brain waves (Berliner, et al., 1997). Another study produced an increase in the cardiac frequency or rate (Berliner, Jennings-White, Monti-Block, and Diaz-Sanchez, 1996). "The heart rate was determined from R-intervals of the EKG. The pheromone increased cardiac rate by 3.8 beats/minute. These changes developed about 10 seconds after a single VNO

stimulation with the PH-15; after approximately 2 minutes, the heart rate returned to control values" (Berliner, Jennings-White, Monti-Block, and Diaz-Sanchez, 1996, p. 259).

Concurrently with the changes, an increase in parasympathetic tone and an amelioration of anxiety effects were observed (Berlinger, Jennings-White, Monti-Block & Diaz-Sanchez, 1996). "Alpha waves are described as the brain waves associated with a transition or lightening of sleep, while beta waves are emitted during consciousness, and theta waves are associated with stage 1 and 2 sleep" (V. Pegram, personal communication, May 1, 2000).

Early Verification of a Functioning VNO

To probe the function of the human VNO, Luis Monti-Bloch devised a combination electrode and microspritizer that he used to blow small amounts of the compounds Berliner had isolated from human skin directly into the either the VNO or olfactory epithelium of volunteers, while simultaneously recording the surface electrical potential of the tissue. This produced a decreased potential in the VNO, similar to that caused by odorant molecules when they bind to the olfactory epithelium. Furthermore, the response varied by gender; one compound elicited a stronger VNO response in men than in women, and another induced a stronger response in women than in men. The results suggested that the VNO can at least respond to specific compounds, a necessary first step in including a physiologic or behavioral effect. Also, the fact that the compounds did not elicit a response from the olfactory epithelium at the concentrations tested indicates they may exert an effect without eliciting a conscious awareness of any odor ("Chemical Messengers," 1995)

In another test, Monti-Bloch tested subjects with an apparatus that measured the electrical response of the VNO. Small amounts of different substances were delivered to the VNO, and results were recorded. Four substances were used in the test: plain air, synthesized human pheromones, a solution with pheromones, and a fragrant, non-pheromone, clove-essence mixture. Monti-Bloch used a double-blind procedure, where neither the subject nor the clinician could be influenced by knowing which one of the several substances was released into the nose.

A small probe measured the electrical response of the VNO. The VNO reacted only when the pheromone solutions were released into the nose. Monti-Bloch concluded that the synthesized human pheromones triggered a reaction in the VNO, whereas other substances did not. He repeated the experiment, measuring the response of the olfactory organ in the nose, which governs the sense of smell. This time, only the clove essence triggered a reaction. These experiments confirmed that there are two sensory systems in the nose, each of which is stimulated by a different class of molecules (Erox Corporation, 1997).

The last preliminary study was reported in the journal *Brain*. That study indicated that Berliner's female-derived substance induced magnetic resonance imaging (MRI) observable brain activity patterns in male (but not female) subjects similar to those induced in other animals by VNO stimulation (but not by olfactory stimulation). This study suggests that the relevant brain structures and supporting neural connections to the VNO are in good working order (Goldman, 1999).

Referenced Studies

In 1991, Monti-Block and Grosser reported that 49 human subjects of both sexes (18 to 55 years old) were exposed to 15-25 picograms of human pheromones, clove oil (an olfactant), and a diluent. These substances were administered to the VNO or olfactory epithelium (OE) in .3 to 1 second pulses from a nasal cannula. One of the pheromones (ER-830) significantly and primarily stimulated males ($P < 0.01$; $n = 20$) while another (ER-670) produced a significant effect on the females alone ($P < 0.001$; $n = 20$). The other pheromones tested fail to show significantly different effects in either the male or female test population ($P > 0.1$) (Monti-Block and Grosser, 1991). Responses were indicated by the measurement of electrical activity generated in the VNO or OE after exposure to a substance.

A follow-up study (using the same methodologies) affirmed the chemo-sensory functionability of the human VNO and that it exhibited a sexual dimorphic specificity. Six vomeropherins (PH 15, PH 78, PH 84, PH 30, PH 56, and PH 94B) and two olfactants (1,8 - Cineole, and *l*-carvone) were selected as conditions for this 60-subject (30 males and 30 females) trial. Once again, vomeropherins generated an electrical response isolated to the VNO, while the olfactants affected the OE alone. It should be noted that the (chemical) conditions of this test were different from the first, but the results were the same. Additionally, however, certain autonomic parameters were accessed to determine the VNO's ability to cause modulations within them. Electrodermal (sweating), skin temperature, and α -cortical (alpha brain wave) activity were evaluated to determine whether the VNO was capable of transducing signals that caused change in these parameters. "Galvanic skin responses were recorded using a pair of 8.0 mm silver electrodes in contact with the palmer skin of the medial and ring finger. This was accomplished through a conductive gel interface that passed a continuous electrical signal having amplitude of 10 μ amp DC through one of the electrodes. Skin temperature was recorded by a small (1.0 mm) thermistor probe attached to the right index finger" (Monti-Bloch, Jennings-White, Dolberg, & Berliner, 1994, p. 803). When questioned, none of the subjects were able to smell or otherwise consciously detect PH 15, and it produced no effect on the olfactory epithelium. The administration of PH 15 and PH 78 to the conscious male subjects significantly increased electrodermal activity, skin temperature, and α -cortical activity. The same pheromone produced a limited effect on females. Parallel to the male responses, pheromones PH 94B and PH 56 induced significant increases (among the parameters mentioned) for female subjects and limited results in the male population. The other pheromones considered in the test failed to produce significant responses in each of the four categories. Once again, the results indicated the same gender sensitivity previously stated. Long-lasting stimuli produced an adaptation response in the VNO characteristic of other types of chemoreceptive tissue (Monti-Bloch, Jennings-White, Dolberg, & Berliner, 1994).

A third study entitled *The Functionality of the Human Vomeronasal Organ (VNO): Evidence for Steroid Receptors* demonstrated that the VNO is a functional organ able to influence the hypothalamic pituitary system by producing changes in blood luteinizing hormone (LH) and follicle-stimulating hormone (FSH) following its exposure to a steroidal vomerophrine. Twenty volunteers (10 males and 10 females) were exposed to one-second pulses of PDD (pregna-4, 20- diene-3, 6-dione) every 10 minutes during a six-hour period. In males, the steroid decreased LH hormone pulsatility, which resulted in a statistically significant reduction of

plasma LH levels ($P < 0.009$) and FSH pulsatility ($P < 0.021$), but it produced no significant effect in female subjects (Berliner, Jennings-White, Monti-Block, and Diaz-Sanchez, 1996). Also noted were the biological responses of decreasing respiration and cardiac frequency, augmentation of the alpha brain waves, and the decrease of serum testosterone ($P < 0.01$). Because it is well known that the skin actively metabolizes steroids, this study advanced the hypothesis that human skin produces gender specific pheromones and delivers them to the environment. These results contribute additional evidence supporting the functionality of the human VNO and its repercussions in autonomic and psychophysiological functions as well as in neuroendocrine secretions (Berliner, Jennings-White, Monti-Block, and Diaz-Sanchez, 1998).

Another background study chosen for review involved 135 volunteers (60 women and 75 men, 20 to 45 years old). It was found that a pheromone-induced stimuli as recorded by ECG was followed (after a latency of 340-600 minutes) by a mild bradycardia and bradyapnea, increased parasympathetic tone (measured through physiologic sinus arrhythmia), small but significant increase of core temperature, and decreased frequency of electrodermal activity events. The data suggests that chemosensory information processed in the VNO is reaching different areas of the central autonomic nervous system through a polysynaptic path (Berliner, Jennings-White & Monti-Block, 1998).

Finally, in a study performed at the University of Utah School of Medicine, androstadienone (a male pheromone present on male human auxiliary hair and on the male axillary skin surface) was administered to normal female subjects to determine whether it was capable of altering behavior as well as autonomic function. Forty female subjects were used in this randomized, double blind study. The agent (as well as a control) was directly administered to the VNO in picogram amounts. The administration of this steroid resulted in a reduction of nervousness, tension, and other negative feelings, and concordant changes in autonomic physiology (Grosser, Monti-Block, Jennings-White, and Berliner, 1999).

Differences between Olfaction and VNO

The following can be said to summarize the differences between VNO and olfactory functions:

1. When an odorous molecule contacts its specific receptor, an olfactory nerve transmits a signal to the limbic portion of the brain where the odor is recognized as such. On the other hand, vomeropherins contact the VNO receptor, and signals are transmitted through neural pathways, primarily to the hypothalamus (Berliner, et al., 1997).
2. The medial wall of the human VNO is lined with epithelial elements, which constitute a distinctive subset of peripheral chemosensory receptor cells (Berliner, et al., 1997). The sensory elements of the VNO consist of distinctive elongated bipolar neuroepithelial cells with an apical membrane provided with microvilli and lacking cilia, which makes them distinctive and different from olfactory receptor cells (Monti-Block, Jennings-White, Dolberg, & Berliner, 1994).

3. Though both the VNO and olfactory systems connect to the hypothalamus region of the brain, the VNO nerves project to the accessory olfactory bulb, while the olfactory nerve does not (Doty, 1995).
4. Most vomeropherins excite the VNO, but not the olfactory epithelium; human subjects report most of them to be odorless. Furthermore, common olfactory stimulants, such as cineole and clove oil, do not stimulate the human VNO. The literature suggests that the olfactory system and the VNO are stimulated by entirely dissimilar agents. In addition, the response of the VNO to vomeropherins varies with the sex of the subject; some vomeropherins stimulate males more than females, and vice versa. The human VNO receptor responses to vomeropherins display electrophysiological characteristics quite similar to those olfactory receptors display to odorants (L. Monti-Block, personal interview, October 25, 1999).

The aforementioned background warrants the investigation of chemical fire detection. The potential of pheromones to protect lives currently at risk to night fires in the City of Irondale, Alabama, warrants the effort of this research endeavor. If pheromones can be relied upon to provide chemical fire detection-awareness, the Irondale Fire and Rescue Service will become more effective in preventing future deaths and injuries from fire. To secure funding for the exploration of this issue the researcher presented the concept of sensual fire protection to the Pherin Pharmaceutical Company in a common vision influencing style that relied on reward power (marketability and legacy issues), expert power (fire and emergency service background), and information power (previous research). These issues are addressed in Chapter 5 "Influencing" of the *Executive Leadership Course Student Manual* of the National Fire Academy (2000).

LITERATURE REVIEW

There were only three referenced studies discovered that included the use of PH 15. The same pheromone investigated in this study was used in a Stanford University project involving functional magnetic resonance imaging technology and airborne compounds of oestra-1,3,5 (10), 16-tetraen-3yl acetate (also known as PH 15). Utilizing high and low concentrations of PH 15, the researchers observed a significant compound-induced brain activation in eight healthy males. The subjects were exposed to a concentrated air stream that passed over the PH 15 compound diluted in mineral oil while positioned in a functional MRI. The placebo condition was presented in the same manner but did not include the active agent PH 15. Varying between "stimulus" and "no-stimulus" conditions, the researchers observed a contrast between the MRIs taken before and during the "stimulus" portion of the tests. A number of t-tests for paired samples and single samples were used to evaluate post-presentation MRI images of the brain.

Activation in the inferior frontal gyrus during the high concentration condition was significantly greater in the right than in the left hemisphere ($P=0.30$). A trend toward greater thalamic activation was observed for the high concentration than the low concentration compound ($P=0.08$). These findings localized human brain activation that was induced by an undetectable air-borne chemical (the low

concentration compound). Although the subjects (eight males with a mean age of 29) were unaware that any compounds had been present, the findings confirmed localized male human brain activations that were induced by an undetectable airborne chemical known as PH 15 (Sobel, et al., 1999, p. 209).

Earlier in this paper, a referenced study by Monti-Block, Jennings-White, Dolberg & Berliner (1994) concluded that PH-15 increased electrodermal activity, skin temperature, and α -cortical activity in males and had a limited effect on females. In all, thirty males and females between the ages of 20-45 were involved in the study. The subjects were presented six different pheromones and two odorants. Procedures called for a direct stimulation of the VNO by a variety of pheromones. All the subjects were conscious during this study. The degree of response to PH 15 in the male population was significantly different from that in the female population in all categories except skin temperature. There was not a significant difference in that category. Significant bio-changes that occurred in the four categories were observed after the delivery of PH 15 ($P < .01$) (Monti-Block, Jennings-White, Dolberg & Berliner, 1994).

Sleep research involving pheromones is quite rare. To date, only one unpublished study (Monti and Monti, 1999) has been performed using the steroidal pheromone PH 15. Pherin Pharmaceuticals sponsored a study to examine the psychopharmacological effects of PH 15 on the sleep cycles of normal young adult male and female human volunteers (mean age 27 years). The pheromone was studied using a randomized, single blind, placebo-controlled experimental design. In all cases, a single dose of pheromone and placebo was used. The pheromone was dissolved in ethanol at a concentration of one milligram/milliliter. A total of 800 pg were administered in two different dosages. It was administered bilaterally and direct using a manual vomeronasal applicator (MVA). The delivery device consisted of a chamber containing thirty milligrams of cotton that had been previously soaked with one milliliter of pheromone solution, or vehicle, and allowed to evaporate overnight. Therefore, the MVA chamber delivers dry vapors of the pheromone. The MVA contained a one-way flow valve, and it was calibrated to deliver a pulse of one milliliter of air containing vapors of PH 15 or control (air was the placebo). The three sleep variables evaluated in this study included total sleep time (TST) or amount of sleep during the recording period, sleep efficiency (SE) or percentage of sleep, and sleep onset latency (SOL) or time to fall asleep after the recordings began. Only the first hour of sleep was recorded. The balance of time was monitored. The study was performed in random order. PH-15 was used with Group B of this study, and it included four males and four females. One half were tested with the active agent and one half with a placebo agent. The other groups were not comparable to this study. PH 15 produced only male gender-specific effects. The effects of pheromone PH 15 in females was comparable to that of the placebo. To the contrary, the data indicated that PH 15 increased sleep latency and decreased the total sleep time ($P = 0.05$ as compared to the placebo), thus suggesting a psychostimulant action in males. Both males and females showed variations in their total sleep time. The group of males treated with PH 15 reported total sleep duration between 4 and 6 hours, while their placebo-treated counterparts reported sleeping for 7 to 8 hours. Though PH 15 included a primary arousing effect (evidenced by a decrease in the total sleep time), it did not affect the amount of awakenings in either the male or female populations. The study suggested that this pheromone could be ideal for treating patients with primary hypersomnia, circadian rhythm sleep disorders (delayed sleep, jet lag, shift work, and unspecified), dyssomnias, and parasomnias (Monti and Monti, 1999).

The work that Sobel et al. performed influenced this project by suggesting that PH 15 activates certain regions of the brain. The work that Monti and Monti (1999) performed influenced this project by suggesting that the α cortical activity that accompanies wakefulness and the administration of PH 15 produced a higher sleep latency threshold and a decreased sleep time in males. Monti-Block, Jennings-White, Dolberg & Berliner's project (1994) examined the relationship of PH 15 administration and α cortical activity. That relationship caused the researcher to wonder if the administration of PH 15 would disrupt sleep patterns enough to cause a sleeping male to awaken. Finally, the work that Monti and Monti (1999) performed influenced this project by suggesting that the α cortical activity that accompanies wakefulness and the administration of PH 15 produced a higher sleep latency threshold and a decreased sleep time in males.

PROCEDURES

Key Words

The following is a review of the key words used in this report.

α -cortical--alpha brain wave or the presence of alpha brain waves (V. Pegram, personal communication, January 15, 2001).

alpha waves--A transition, lightening of sleep (V. Pegram, personal communication, January 15, 2001).

beta waves--wakefulness (V. Pegram, personal communication, January 15, 2001).

Declaration of Helsinki--The Helsinki accords (1975) were embodied in a "declaration of policy intent" signed in Helsinki, Finland, by the United States, Canada, the USSR, and 32 European countries at the end of the Conference on Security and Cooperation in Europe (1973-75). The accords declared inviolable the frontiers of all the signatory nations, thus legitimizing the USSR's World War II territorial gains; provided for scientific, technological, and cultural exchanges; and pledged the signatories to respect human rights, including "freedom of thought, conscience, religion, or belief." Helsinki human rights committees were established in various countries throughout the world to work for implementation of the Helsinki accords principles. Many of these groups continue to be active in human rights causes today (Declaration of Helsinki, 1996).

delta waves--stage 3 & 4 sleep, deep sleep (V. Pegram, personal communication, January 15, 2001).

dendrites--a branched part of a nerve cell that transmits impulses toward the cell body (Morris, 1978).

HEPA--high efficiency particulate air (Morris, 1978).

ionize--a device on an air purifier that releases negative ions into the outgoing filtered air. The negative ions help the air purification process by attaching themselves to very small airborne particles in the room. These particles take on a negative charge and may join with positively charged particles such as dust, pollen, smoke, and pet dander to form larger particles that are then more readily captured by the filter system (Morris, 1978).

limbic system--an evolutionary old part of the brain that regulates survival behaviors such as feeding, fleeing, fighting, and reproducing. The limbic system is involved particularly with the sense of smell and with certain complex emotional responses, but it plays a role in regulating basic body functions (Morris, 1978).

MMD--micrometer diameter, a micron is one thousandth of a millimeter (Morris, 1978).

mucosa--same as mucus membrane (Morris, 1978).

nebulizer--a device used to convert liquid into a fine spray (Morris, 1978).

pheromones--Greek, **phero** (I carry) and **hormone** (to excite). Pheromones are chemosensory substances whose effect is mediated through the vomeronasal organ (Louis Monti-Bloch, personal communication, October 15, 1999).

Pherin--to carry (Louis Monti-Bloch, personal communication, October 15, 1999).

Picogram--one millionth of a billionth of a milligram (Louis Monti-Bloch, personal communication, October 15, 1999).

Vestigial--structure or organ that occurs or persists as a rudimentary or degenerate structure--an evolutionary relic (Morris, 1978).

Vomerophrine--a synthesized pheromone (Louis Monti-Bloch, personal communication, October 15, 1999).

VNO--The vomeronasal organ is a blind-ending tubular structure located close to the base of the nasal septum and separated from the olfactory epithelium by a large field of nonsensory respiratory epithelium (Louis Monti-Bloch, personal communication, October 15, 1999).

theta waves--stage 1 & 2 sleep, lighter sleep (V. Pegram, personal communication, January 15, 2001)

This research project began with an extensive literature review. The published works, references, and concept of sensual fire protection were presented to the Pherin Pharmaceutical Company in Menlo Park, California, in a conceptual meeting on October 25, 1999. Shortly after this date, Pherin agreed to accept the proposal outlined in appendix A under the stipulation that the study must be performed under the auspices of an institutional review board. The Western Institutional Review Board granted approval of the study on August 16, 2000 (see appendix D

for certificate of approval, consent form, and insurance certificate). The certificate of approval was granted to Dr. G. Vernon Pegram, Ph. D. He is the director of the Sleep Disorders Center of Alabama (SDCA), Incorporated.

This single-blind study consisted of the presentation of an airborne dosage of active agent (PH 15) and placebo (distilled water) to sleeping males and females. After careful consideration, it was determined that both the active agent and the placebo should be delivered through the ambient air from a position up to 187.96 centimeters from the sleeping patient's face. The active and placebo conditions (agents) were administered in stage 2, stage 3/4, and REM sleep. The intention of this study was to present ALL subjects to the six conditions by a chart of randomized order. Because this may not be possible in one night, thirty sleep nights were calculated into the expenses of the project.

The active agent was supplied by Human Pheromone Sciences International (HPSI), and the placebo will be locally obtained distilled water. The concentration of PH 15 will be formulated at 3.25 mg/ml.

Inclusion criteria were men and women between (and including) the ages of twenty and fifty with no history of sleep disorders and that are drug free. Exclusion criteria were pregnancy, a history of smoking within the previous year, a respiratory or nasal infection, poor sleeping habits or associated sleep pathologies, allergies, acute or chronic illnesses, previous nasal surgery, or past head trauma. The subjects were paid for their participation in this study. The subjects were paid one hundred dollars (\$100.00) for the first night of the study and fifty dollars (\$50.00) if an additional night of study was required.

Sleep disorders among the subjects were ruled out by interview, medical examination, sleep history questionnaire, and sleep disorder screening procedures. It was very important to rule out sleep disorders in subjects. A criticism that the researchers were attempting to avoid was that arousals and/or awakenings were due to apnea, myclonus, or reflux. Regardless of the screening, the researcher anticipated that some of the subjects would fail an experimental night because of these problems.

All subjects were screened for the presence of a vomeronasal organ. The screening was coordinated with an HPSI designated consultant and occurred on a Friday afternoon. The screening was performed at a local otorhinolaryngologist's (ear, nose, and throat physician) office utilizing a magnified and lighted endoscope that was equipped with a fiber optics camera. The internal image of the nasal cavity was transmitted to a television monitor to help identify the entrance of the VNO. (Figure E1 is a picture of the screening process.) The local physician was trained to perform this examination process so that replacement subjects could be screened.

EEG electrodes were secured for the recording of sleep stages using the following electrode placements: C3, C4, O1, O2, left and right mastoids. In addition to the EEG, eye movement or EOG (outer canthi, above and below midline), and EMG or muscle movement (supra- and submental) were used to score sleep and rule out sleep disorders. EEG's were portioned to allow recording and scoring by the standard Rechtschaffen and Kales system. To monitor EEG arousals, the procedures as outlined in *EEG Arousal: Scoring Rules and Examples*

(American Academy of Sleep Medicine, 1992) were used to score the subject's sleep experience. The protocol also specified that arousals and/or awakenings occurring within five minute after an administration of PH 15 or distilled water formed the basis of the statistical reporting. Those arousals were noted on the sleep chart (appendix G) by SDCA personnel. Other physiological measures included SPO₂, respiratory effort, and the autonomic responses of pulse and heart rhythm (modified Lead II).

Cardiac frequency (CF) was determined by observing the "R-wave" to "R-wave" spikes on the sleep records to determine if the active agent resulted in a change in the heart rate. To determine if the active agent resulted in a change in heart rate (CF), several base-line samplings were recorded on each subject. Heart rates were also determined on each subject 20 seconds after active agent and placebo agent administration.

On each subject, the mean of the baseline and active agent and placebo agent samplings were determined. The mean of the active agent and placebo agent was compared to the baseline mean to determine a positive or negative influence on each subject. Those factors were then averaged for male as well as female subjects. This process indicated that PH 15 produced a mean cardiac frequency value of + .77 beats per minute for males and + .74 beats for females.

The subjects arrived at the SDCA at 2030 hours to be prepared for the night's monitoring. The staff of the SDCA explained the research project and presented the Institutional Review Board documentation. The IRB includes a study-specific consent form that the subjects are required to sign in order to participate in the study. The patients were then given an orientation to the various monitoring leads that are customarily attached to a sleep study patient. Electrodes were secured for recording central responses known as brain waves or EEG (C3, C4, O1, O2, left and right mastoids), autonomic responses of pulse and heart rhythm (modified Lead II), eye movement or EOG (outer canthi, above and below midline), muscle movement or EMG (supra- and submental), oxygen concentration, and breathing muscle movement. The respiration belt was secured comfortably around the rib cage at or about the 4th or 5th ribs. For approximately thirty minutes, the staff of the SDCA calibrated their monitoring devices to choreographed movements the subjects were required to perform. Once the calibration ritual was complete, the subjects were allowed to go to sleep. The polysomnography machine used during this study was a Nihon Kohden model 125.

Observations of the subjects during sleep were also of a visual nature. In addition to a regular closed circuit camera, the SDCA utilized an infrared camera by which behavioral responses of the subject could be recorded in total darkness from "lights out" to "lights on."

The subjects slept in electrically shielded and sound-attenuated bedrooms. The rooms in which the subjects slept contained approximately 32.5 cubic meters of ambient atmosphere (appendix F is a diagram of the bedroom). To isolate the subject's environment, the entrance doors of the sleep rooms were shut. The HVAC (heating, ventilation, and air conditioning) system discharge and return vents were dampered to isolate the sleep room. A convectional baseboard heater that did not produce air currents provided any heat that was necessary.

The target number of male subjects was twenty; however, this was dependent on the effective dosage and duration of the pheromone exposure. A minimum of ten male subjects was considered. A target of five was used for the minimum number of female subjects included within the test population.

The dosage administration time, latency period, and effective duration of the dosage was determined in consultation with Human Pheromone Sciences International. It was determined that the pheromone could be delivered in fifteen seconds followed by a five minute latency period for reaction and a thirty minute effective dosage (duration) period.

Equipment

These specifications of equipment were for each of the sleep rooms used during the trial. There was sufficient reserve equipment to continue the testing in the event of an equipment failure.

There were two remotely controlled nebulizers: one for the active agent and the other for the placebo or control. The nebulizers were located outside the subject's room to control noise stimuli. Appendix H is a copy of the guidelines the sleep technologist used to conduct and monitor the tests. The sleep technologist recorded his/her observations during the test.

Nebulizer Specifications:

The nebulizer chosen for use in this study was the DeVilbiss® Model 099HD\Ultra-Neb® 99 large volume ultrasonic nebulizer (figure E2 is a picture of the nebulizer). The principal nebulizer features associated with this study are as follows: (a) a 150 milliliter medicine dispenser, (b) a 6.0 milliliters per minute nebulization rate, and (c) a < 4.0 average micron/millimeter diameter particle size (MMAD). The nebulizer discharged into a delivery hose of 2.5-centimeter (minimum i.d.) corrugated plastic polyvinylchloride ventilator hose approximately 2.44 meters in length. This hose was routed through the ceiling membrane in the hallway, through the double firewall barrier with its insulation, and down through the ceiling membrane of the subject's room. Because the hose was flexible and semi-translucent, installation took place in such a way that the fire wall integrity was never compromised during the study. The hose terminated directly above the "pillowed" area of the bed (figure E3 is a picture of the ceiling discharge). The distance from the end of the discharge hose to the subject's pillow was 187.96 centimeters. Five seconds of additional nebulizer operation time was required to purge the delivery hose on each presentation. This increased the delivery time to twenty seconds per condition. Since the nebulizer delivers 6.0 milliliters per minute, each condition required 2 milliliters of PH 15 or distilled water. The unit functions on AC power. A special panel of on/off switches was installed in the control room to remotely control the nebulizers. This control box engaged the nebulizer during the tests. The intent of the two delivery systems was to deliver PH-15 and distilled water to the ambient atmosphere of a sleeping subject's room from a sound-isolated remote location. Once the PH-15 or distilled water was delivered, the procedures specified a one-minute delay before operating the air purifier. This allowed a

complete natural disbursement of the PH-15 before air currents were introduced into the sleep room.

Air Purifier Specifications:

The air purifier chosen for use in this study was the Holmes Model HAP-240 air purifier with independent electronic ionizer. The unit features a multi-speed fan switch that affects the efficiency of the unit. On the "quiet" setting, the unit is rated at 54 cubic feet per minute. At that rated capacity, it takes 1.82 minutes (1 minute, 50 seconds will be used) to clear a sleep room with the dimensions of 32.5 cubic meters. Two minutes were used in this study. The unit functions on AC power and can be controlled remotely (E4 is a picture of the various controls). Please note on the room diagram that the air purifier was located beside the subject's bed. The air purifier was connected to a remote AC switch located in the control room.

Smoke Detector

To prevent any potential conflict, an ionization/photoelectric smoke detector was in operation during the test. The detector chosen for this was the First Alert Double Sensor[®] Model-SA301C.

Carbon Monoxide Detector

To rule out any potential conflict, a carbon monoxide detector was in operation during the test. The detector chosen for this was the Kidde Nighthawk[®] Model-KN-COB-DP.

Convectional Baseboard Heater

The sleep room was isolated from the HVAC system. If auxiliary heat was required for the study, a convectional baseboard heater was used because it did not create a draft or air currents.

Data Analysis

The results of this study were reported statistically from a chi-square format and a t-tests for paired samples format. The results were obtained with the assistance of a computer program known as SPSS for Windows 6.1[©] - PC Plus Student Ware. The program is manufactured by the Statistical Package for Social Sciences Company located in Chicago, Illinois. These methodologies of reporting are non-parametric forms used to test hypotheses about the relative proportion of cases falling into several mutually exclusive groups and comparing the mean values of two samples.

The study was designed to introduce the active agent and the placebo agent during stage 2, stage 3-4, and rapid eye movement (REM) sleep. By design, the researchers planned to report all six conditions of each of the subjects. The first page of appendix I (the SPSS report) contains a five-column chart of data entries. The first and second columns are demographic in nature. The third column is labeled "NUMBCOND," and it lists the number of sleep stages in which a subject was tested during the study. Columns four and five specify the number of arousals and/or awakenings that occurred in response to the administration of the active and placebo agents. Columns six and seven indicates whether a subject responded to the active and/or placebo agents. Excluding the respiratory-event arousals, responses that occurred within five-minute post delivery thresholds were considered in the data. The records were reviewed for each active and placebo agent delivery. Each individual arousal or awakening was counted and recorded in either column four or five.

In this study, each subject had the opportunity to respond to the active or placebo agent one or more times in any of the stages of sleep that they reached during the test.

Assumptions and Limitations

The first limitation concerns the amount of literature published about PH 15. The researchers could identify only three sources of information to compare and contrast. It would have been helpful to have had additional sources.

None of the subjects participating in this study had been previously diagnosed with a sleep disorder. All respiratory arousals were eliminated from consideration in the scoring process. Any subject that appeared to have a marginal sleep disorder was counseled and referred. A decision was made not to replace those subjects. In a longitudinal study, those subjects would have been eliminated and replaced by substitutes.

Although the agent delivery systems (identified under the procedures section) can be objectively reproduced, diffusion would vary the amount of exposure according to the subject's sleeping position and the time at which a sample was taken. The disbursement patterns were consistent with all presentations due to controlled ambient airflow.

Based on the sponsor's earlier work, this study was primarily designed to test male subjects and to use the female population as a control. As a result, the statistical reporting will be unbalanced toward the male population. All the subjects in this test were healthy non-smokers, and medication free. In addition, all of the subjects were Caucasians. This was not designed into the study. The pool of subjects came from a group affiliated with the sleep center and did not include various races. Since this study was a pilot program to confirm or deny the effectiveness of PH-15 in the ambient environment, it may be that, in the future, the same methodology will be used to test a more diverse population.

Another possible limitation of this study involves the design and type of analysis performed. Each subject had one opportunity in each of the stages of sleep to respond to the two agents. A better analysis might be performed in a repeated-measures type of study in which each

subject would have multiple opportunities to respond in the various sleep stages, and a percentage of response could be determined. This was not possible due to the number of sleep nights calculated into the study's budget.

The test group population was quite small for reporting with the greatest degree of certainty. Most sleep studies utilize small test groups, and this study was no exception.

Normally, a researcher applies a Yates or similar correction to a chi-square statistical study involving cells with a frequency of less than five. In this case, that was not performed due to the relative strength of the chi-square significance or non-significance.

None of the customary fire gases that contribute to the problem of fire deaths were present. For example, an ambient exposure resulting in a 20-percent blood saturation of carbon monoxide (a common fire gas) will cause disorientation. Increase this exposure to a 40-percent saturation and unconsciousness will occur. Many of the common fire gases tend to cause loss of smell and depression of the central nervous system. After a limited exposure, a few of the fire gases will actually cause a sleeping person to fall deeper into unconsciousness (Meidl, 1970). The results of a sleep study performed in an environment of fire gases would probably be heavily influence by this condition.

RESULTS

Appendix G (Sleep Chart) and appendix I (SPSS Report) illustrate the results of the active agent and placebo agent tests. Each of the 15 subject's sleep experiences were scored by the procedures as outlined in *EEG Arousal: Scoring Rules and Examples* (American Academy of Sleep Medicine, 1992). The sleep records were scored twice. Once by the sleep technologist and once by the research coordinator. If any non-respiratory related arousals and/or awakenings occurred during a test condition, the subject was scored for each occurrence.

Answers To Research Questions

Research Question #1. The first question was if bio-measurements confirm an ambient exposure to pheromones. The answer is yes. Electroencephalograms were the primary bio-measurement used to determine human response. For the overall group, there were 44 non-respiratory arousals and/or awakenings that occurred in response to the ambient airborne presentation of the active agent. There were only 11 non-respiratory responses that occurred in response to the ambient airborne presentation of the placebo agent.

Research Question #2. The second question was if pheromones cause arousals in sleeping subjects. The answer is yes. There were 29 male arousals and 15 female arousals that occurred in response to the ambient airborne presentation of the active agent. There were only 6 male and 5 female arousals in response to the ambient airborne exposure of the placebo agent. Those arousals were in response to the following conditions: overall-38 active, 25 placebo; males-26 active, 14 placebo; females-12 active, 11 placebo.

Research Question #3. The third question was if pheromones cause awakenings in sleeping subjects. The answer is yes. It should be noted that only 4 awakenings occurred in response to the ambient airborne presentation of the active agent. These statistically significant awakenings were experienced by only three subjects, all of them male, and were made in response to the 38 active presentations. Three of the awakenings occurred during REM.

Notes Pertaining to Appendix I (SPSS Report):

The table on page 7 refers to the subject number, the subject's sex, the number of conditions or sleep stages a subject reached during the test, the number of arousals and/or awakenings that occurred within the five-minute post active-agent presentation latency period, the number of arousals and/or awakenings that occurred within the five-minute post placebo-agent presentation latency period, and whether or not a person responded to active and/or placebo agents.

Page 12--The mean number of conditions (overall) was 4.20. 2.933 was the overall mean for active agent while .73 was the placebo mean.

Page 22--The Chi-square significance of .919 for the overall group in active agent responses indicates uniformity.

Page 23--The Chi-square significance of .449 for the overall group in placebo agent response indicates significant difference.

Page 24--A Chi-square (goodness of fit test) comparison for response and no response to the active agent and chance yielded a significant difference of .020 for the overall group. A Chi-square (goodness of fit test) comparison for response and no response to the placebo agent and chance yielded a non-significant difference of .796 for the overall group.

Page 32--A t-test for paired samples comparing the mean of the active agent responses to the mean of the placebo agent responses overall was performed to determine any magnitude of difference. The resulting "P" value of .003 indicated a significant magnitude of difference and thus eliminated chance.

Page 44--The Chi-square active agent responses for males was insignificant in difference at .849. The Chi-square placebo agent response for males was significant in difference at .273.

Page 44, and 49--The females experienced slightly more complete sleep (.655 significance) as compared to the males (.558).

Page 50--A Chi-square significance of 1 indicated all female subjects responded to the active agent.

Page 51--A Chi-square significant of .819 indicated a strong degree of uniformity to placebo agent responses for females.

Page 55--The female population in the test group progressed through more sleep stages (mean 4.60) than the males (4.20, page 12).

Conclusion

Based on these statistics:

The overall, male, and female responses to the active agent were uniform (.919, .849, 1.00).

There was significant difference in the overall and male response to the placebo agent while the female population was more consistent (.449, .273, .819).

A comparison of the overall group response to the active agent was compared to that of chance, and a significant difference was determined (Chi-square .020).

An unexpected finding was the high number of female responses to both the active (Chi-square significance of 1.000) and placebo (Chi-square significance of .819) agents.

A number of research-dependent statements can be made concerning this project and subject population.

The arousals were in response to the following conditions: overall 38 active, 25 placebo; males 26 active, 14 placebo; females 12 active, 11 placebo.

Statement #1. PH-15 causes arousals and/or awakenings in males and females significantly above that of chance.

Statement #2. The placebo arousals and/or awakenings were consistent with those of chance and were different from those of the pheromone.

Statement #3. There is a significant difference between active and placebo responses for the test population.

Statement #4. The pheromone PH-15 causes arousals and/or awakenings in the overall test population when administered in the ambient atmosphere.

Statement #5. The placebo did not cause arousals (in significant numbers) and/or awakenings in the overall test population when administered in the ambient atmosphere.

DISCUSSION

The presentation of the active agent in the study entitled *Blind Smell: Brain Activation Induced by an Undetected Air-borne Chemical* (Sobel, et al., 1999) was a concentration air stream as opposed to a natural ambient drift pattern utilized in this study. Sobel's subjects sniffed the air stream that was supplied to them while positioned in an MRI diagnostic machine. "Following the scans, all eight of the eight subjects verbally reported that they could not detect an odor, and they were guessing throughout the experiment" (Sobel, et al., 1999, p. 212). Only males were evaluated in this study, and they were conscious. The results as reported by Sobel, et al., were similar to the results reported here (Sobel P=0.03, this project P=0.02 for males), although the methodologies were clearly dissimilar. "Both high and low concentrations of the compound induced significant brain activation in all subjects" (Sobel, et al., 1999, p. 212). Sobel went beyond this project, investigating the specific region of brain activation. This project concentrated on determining if a natural ambient drift pattern delivery method would cause arousals. Sobel's work focused on males alone, while this project evaluated a mixed-gender population. He cited that the "EEG and behavioral evidence suggest, that air-borne chemicals can affect the nervous system without being consciously detected" (Sobel, et al., 1999, p. 209). Sobel's work and this study confirmed that specific areas of the human male brain would respond to an airborne presentation of PH 15.

Monti-Block, Jennings-White, Dolberg & Berliner (1994) also used different parameters (demographics and protocol) in their study of conscious subjects. Statistically, the results of this study concentrated on the effect that PH 15, PH 78, and PH 84 have on conscious males, and that PH 56 and PH 94B exhibit on conscious females. Additionally, two odorants were used in the test. "Stimulation of the OE with the same quantity of odorant 1, 8-cineole and *l*-carvone produced depolarization of 6.8 ± 2.6 mV, but little or no response in the VNO" (Monti-Block, Jennings-White, Dolberg & Berliner, 1994, p. 673). No odorants were used in this study. Though the resulting effects of a PH 15 exposure on females was indicated on a bar graph, the exact influence was not reported. It is unfortunate that the female population cannot be statistically studied and compared to the results of this study. For the male population, the changes in the four categories (EVG mV, α -cortical activity, electro-dermal, and skin temperature) were significant ($P < .01$) and inferentially comparable to the results of this study ($P = 0.02$). The PH 15 was administered by direct application to the VNO. Monti-Block, Jennings-White, Dolberg & Berliner reported that "the human VNO is more sensitive to vomeropherins than to any of the olfactants tested. While the human OE may respond to some vomeropherins, it is apparent that the olfactory sense and vomeronasal sense are independent. Furthermore, vomeropherins induced autonomic changes through the VNO while olfactants do not" (1994, p. 683).

Monti and Monti's (1999) work was the only sleep study reviewed that utilized PH 15 as the active agent. Once again, the researchers used different parameters (demographics and protocol) to perform their study. The PH 15 was "administered bilaterally using a manual vomeronasal applicator" (Monti and Monti, 1999, p. 8). One milliliter of dry air accompanied the delivery of the agents in Monti and Monti's test, while two liters of moist air were used in this test. The active agent was actually tested on two males and two females. The administration of PH 15 occurred before and between sleep periods, as opposed to being presented during sleep.

Monti and Monti recorded the first hour of sleep on a polysomnography machine. They reported that "our criteria for this short recording was based on previous findings that a single dose VNO stimulation with vomeropherins induced effects within one hour after stimulation" (Monti and Monti, 1999, p. 8). This study recorded the subject's experience for the entire sleep period. The results of the active agent testing on males was somewhat transitional, at $P=0.05$ compared to this study at $P=0.02$. The effect of PH 15 on the females was not as clearly reported as the male experience. Monti and Monti reported that "the effects of vomeropherin PH 15 in females were compared to placebo" (1999, p. 13). This is consistent with the findings reported in this study (Chi-square female active agent 1.00, placebo .819), except on the opposite end of the scale. Females experienced a high number of responses to the active and placebo agents in this study. Perhaps the sleep duration explains Monti and Monti's findings the best because they stated that "the group of males treated with PH 15 reported total sleep duration between 4 and 6 hours while their placebo treated counterparts reported sleeping for 7 to 8 hours" and that the "treated females and placebo treated female subjects indicated sleep duration between 7 and 8 hours" (Monti and Monti, 1999, p. 15). Both groups were extremely small sampling populations. Like the previous study, the PH 15 was directly administered to the subjects by a vomeronasal applicator, as opposed to the natural ambient drift pattern.

The researchers were surprised to see the large number of responses in the female population. Perhaps the female sampling size was too small to properly analyze. The researchers trust that projects beyond this pilot study will answer those questions.

The experience of this study implies change will occur in the way informed citizens of Irondale, Alabama, will choose to protect themselves in the future. The Irondale Fire and Rescue Service is committed to continuing its participation in studies, education, and product development that focus on pheromone fire detection-awareness systems.

From a fire protection point-of-view, this study is a landmark for further investigations of the pheromone-enhanced fire detection-awareness concept. This first effort in determining the effectiveness of an ambient-delivered pheromone in disrupting sleep patterns was successful! Unlike previous sleep work that relied on meaningful stimulus (i.e., Carskadon, et al. [n.d.], Perrin, Garcia-Larrea, Manguiere, & Mastuji [1999], and Oswald, Taylor, & Treisman [1960], etc.) this protocol introduced subjects to an odorless ambient presentation during sleep. The reactions observed were biologically induced and not part of the conscious or unconscious thought process (active-placebo, t-test for paired samples two tailed significance .003). This is promising for the entire industry. This study can be used as a foundation for establishing the possible effectiveness of an ambient administration of other pheromones. There were limitations in the sampling size and subject demographics; however, these limitations seem to be consistent with sleep studies.

The results indicate that PH 15 is effective in disrupting sleep patterns in males and females; however, there was an insignificant number of actual awakenings (five) experienced during the study. Knowing that the difference between arousals and awakenings is in the degree of sleep interruption, the research indicated that PH 15 had the potential of disrupting sleep patterns to the point of waking a sleeping subject. Although it is beyond the scope of this study, the researcher does suggest that the dosage, delivery method, or specific pheromone may need to

be altered in order to find the most effective combination to awaken people. As reported by Carskodon, et al. (n.d.) and Pollack (1996), REM proved to be the easiest stage of sleep in which to generate arousals. The female findings in this study were different from those in other studies. The referenced studies indicated that PH 15 had little or no effect on females, whereas the statistics reported here show a strong correlation between arousals and the administration of the active agent. This is similar to the Chi-square significance reported between male and female active agent findings. The active agent findings in this study were different than those that would occur by chance. The placebo agent findings in this study were consistent with those of chance. Overall, the active agent results were significantly different from the placebo agent results. Though none of the referenced studies examined cardiac frequency (CF), it was determined that males and females responded to the exposure of PH 15. One of the studies identified in background and significance examined the cardiac frequency as a method of testing central nervous system reaction to the administered pheromone. This study states, "The heart rate was determined from R-intervals of the EKG. The pheromone increased cardiac rate by 3.8 beats/minute. These changes developed about 10 seconds after a single VNO stimulation with the PH-15; after approximately 2 minutes, the heart rate returned to control values" (Berliner, Jennings-White, Monti-Block, and Diaz-Sanchez, 1996, p. 259). The increase in cardiac frequency is much smaller in this study (+ .77 beats per minute for males and + .74 beats for females), but it is important to note that the increase in cardiac frequency verifies the central nervous system effects of PH 15 and corroborates the statistical evidence that arousals were caused by the active agent.

The material presented in this study truly causes the researcher to anticipate the development of new delivery methods and uses of pheromones. Therefore, it is one of the intentions of this report to acknowledge that the beginning of the pheromone revolution has occurred. The researcher believes that pheromones will be a household word in five years and be in most medicine cabinets in ten.

RECOMMENDATIONS

The following recommendations are offered as a result of this research project.

Recommendation 1. The vomeronasal organ (Jacob's organ) is rarely mentioned in the medical literature. This has contributed to a non-awareness of its presence or function. The VNO exists in "most (if not all) humans," according to a published study by Doty (1995, p. 816). That research did not indicate the VNO frequency of existence in the general population, nor in the various gender and ethnic groups. Furthermore, little is known about the effect that age, chemical exposure (smoking, dust, pollution, inhaled illegal drugs, etc.), or disease process have on the VNO. A longitudinal study should be undertaken and published by a medical school of otorhinolaryngology to determine the frequency of existence and the various subset deviations.

Recommendation 2. Present PH-15 to a larger sampling of males to determine if the agent is effective in waking subjects that are (a) smokers, (b) on medications, (c) younger and/or older than the test population, and (d) of different races of people. These tests should be performed with various concentrations of the pheromone to determine the minimum effective

dosage per cubic meter of air. The methodologies utilized should be similar to the one used in this test.

Recommendation 3. Experiments should be undertaken to discover the most effective type of pheromone, delivery dosage, and delivery method for disrupting sleep patterns in males and females.

Recommendation 4. Pheromone research and development should continue. Although the scope of this study was the fire protection aspect of pheromones, there are a number of other applications for these special substances. The widespread development of the pheromone industry will correspondingly result in improved pheromone-enhanced fire protection. Aside from the prescribed market, there are many possible consumer applications for PH-15. For example, the arousing effect of PH-15 makes it a natural choice for anti-fatigue applications. From long-haul truckers to sensitive military applications, the demand for a safe, non-habit-forming, inhaled anti-fatigue medication would be significant. Imagine a surgeon who uses PH-15 to assist himself in conducting a twenty-hour surgery and then uses the same drug to arouse his patient in the recovery room. Other possible uses include the manned space program, deep-sea exploration, extended rescue operations, breathing systems for airplane pilots, and even air treatment systems for casinos. This should not be surprising, since the National Aviation and Transportation Center is working on a project to pipe citrus and wintergreen essential oils into the cockpits of airplanes to determine if these scents can increase and promote alertness (Kodis, Moran, & Houy, 1998). With this in mind, one might say that it is just a matter of time until the term **pheromone** is a household name and a category of products found in household medicine cabinets.

Recommendation 5. What effects (if any) PH-15 produces on narcoleptic and (consciousness altering) drug overdose patients should be studied to determine if this pheromone could be used as a therapy for these disabling conditions. Narcolepsy is a sleep disorder characterized primarily by irresistible sleepiness during the day. It is found in 6 out of 1000 people (V. Pegram, personal communication, January 15, 2001).

Recommendation 6. Active or passive delivery systems should be engineered that will be capable of presenting PH-15 (and other pheromones) in residential and workplace environments. Picograms of pheromones can be delivered actively or passively. An active process would be the release of a pheromone sympathetic to a sensing or triggering device. The incorporation of a pheromone delivery system in a smoke detector, sound-actuated bedside device, or in a modified electrical outlet-based air scent and warming system (Wizard[®] and Glade[®] are among the manufacturers that produce these now) would be examples of an active delivery system. Passive pheromone delivery systems would feature pheromones incorporated within the physical structure of building components. A pheromone could be added to the cellulose covering on each side of sheet rock, to the individual yarn fabrics of carpeting, wallpaper, furniture upholstery, and to the various spacklings, compounds, paints, and adhesive mixtures used in building construction. Conceptually, the pheromone would be released during the occurrence of degradation of the building component by heat or fire.

Recommendation 7. Heating, ventilation, and air conditioning (HVAC) pheromone delivery systems should be engineered to interface with central detection systems to deliver effective dosages throughout hospitals, nursing homes, apartment buildings, and hotels. Mechanical engineering studies should be performed to model the disbursement patterns and concentrations required for total building applications.

Recommendation 8. Consideration should be given to incorporating replaceable pheromone delivery components into a multifunctional detector.

Recommendation 9. If pheromones are incorporated into passive systems through some type of encapsulating process, toxicity test, should be performed on the encapsulated products to determine their suitability of use in occupied spaces.

Recommendation 10. Toxicity tests should be performed to determine the effect common products of combustion have on PH-15 and any encapsulated product.

Recommendation 11. The concept of active and passive pheromone delivery systems should be addressed within the National Fire Alarm Code (National Fire Protection Association-NFPA 72). The current code cycle for that standard is 2002.

Recommendation 12. The fire suppression and detection industry is an isolated service industry that typically embraces new technology when it becomes aware of its usefulness. A demand for pheromone-enhanced protection could influence the amount of funding available to perform recommended research. Since the fire service could create this demand, the results of this study should be reported in fire industry trade magazines and at major fire industry conferences.

Recommendation 13. Based on this project's results, additional research should be performed utilizing other pheromones to determine their potential use in the ambient atmosphere.

Recommendation 14. Earlier, a limitation suggested that PH 15's influence in an atmosphere of fire gases might be very different from the results reported here. This warrants further investigation. An associated issue involves the effect PH 15 may have on a person taking mind-altering medication or a person that is experiencing a blood alcohol level that results in intoxication. Perhaps an exposure of PH 15 or another pheromone could counteract the effects of alcohol, medication, or any of the anesthetic gases produced in a fire. Research should be performed to determine if a pheromone can counteract any of these disabling scenarios.

All of these recommendations support the concept of a pheromone-enhanced fire detection-awareness system. Since these recommendations are global in nature, the marketplace is much larger than the corporate limits of Irondale, Alabama. Therefore, in order to provide pheromone-enhanced fire protection for the citizens of Irondale, these recommendations must be addressed by the marketplace influences first.

Replication of this process would depend on establishing the various relationships that made this project possible and following the protocol included in the appendix.

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Synthetic hormone spray relaxes jittery kitties. (December 18, 2000). *The Birmingham News*, p. D-1.

Sobel, N., Prabhakaran, V., Hartley, C.A., Desmond, J.E., Glover, G.H., Sullivan, E.V., & Gabrieli, D.E. (1999). Blind smell: Brain activation induced by an undetected air-borne chemical. *Brain*, 122, 209-219.

Stevens, J.C., Cain, W.S., & Weinstein, D.E. (1987, August). Aging impairs the ability to detect gas odor. *Fire Technology*, 23 (3), 198-204.

Taylor, R. (1994, January). Brave new nose: Sniffing out human sexual chemistry. *The Journal of NIH Research*, 6.

Voss, U., & Harsh, J. (1998). Information processing and coping style during the wake/sleep transition. *Journal of Sleep Research*, 4, 225-232.

Weiss, R. (1997, February 15). Scientists find proof of human pheromone signaling system. *The Washington Post*, pp. 1A, 2A.

Williams, H., Hammack, J., Daly, J., Dement, W., & Lubin, A. (1964). Responses to auditory stimulation, sleep loss and the EKG stages of sleep. *Electroencephalography Clinical Neurophysiology*, 16, 269-279.

Format changes have been made to facilitate reproduction. While these research projects have been selected as outstanding, other NFA EFOP and APA format, style, and procedural issues may exist.

Appendix A Study Proposal

Format changes have been made to facilitate reproduction. While these research projects have been selected as outstanding, other NFA EFOP and APA format, style, and procedural issues may exist.

**Arousals and/or Wake Patterns Associated
With Pheromones Administered in the
Ambient Environment During Sleep**

05-07-2000

Format changes have been made to facilitate reproduction. While these research projects have been selected as outstanding, other NFA EFOP and APA format, style, and procedural issues may exist.

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Format changes have been made to facilitate reproduction. While these research projects have been selected as outstanding, other NFA EFOP and APA format, style, and procedural issues may exist.

ABSTRACT

This proposal is pursuant to the research recommendation of the report "Nocturnal Olfactory Response to Smoke Odor" wherein the author stated the need for identifying substances (in this case pheromones) that were likely to arouse humans from sleep. That report, along with several other studies, are appendices to this proposal and form the basis of literature that support the need to investigate the potential arousal effect pheromones have on the various stages of sleep. Based on the understanding developed in the numerous telephone conversations, conference calls, e-mails, and the conceptual meeting that was held on October 25, 1999, in Menlo Park, California, this proposal is presented in an abbreviated format. This proposal, when approved, will be conducted under the auspices of Human Pheromone Sciences, Incorporated (HPSI).

PROBLEM STATEMENT, PURPOSE, AND RESEARCH QUESTION

The problem is that we do not know whether an ambient environmental exposure to pheromones can awaken and/or arouse subjects in the various stages of sleep.

The purpose of this research is to determine whether pheromones can awaken and/or arouse subjects in the various stages of sleep.

Research Question:

#1 Will an ambient environmental exposure to pheromone cause arousals and/or awakening(s) in sleeping subjects.

BACKGROUND

There are a number of contributing facts that support this study is being performed at the Sleep Disorders Center of Alabama, Inc.

First and foremost, Dr. Pegram and his staff are nationally recognized in the field of sleep research. In addition to the clinical practice, the SDCA is a teaching institution. Physicians, nurses, and technicians from all over the United States attend educational and certification programs at the center. Dr. Pegram is affiliated with Sleep Science, Inc., and helps direct the Sleep Disorder Center of Alabama and the Sleep/Wake Center at the University of Alabama in Birmingham (UAB). At UAB, Dr. Pegram has an appointment as professor in the division of Pulmonary and Critical Care Medicine. Dr. Pegram is also a consultant to the Sleep Center at the Children's Hospital of Alabama. Dr. Pegram's vitae is included with this proposal.

Chief Lynch is currently the Fire Chief of the city of Irondale, Alabama. The city of Irondale is located close to the SDCA. Chief Lynch is actively involved in life safety issues. He is affiliated with the United States Fire Administration, the National Fire Protection Association, and the Society of Fire Protection Engineers. He is currently serving on a number of fire behavioral groups and is part of the planning committee of the 2nd Annual International Behavior in Fire Conference scheduled for May of 2001 in Boston, Massachusetts. Any publications or presentations regarding the design, conduct and results of such studies must have prior approval from HPSI. Chief Lynch's resume is included with this proposal.

Summary of facts that indicate the need for pheromone-sleep research:

- (1) Some people are deaf and cannot hear conventional smoke alarms.
- (2) The ability to disrupt sleep patterns in people at stage 3/4 sleep and also "hard" sleepers that may not hear an alarm would be an important development in human fire detection.
- (3) In any form of communication, it is desirable to touch as many senses as possible.
- (4) Carbon monoxide and other fire gases are present during fires. Relatively small concentrations of these gases lead to confusion, unconsciousness, and death. It is not known whether pheromones can counteract the confusion caused by these gases.

- (5) Static fire protection would not depend on batteries. What if the pheromone could be liberated from building furnishings and furniture when it starts to decompose from heat? The treatment of materials with pheromones may provide static protection. Imagine "fire safe" carpet!
- (6) Teaming up with a smoke detector company may be a financial opportunity.

Please reference the background issues addressed in the appendices.

FIRE FACTS

The United States has one of the most severe fire problems among the industrialized nations. Although our per capita death rate is nearly half what it was in the late 1970's, and down 36 percent since 1986, current international data (1994) suggest that the United States has a fire death rate two to three times that of several European nations and at least 20 percent higher than most. In 1994, our fire death rate was reported at 19.1 deaths per million population. Switzerland's rate was 5.5 per million population; Canada's was 15.2. In fact, of the seventeen industrial nations that are examined by the World Fire Statistics Center, the U.S. rate was higher than all but two, Finland and Hungary.

The declining U.S. trend in fire deaths rate over the past ten years was not a single event; all countries except Hungary and Finland also trended downward. Furthermore, although statistical data are not available, the United States is widely believed to have many more residential fires on a per capita basis than any other country studied.

The United States has placed greater emphasis on improving the technology in fire suppression and fire service delivery mechanisms than other nations, but these nations tend to surpass the U.S. in practicing fire prevention. The United States would be well served by studying and implementing international fire prevention programs that have proved effective in reducing the number of fires and deaths.

The Cost of Fire

The total cost of fire to society is staggering--over \$100 billion per year.

Regional Differences

The Southeast of the United States continues to have the highest fire death rate in the nation and one of the highest in the world.

The highest numbers of fire deaths occur in Mississippi, **Alabama**, Alaska, and Arkansas. The lowest are Utah, New Mexico, California, and Hawaii.

Gender

Men continue to have almost twice as many fire deaths as women. Injuries per capita for males are one and one-half to two times the female rate until age 70.

Age

People over 60 have a much higher fire death rate than other age groups (17.4 deaths per million population).

Residential Fires

Residential fires have the highest death and injury rates, another important reason for prevention programs to focus on home fire safety.

Non-Residential Structures

Non-residential structures have by far the highest dollar loss per fire.

Smoke Detectors

The relationship between low-income status and the presence of operational smoke detectors has not been firmly established.

Source:

National Fire Center. (1998). *Fire in the United States: 1986-1995* (FA-183). Emmitsburg, MD: Author.

When Fire Occurs

Fire incidents peak from 5:00 p.m. to 7:00 p.m., when cooking fires most often occur. Although fire incidents drop when people sleep, deaths are usually associated with fires that start late at night and early in the morning. **Nearly half of residential fire deaths occur in fires that start from 11:00 p.m. to 6:00 a.m.** The peak night hours are from 2:00 a.m. to 5:00 a.m. when most people are in deep sleep. Fire injuries occur more uniformly throughout the day, peak slightly during dinner hours when people cook, and actually drop to their low point in the early morning hours. The peak in dollar loss is between 7:00 p.m. and 8:00 p.m. Residential fires and fire deaths are most frequent during winter months when heating systems play a dominant role. Forty percent of all deaths occur from December through February. The incidence of residential fires is uniformly spread over the entire week, but one-third of all deaths occur on the weekend, when a large portion of the populace is at home.

National Fire Center. (2000). *Fire in the United States: 1987-1996* (FA-183). Emmitsburg: MD: Author.

Fire Deaths

In the United States, four of every five fire deaths occurred in home structure fires. Although only 17 percent of all reported fires occurred in one- and two-family structures, these fires caused 67 percent (2,700) of the fire deaths. Apartment fires accounted for 5 percent of all reported fires, but resulted in 16 percent (660) of the deaths.

Home Fires

According to a recent survey performed for NFPA, 53 percent of U.S. residents feel safest from fire at home. It is estimated that Americans spend 55 percent-75 percent of their time at home, yet 78 percent-83 percent of all fire deaths result from home structure fires.

Kitchens were the leading area of origin for home structure fires and for home civilian fire injuries.

Only 39 percent of the reported home fires occurred in properties protected by working smoke or fire alarms.

Cooking equipment was the leading cause of home fires.

Smoking materials were the leading cause of fire deaths.

Causes of civilian deaths and injuries in dwelling and manufactured home structure fires are as follows:

- (1) Smoking
- (2) Heating Equipment
- (3) Incendiary or Suspicious.

Causes of civilian deaths and injuries in apartment structure fires are as follows:

- (1) Smoking
- (2) Incendiary or Suspicious
- (3) Child Playing with Matches or Lighter.

Source:

Ahrens, M. (1999). *The U.S. fire problem overview report- leading causes and other patterns and trends*. Quincy, MA: National Fire Protection Association.

"Smoking and heating related fires were the leading cause of fire deaths among victims with positive blood alcohol levels (BALs) as well as those from which no BAL was recorded. Although the percentages of deaths between alcohol-impaired and non-alcohol-impaired deaths were similar for heating fires, a stark difference exists for smoking fires. Nearly two-thirds (64 percent) of the alcohol-impaired fire deaths were caused by smoking fires, as opposed to 37 percent of the non-alcohol-impaired fatalities. Approximately 46 percent of deaths caused by smoking fires had positive BALs. In addition, over one-third of cooking fire fatalities and one-fourth of heating fire fatalities were under the influence of alcohol at the time of the fire" (USFA, 1999, p. 38).

Source:

United States Fire Administration. (1999, October). *Establishing a relationship between alcohol and causalities of fire* (National Fire Data Center). Arlington, VA: TriData Corporation.

It is likely that the number of victims under the influence of alcohol and other drugs was, and will continue to be underestimated. One reason is the difficulty in determining alcohol or drug impairment in a person who has already died. Studies that can more systematically determine victim impairment and focus on that condition alone have been rare. The best is still a study by Berl and Halpin of 1972-1977 Maryland fire deaths, which found that 51 percent of fire victims ages 20 and over were legally intoxicated" (Hall, 2000, p. 24).

Source:

Hall, J. (2000, April). *Patterns of Fire Casualties in Home Fires by Age and Sex*. Quincy, MA: National Fire Protection Association.

Fire occurs in a U.S. residence every 74 seconds.

Every 21 minutes a civilian is injured by fire.

Women make seventy-seven percent of smoke detector purchases. From the Better Homes and Gardens Home Enthusiast Panel 2000.

Source:

Keith, G. (2000, October). *Home Sprinkler Coalition*, Lecture presented at the President's Forum, NFPA Headquarters, Quincy, Massachusetts.

U.S. versus Canada

The U.S. population is nine times that of Canada.

There were more than 30 times the reported fires in the U.S. than there were reported in Canada.

For residential fires, the ratio was 17 U.S. fires to 1 Canadian.

Municipal fire departments went to 1,823,000 fires in 1999, which reflected an increase of 3.8 percent.

Fires in the U.S. caused \$10 billion in direct property loss in 1999, which reflects an increase of 16.2 percent

Home fires caused by candles have more than doubled since 1990.

Source:

Ahrens, M. (2000, October). *The Fire Problem Update*, Lecture presented at the President's Forum, NFPA Headquarters, Quincy, Massachusetts.

Most homes have smoke alarms, but 42 percent of reported home fires and 59 percent of home fire deaths occur in homes with no smoke alarms. As of 1995, 13 of every 14 (93 percent) U.S. homes had at least one smoke alarm.

The usual socioeconomic factors correlated with fire risk are less useful as predictors of smoke alarm usage.

Smoke alarm failures usually result from dead, missing, or disconnected batteries.

If a home fire occurs, smoke alarms reduce the risk of death by 40-50 percent.

When alarms are present, 40.5 percent of the victims of fatal fires in dwellings, duplexes, and manufactured homes are in the room of fire origin at ignition.

In the National Smoke Detector Project, roughly half of the smoke alarms collected were inoperable and were more than 10 years old, making them older than the currently recommended replacement age.

Source:

Ahrens, M. (1998). *U.S. experience with smoke alarms and other fire alarms: Who has them? How well do they work? When don't they work?* Quincy, MA: National Fire Protection Association.

Rules are constantly changing on smoke detector use in dwellings. On May 18, 2000, the Department of Housing and Urban Development (HUD) issued a proposed rule on the placement of smoke alarms in manufactured houses. The new standard requires manufacturers to install more smoke detectors per home, and all smoke detectors must be interconnected.

Source:

Coughlin, P. (2000, July). Department of Housing and Urban Development Proposes Rule on Smoke Detectors in Manufactured Homes. *Operation Life Safety*, 15, 7.

"One of the key characteristics of residential fires is the fact that they often ignite and develop during the night, trapping sleeping occupants" (Derry, 1979, p. 76).

"Many people are overcome in their sleep or wake up too late or too confused to escape. Most of the deaths between these hours occurred in fires that gained large headstarts before discovery. Often these nighttime fires are not discovered and the alarm turned in until smoke or flame is visible externally to neighbors or passersby. Unfortunately, the responding fire department, no matter how skilled at rescue and fire suppression, cannot save any of these victims, since they are dead by the time the alarm is given" (Derry, 1979, p. 76).

Source:

Derry, L., (1979). Fatal fires in America: How they happen, where they happen, how to stop them. *Fire Journal*, 73, 67.

Nearly 50 percent of the deaths occur in fires reported from 11:00 P.M. to 6:00 A.M. (National Fire Data Center, 1993, p. 82).

Source:

National Fire Data Center. (1993). *Fire in the United States: 1983-1990* (FA-140). Emmitsburg, MD: Author.

"Studies by the National Association of Home Builders have found that the fire death rates in homes built before 1970 were more than five times as great as in homes built to the more stringent standards required today" ("Home fire death," 2000, p. 16). If smoke detectors were present at all, almost all of the homes built before 1970 would have battery-powered smoke detectors.

Source:

Home fire deaths reduced through fire safety efforts. (December 16, 2000). *Nation's Building News*, p. 12.

Olfaction and sensitivity to smoke odor during sleep was examined in an earlier study. That study was entitled *Nocturnal Olfactory Response to Smoke Odor* and can be referenced in entirety at the following electronic address: http://www.usfa.fema.gov/nfa/tr_97jl.htm.

Lynch verified that overall responsiveness to olfactory stimuli presented in sleep was low. Only two of ten subjects awoke from an ambient exposure to wood smoke odor (Lynch, 1997).

Source:

Lynch, J. L. (1997). *Nocturnal Olfactory Response to Smoke Odor*. Executive Fire Officer Research Paper, Emmitsburg, MD: National Fire Academy

The Need for New Technology and the Disabled

Among the citizens accountable for their own safety, four distinct groups emerge as being particularly susceptible to fire. The four groups are the mobility impaired, the blind or visually impaired, the deaf or hard of hearing, and older adults. These groups are usually included in any description of the disabled. According to the National Center for Health Statistics (NCHS), "20 percent of the U.S. population, or 54 million people, have some type of disability. A disability is defined as (1) a physical or mental impairment that substantially limits one or more of the major life activities of such an individual; (2) a record of such an impairment; or (3) being regarded as having such an impairment" (United States Fire Administration (USFA), 1999c, p. 7). Fire safety is a much-overlooked problem among the disabled. The disabled do not receive the same media, educational, or industry attentions as the mainstream population. Many advancements in fire injury and death prevention over the past century have not addressed the fire safety needs of the disabled community.

People with mobility impairments are limited by time and physical means for mobility when it comes to escaping a fire emergency (USFA, 1999d). The impairment may restrict their ability to take swift action when faced with a small fire or to escape a larger fire. Because of the impairment, the United States Fire Administration considers the use of smoke alarms as "the single most important piece of fire safety technology employed today in populations where physical limitations may increase the time needed to safely exit a burning building" (USFA, 1999c, p. 13).

For people with sight, the sense of vision is the primary means for assessing and interpreting clues in an external environment. The blind or visually impaired are faced with many challenges. Depending on the severity of vision loss, they may be more likely to accidentally start a fire while being less likely to extinguish or escape one. The senses that a blind or visually impaired person relies on may be overwhelmed during a fire. The high decibel smoke alarm may make it difficult for the blind individual to effectively process audible cues or instructions (USFA, 1999b). "By the year 2030, twice as many people will be blind as there are today" (USFA, 1999a, p. 9).

Paul Revere used his voice to warn of the impending British invasion. During the height of the Cold War, warning sirens were used in air raid exercises to alert Americans to the possibility of nuclear attack. These modes of communication were the most effective ways to reach the greatest number of people. Fire and smoke alarms are no different. However, these life-saving devices are of little use to an individual who is hearing-impaired. "Light-equipped smoke alarms have been developed, but they are expensive and not widely available" (USFA, 1999a, p. 5). Deaf occupants will not hear this audible warning and may remain in the building until escape is no longer possible. Even if the smoke alarms in the hallways are equipped with flashing lights, they are of little help unless the deaf person is close to them. In one study of actual fires involving deaf or hard of hearing people, the estimated time from the first alarm of fire until the occupants were evacuated was 30 to 60 minutes. None of the respondents had specialized smoke alarms installed in their apartments. The National Institute of Health estimates that "there are 28 million deaf and hard-of-hearing individuals in the United States" (USFA, 1999b, p. 7).

The Social Security Administration states that there are 28 million Americans that are 65 years old and older. In twenty years, they project that there will be 70 million. This is the fastest growing segment of the American society (J. Harris, personal communication, May 1, 2000). That growth is due to "baby boomers" reaching retirement age and a steady climb in the average life expectancy over the past century. The elderly suffer from mobility impairment, hearing problems, and vision deficits to a much greater degree than does the general population. They also experience sensory impairments (diminished visual acuity, depth perception, hearing, and sense of smell, as well as deficits in mobility and balance) that tend to make them more vulnerable to the dangers of fire and burns. Furthermore, approximately 20 percent of older adults live at or below the poverty line, and the relationship between poverty and fires is a compounding fire risk. As the nation's elderly population grows, the fire death toll will likely rise in direct proportion to that growth, unless measures are taken to ameliorate the risks associate with this group. "Two-thirds of fire deaths in the elderly occur when the victims are sleeping or trying to escape" (USFA, 1999, p. 12).

In 1990, the United States Congress passed the Americans with Disabilities Act (ADA), which extended civil rights protection to individuals with disabilities. Title III of the ADA is most applicable to fire safety, as it prohibits discrimination against disabled persons in places of public accommodation. The proprietors of such businesses are responsible for making their establishments more physically accessible to people with disabilities. "The ADA requires the installation of emergency alarms in public places that serve both hearing and non-hearing patrons, the installation of entrance and exit ramps, as well as the widening of doorways to accommodate wheelchairs" (USFA, 1999b, p. 5). Title II of ADA specifies that landlords that benefit from a variety of federal government programs or other federal subsidies are required to provide visual fire alarms to their deaf and hard-of-hearing residents at no cost. In fact, the ADA stipulates that the responsibility for providing all interpreter services, adaptive equipment, or accessibility to other services or facilities rests with the proprietor of the building entity. This includes everything except private dwellings. The legislation has been established, but many disabled Americans are unaware of the provisions of the law. Consequently, the widespread implementation of ADA has yet to be achieved.

Alarmingly, several noteworthy reports indicated "that being identified as 'special' or 'needy' was a concern for individuals with disabilities. Impaired individuals reported that official concern or focusing on them for fire safety can restrict their freedom of choice and increase their chances for falling victim to crime" (USFA, 1999c, p. 19).

Clearly, there are many disabled Americans that have special fire protection needs. The ADA mandates technological and structural changes that will allow compliance with the law. Ignorance, anxiety, and the lack of vision have limited the scope of the legislation (USFA, 1999c).

The National Fire Protection Association (NFPA) reports that "half of the home fire deaths occur in the 6 percent of homes with no smoke alarms," and "when the homes without smoke alarms are added to homes with only non-working alarms, we see that one quarter of U.S. households do not have the protection of even one working smoke alarm" (USFA, 1999d, p. i).

Sources:

United States Fire Administration. (1999, October). *Fire risks for older adults*. Emmitsburg, MD: Author.

United States Fire Administration. (1999a, October). *Fire risks for the blind or visually impaired*. Emmitsburg, MD: Author.

United States Fire Administration. (1999b, October). *Fire risks for the deaf or hard of hearing*. Emmitsburg, MD: Author.

United States Fire Administration. (1999c, October). *Fire risks for the mobility impaired*. Emmitsburg, MD: Author.

United States Fire Administration. (1999d, September 20). *Solutions 2000*. Emmitsburg, MD: Author.

The issue of hearing smoke alarms also impacts the young. An experiment conducted with children aged 6-17 years old demonstrated that 85 percent of them slept through a smoke alarm activated during 3 minutes at 60dBA.

Source:

Bruck, D. (1999). Non-awakening in children in response to a smoke detector alarm. *Fire Safety Journal*, 32, pp. 369-376.

Many products are marketed as safety appliances for the deaf. Sound usually causes these products to either amplify sound, strobe with intense light, or produce vibration in a bed or under a pillow. Through a variety of electrical interfaces, remote applications as well as household communication devices can be incorporated within the disability appliances. A single station application normally costs less than five hundred dollars.

In 1995, the prevalence of hearing impairments was 85.8 per 1,000 persons in the United States. Accepting this as the norm, over 850 residents of the city of Irondale (population 10,000) could have a hearing impairment.

Source:

National Center of Health Statistics. (1995). *Current estimates for the national health interview survey* (Series 10, No. 199). Atlanta, GA: Center for Disease Control.

Attitudes also affect human behavior during fire. Negative attitudes that contribute to greater fire risks (deaths) were outlined in the NFPA's *1997 National Fire Escape Survey*. That study revealed that fewer than 10 percent of Americans believe there to be a major risk of a fire

occurring in their homes and that a large majority of them (84 percent) do not have a plan that they practice. Gender, the presence of children, income level, and years of formal education all seem to be contributing factors in forming a life-saving (positive) attitude (NFPA, 1997).

Source:

National Fire Protection Association. (1997, October). *1997 NFPA national fire escape survey*. Quincy, MA: Author.

A recent survey performed by the United States Products Safety Commission found that 90 percent of U. S. households have smoke alarms. The same survey reported that the smoke alarms do not work in twenty percent (16 million) of these homes. Missing or dead batteries are usually responsible for the failures ("CPSC warns that," 1999).

Source:

CPSC warns that smoke alarms in about 16 million homes do not work. (1999, November/December). *Operation Life Safety, 14*, (10, 11) p. 5.

Rural Fire Information

The lack of working smoke detectors is a significant problem in rural areas. Smoke detectors were present and operational in only 27 percent of rural residential fires (versus 35 percent of non-rural fires).

Fire death rates are significantly higher (35 percent higher) in rural areas compared to non-rural areas. These differences are even greater when comparing fire death rates across racial and ethnic groups.

Within rural areas, the majority of annual fire death victims are white. In per capita terms, however, African Americans and native Americans have higher risks of dying as a result of fire than do whites.

Source:

United States Fire Administration. (1998, August). *The rural fire problem in the United States*. FA-180. Emmitsburg, MD: Author.

The relative risk for people in homes without smoke detectors is 10.4 times that for people in homes with smoke detectors.

The fire fatality rates are increasing in one- and two-family dwellings, as calculated by the number of fires vs. the number of fatalities.

Even in a home with working smoke detectors, there is a 29.6 percent greater chance of dying in a fire if the fire does not start in a room that has a working smoke detector.

Source:

Crapo, W. F. (2000, May). Smoke detectors and life safety. *Fire Engineering*, 153 (5).

In addition to the literature mentioned earlier, a review of the articles provided by Pherin at the conceptual meeting on October 25, 1999, in Menlo Park, California was completed prior to developing this proposal.

Those articles include:

The Functionality of the Human Vomeronasal Organ (VNO): Evidence for Steroid Receptors Modulation of Serum Testosterone and Autonomic Function through Stimulation the Male Human Vomeronasal Organ (VNO) with Pregna-4, 20-diene-3, 6-dione.

The Human Vomeronasal System: A Review

The Human Vomeronasal System

David Berliner: The Man That Followed His Nose

Vomeropherins: A Revolutionary Discovery for Therapeutics

Handbook of Olfaction and Gustation

Steroidal Substances Active in Human Vomeronasal Organ Affect Hypothalamic Function

Effect of Putative Pheromones on the Electrical Activity of Human Vomeronasal Organ and Olfactory Epithelium Pioneer Endocrinologist Proves Pheromones Can Manipulate Ovulation in Women

PROCEDURES

Tests will be performed at:

The Sleep Disorders Center of Alabama, Inc.

A Partner of Sleep Science, Inc.

790 Montclair Road, Suite 200

Birmingham, Alabama 35213

(205) 599-1020

Toll Free: 1-800-874-4948

Researchers

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Should it be desired, representatives of Human Pheromone Sciences are encouraged to perform a site visit of the Sleep Disorders Center of Alabama, Inc. The expenses of the site visit were not considered in the cost projections of this study. The researchers will assist Human Pheromone Sciences in arranging accommodations.

The study will consist of the presentation of an airborne dosage of active agent and placebo to sleeping males and females. After careful consideration, it was determined that both the active agent and the placebo will be delivered through the ambient air from a position up to 187.96 centimeters from the sleeping patient's face. The discharge will be from the ceiling. The active and control conditions will be stage 2, stage 3/4, and REM sleep. The intention of this study is to present ALL subjects to the six conditions. A chart of randomized order will be used to determine whether an active or control condition will be presented first during each sleep stage. After each active agent presentation, the air purifier will be utilized to clear the ambient atmosphere. Because these procedures may not be possible in one night, thirty sleep nights have been calculated into the expenses of the project.

The active agent will be supplied in liquid form by Human Pheromone Sciences, Incorporated, and the placebo will be locally obtained distilled water.

Inclusion criteria will be men and women between (and including) the ages of twenty and fifty with no history of sleep disorders and that are drug free. Exclusion criteria will be pregnancy, a history of smoking within the pervious year, subjects experiencing a respiratory or nasal infection, subjects exhibiting poor sleeping habits or associated sleep pathologies, allergies, acute or chronic illnesses, previous nasal surgery, or past head trauma. The subjects will be paid for their participation in this study. The subjects will be paid one hundred dollars (\$100.00) for the first night of the study and fifty dollars (\$50.00) if an additional night of study is required.

Sleep disorders among the subjects will be ruled out by interview, medical exam, sleep history questionnaire, and sleep disorder screening procedures. It will be very important to rule out sleep disorders in subjects. A criticism that the researchers are attempting to avoid could be that arousals and/or awakenings were due to apnea, myclonus, or reflux. Regardless of the screening, the researchers anticipate some of these subjects will fail an experimental night because of these problems.

All subjects will be screened for the presence of a vomeronasal organ. The screening for this will be coordinated with an HPSI designated consultant(s) and will probably occur on a Friday afternoon or Saturday. This will be performed at a local otorhinolaryngologist's (ear, nose, and throat physician) office utilizing a magnified and lighted endoscope that is equipped with a fiber optics camera. The internal image of the nasal cavity will be transmitted to a television monitor to help identify the entrance of the VNO. The local physician will be trained to perform this examination process so that replacement subjects can be screened. The consultant's expenses were not considered in the cost projections of this study.

EEG electrodes will be secured for the recording of sleep stages using the following electrode placements: C3, C4, O1, O2, left and right mastoids. In addition to the EEG, eye movement or EOG (outer canthi, above and below midline), and EMG or muscle movement (supra- and submental) will be used to score sleep and rule out sleep disorders. EEG's shall be portioned to allow recording and scoring by the standard Rechtschaffen and Kales system. Other physiological measures will include SaO₂, respiratory effort, and the autonomic responses of pulse and heart rhythm (modified Lead II). The respiration belt will be secured comfortably around the rib cage at or about the fourth or fifth rib.

Observations of the subjects during sleep will be of a visual nature. In addition to a regular closed circuit camera, the SDCA utilizes an infrared camera by which behavioral responses of the patient can be recorded in total darkness from "lights out" to "lights on." This will be used in this study and will provide the researchers a method of determining if the nebulizers are operating without disturbing the subjects.

To monitor EEG arousals, the procedures as outlined in *EEG Arousal: Scoring Rules and Examples* (Sleep, Vol. 15, No. 2, 1992) will be used to score the subject's sleep experience. A copy of this article is included for review.

The subjects will sleep in electrically shielded and sound-attenuated bedrooms. The rooms in which the subjects will sleep contain approximately 32.5 cubic meters of ambient atmosphere. To isolate the subject's environment, the entrance doors of the sleep rooms will be shut. The HVAC (heating, ventilation, and air conditioning) system discharge and return vents will be dampered to isolate the sleep room. A convectional baseboard heater that will not produce air currents will provide any heat necessary.

The target number of subjects remains at twenty; however, this is dependent on the effective dosage and duration of the effect of the pheromones. A minimum of ten male subjects will be considered. This has been discussed on several occasions. A target of five will be used for the number of female subjects included within the test population.

The dosage administration time, latency period, and effective duration of the dosage will be determined in consultation with Human Pheromone Sciences, Incorporated. Ideally, the pheromone can be delivered in 15 seconds and then allowed a five-minute latency period for reaction and a one-hour effective dosage (duration) period.

EQUIPMENT

These specifications of equipment are for each one of the sleep rooms used during the trial. There will be sufficient reserve equipment to continue the testing in the event of an equipment failure.

There will be two remotely controlled nebulizers: one for the active agent and the other for the placebo or control.

Nebulizer Specifications

The nebulizer chosen for use in this study is the DeVilbiss® Model 099HD Ultra-Neb® 99 large volume ultrasonic nebulizer. The principal nebulizer features associated with this study are as follows: (a) a 150 milliliter medicine dispenser, (b) a 6.0 milliliter per minute nebulization rate, and (c) a < 4.0 average micron/millimeter diameter particle size (MMAD). The nebulizer shall discharge into a delivery hose of 2.5-centimeter (minimum i.d.) corrugated plastic polyvinylchloride ventilator hose approximately 2.44 meters in length. This hose was routed through the ceiling membrane in the hallway, through the double firewall barrier with its insulation, and down through the ceiling membrane of the subject's room. Because the hose is flexible and semitranslucent, installation took place in such a way that the fire wall integrity was never compromised during the study. The hose terminated directly above the "pillowed" area of the bed. The distance from the end of the discharge hose to the subject's pillow was 187.96 centimeters. Five seconds of additional nebulizer operation time was required to purge the delivery hose on each presentation. The unit functions on AC power. A special panel of on/off switches has been installed in the control room to remotely control the nebulizers. This control box will engage the nebulizer during the tests. There will be one nebulizer for the active agent and another one for the placebo. Please note on the room diagram (see appendix F) that the nebulizer discharge will be directly above and up to 187.96 centimeters from the patient's face and will be located no more than 91.44 centimeters from the subject's face. The discharge shall come from the ceiling line.

Air Purifier Specifications

The air purifier chosen for use in this study is the Holmes Model HAP-240 air purifier with independent electronic ionizer. The unit features a multi-speed fan switch that affects the efficiency of the unit. On the "quiet" setting, the unit is rated at 54 cubic feet per minute. At that rated capacity, it will take 1.82 minutes (1 minute, 50 seconds will be used) to clear a sleep room with the dimensions of 32.5 cubic meters. The unit functions on AC power and can be controlled remotely. Please note on the room diagram that the air purifier will be located beside the subject's bed. The air purifier will be connected to a remote AC switch located in the control room.

Smoke Detector

To rule out any potential conflict, an ionization/photoelectric smoke detector will be in operation during the test. The detector chosen for this is the First Alert "Double Sensor" Model-SA301C.

Carbon Monoxide Detector

To rule out any potential conflict, a carbon monoxide detector will be in operation during the test. The detector chosen for this is the Kidde "Nighthawk" Model-KN-COB-DP.

Convective Baseboard Heater

The sleep room will be isolated from the HVAC system. If auxiliary heat should be required for the study, a convective baseboard heater will be used because it does not create a draft or air currents.

Institutional Review Board

The study will be performed after approval of an Institutional Review Board and Ethics Committee selected by the SDCA in accordance with the principles of the Declaration of Helsinki. The Western Institutional Review Board will be contracted to perform this task. The researchers plan to utilize information in the IRB's report of the Utah sleep test to expedite this study's approval process.

Responsibilities of the Research Center

As part of the study, the SDCA will provide the following:

- A modern state-of-the-art sleep research center with a highly trained staff
- An experienced and qualified management team that understands the issues that are being investigated
- A partner that understands the highly confidential nature of this work
- A medical examination by one of the SDCA physicians to determine if the subject is a candidate for the study
- The reviews of the completed sleep history questionnaires to determine whether a subject is a candidate for the study
- The personnel costs associated with performing the study
- The supplies used in conjunction with the test
- The expenses related to scoring the EEG's
- The expenses related to data analysis and study design
- The ancillary equipment (air purifiers, nebulizers, heaters, etc.)

The expenses related to the Western Institutional Review Board

A report of observations made during this trial in parametric statistics as well as in APA style

General clinical safety assessments (conducted prior to study enrollment as well as 1 and 7 days following exposure to the pheromone or placebo)

Publication of Results

As agreed, after review and comments by HPSI, the researchers will be entitled to publish the results in yet to be determined journals and proceedings.

Time Line

This is the projected time line for the study and reporting the results.

Target Time Line for Implementation And Reporting of the Study

Approval (IRB)	30 days Begin	90 days Finish Testing	135 days Draft Report
-------------------	------------------	---------------------------	--------------------------

We anticipate being able to report the results of the study to Human Pheromone Sciences, Incorporated, within six months of financial approval to begin the study.

Cost of Study

The cost of the study will be \$50,000.00, and that will include the services mentioned earlier.

Pheromones Supplied by Human Pheromone Sciences

The pheromone needed for this trial is a concentration that would allow the target dosage within 2 milliliters. This would allow the dosage to be administered in 15 seconds.

Previous Study

A summary along with the Institutional Review Board findings of the previous sleep study performed in Utah will be needed by Human Pheromone Sciences in order to seek approval of the Western Institutional Review Board.

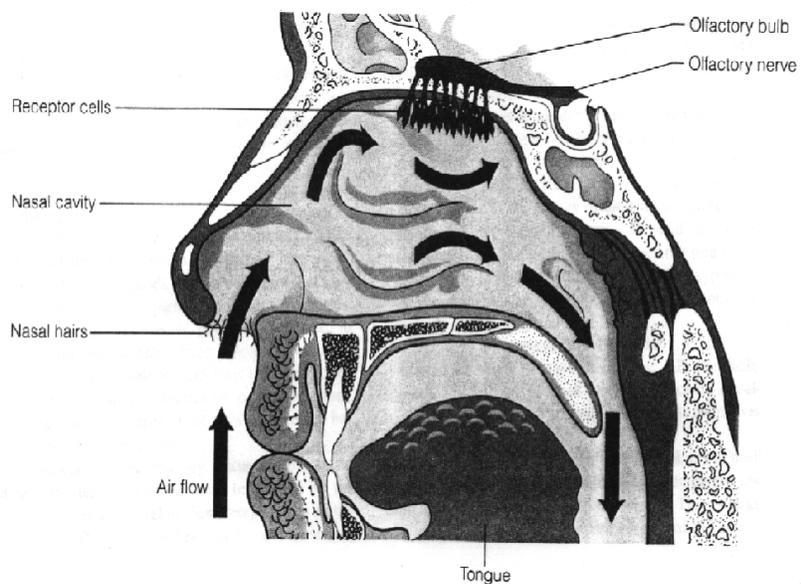
This proposal was submitted on May 7, 2000 by:

G. Vernon Pegram, Ph.D.
Sleep Disorders Center of Alabama, Inc.

Joe Lynch, Fire Chief
City of Irondale, Alabama

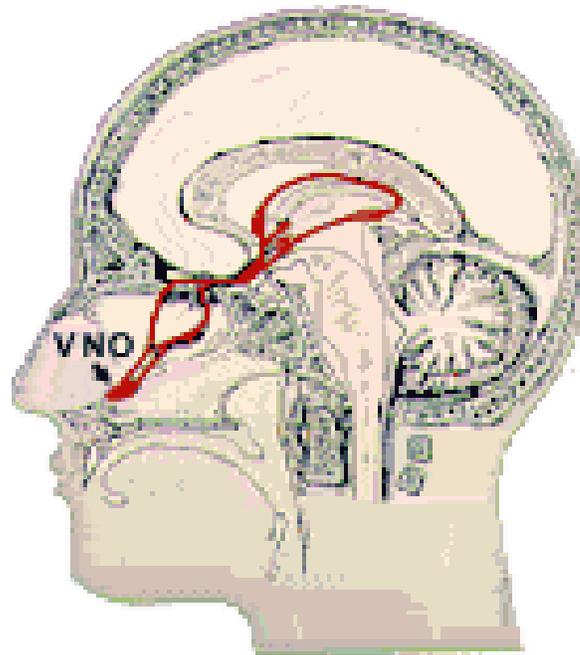
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Appendix B Illustration of Olfactory System



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Appendix C Illustration of the Vomeronasal System



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Format changes have been made to facilitate reproduction. While these research projects have been selected as outstanding, other NFA EFOP and APA format, style, and procedural issues may exist.

Appendix D

Certificate of Approval, Consent Form, and Insurance Certificate

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Western Institutional Review Board®
Western International Review Board®

*Certificate
of
Approval*

(360) 943-1410
FAX: (360) 943-4522
1-800-562-4789

3535 7th AVE S.W. OLYMPIA, WA 98502-5010
P.O. BOX 12029 OLYMPIA, WA 98508-2029

THE FOLLOWING WERE APPROVED:

INVESTIGATOR: G. Vernon Pegram, Ph.D.
Sleep Disorders Ctr. of Alabama
709 Montclair Road, Suite 200
Birmingham, AL 35213 USA

BOARD ACTION DATED: 08-07-2000
APPROVAL EXPIRES: 08-07-2001
STUDY NR: 1019351
WIRB PRO NR: 20001294
INVEST NR: 5318

SPONSOR: Human Pheromone Sciences, Inc.
PROTOCOL NR: 1195 WIRB
AMD. PRO. NR:

TITLE: Arousals and/or Wake Patterns Associated With Pheromones Administered in the Ambient Environment during Sleep

APPROVAL INCLUDES:

Protocol (06-26-2000)
Consent Form - As Modified by WIRB
Investigator

WIRB APPROVAL IS GRANTED SUBJECT TO:

(See Back of this Certificate)

ALL WIRB APPROVED INVESTIGATORS MUST COMPLY WITH THE FOLLOWING:

1. Conduct the research as required by the Protocol;
2. Use only the Consent Form bearing the WIRB "APPROVED" stamp;
3. Provide non-English speaking subjects with a certified translation of the approved Consent Form in the subject's first language. The translated version must be approved by WIRB;
4. Obtain pre-approval from WIRB of any changes in the research activity (except when necessary to protect human subjects; 21 CFR § 56.108(a)(3)); immediately report to WIRB any such emergency changes for the protection of human subjects;
5. Report to WIRB the death, hospitalization, or serious illness of any study subject;
6. Promptly report to WIRB any new information that may adversely affect the safety of the subjects or the conduct of the trial;
7. Provide reports to WIRB concerning the progress of the research, when requested;
8. Obtain pre-approval of study advertisements from WIRB before use;
9. Conduct the informed consent process without coercion or undue influence, and provide the potential subject sufficient opportunity to consider whether or not to participate.

Federal regulations require that WIRB conduct continuing review of approved research. You will receive Continuing Review Report forms from WIRB. These reports must be returned even though your study may not have started.

DISTRIBUTION OF COPIES:

SPONSOR: Human Pheromone Sciences, Inc. CONTACT: Bill Horgan
SMO:
CRO:
OTHER:
INSTITUTION:

IF YOU HAVE ANY QUESTIONS, CONTACT WIRB AT 1-800-562-4789

This is to certify that the information contained herein is true and correct as reflected in the records of the Western Institutional Review Board (WIRB). WE CERTIFY THAT WIRB IS IN FULL COMPLIANCE WITH GOOD CLINICAL PRACTICES AS DEFINED UNDER THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) REGULATIONS AND THE INTERNATIONAL CONFERENCE ON HARMONIZATION (ICH) GUIDELINES.



William C. Jacobs, Chairman

AUG 14 2000

(Date)

APPROVED
Aug 07, 2000
WIRB[®]
Olympia, WA

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

PROTOCOL TITLE: Arousals and/or Wake Patterns Associated With Pheromones Administered in the Ambient Environment during Sleep

PROTOCOL NO.: WIRB[®] 20001294

SPONSOR: Human Pheromone Sciences, Inc.
Menlo Park, CA 94025

INVESTIGATOR: G. Vernon Pegram, Ph.D., A.C.P.
The Sleep Disorders Center of Alabama, Inc.
709 Montclair Rd., Suite 200
Birmingham, AL 35213
(205) 599-1020

You are asked to read the following material about this study. This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

PURPOSE OF THE RESEARCH

This is a research study to evaluate the effectiveness of pheromones in awakening and/or arousing subjects from various stages of sleep. Pheromones are naturally occurring chemicals produced by humans which are dispersed from the skin into the surrounding atmosphere. There will be up to 20 subjects participating in this study.

STUDY PROCEDURES AND DURATION

The study will involve at least two lab visits: a screening visit at which your eligibility to participate in this study will be determined, and an overnight sleep lab visit. You may also be asked to complete an additional overnight visit in the sleep lab.

At the screening visit, you will be tested for the presence of a vomeronasal organ (a nasal structure that allows you to detect the pheromone being used in this study). A physician will examine your nose using a special light to determine whether this organ is present. You will also be asked to complete a questionnaire concerning your sleep, general health, and medical history. You will receive a brief physical examination from a sleep center physician and in addition, if you are a female of childbearing potential, you will be asked to provide a urine specimen for a urine pregnancy test.

APPROVED
Aug 07, 2000
WIRB®
Olympia, WA

COSTS

There will be no charge to you for any of the services provided to you during this study.

PAYMENT FOR PARTICIPATION

You will be paid for your participation in this study based on the following schedule: first sleep night \$100.00, additional sleep lab night \$50.00. You will not be paid for the initial screening visit.

VOLUNTARY PARTICIPATION/WITHDRAWAL

Your participation in this study is voluntary. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled at this site. You are also free to withdraw from the study at any time. Your decision will not change your future medical care at this site. In addition, the study doctor or sponsor may withdraw you from the study without your consent if you fail to follow the study instructions or for any other reason.

QUESTIONS

If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study material, contact:

G. Vernon Pegram, Ph.D., A.C.P.
The Sleep Disorders Center of Alabama, Inc.
709 Montclair Rd., Suite 200
Birmingham, AL 35213
(205) 599-1020.

If you have any questions about your rights as a research subject, you may contact:

Western Institutional Review Board® (WIRB®)
3535 7th Avenue S.W.
Olympia, WA 98502
1-800-562-4789.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all your questions.

COMPENSATION FOR INJURY

There is no compensation available for injury experienced while you are in this study. However, you do not give up any legal rights by signing this consent form.

APPROVED
Aug 07, 2000
WIRB®
Olympia, WA

SOURCE OF FUNDING

Funding for this research study will be provided by Human Pheromone Sciences, Incorporated.

CONFIDENTIALITY

Information from this study will be submitted to the sponsor. Records which identify you and the consent form signed by you may be inspected/copied for research or regulatory purposes by:

- the sponsor;

and may be looked at and/or copied for research or regulatory purposes by:

- the Western Institutional Review Board® (WIRB®).

Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. The results of this research study may be presented at meetings or in publications; however, your identity will not be disclosed in those presentations.

CONSENT

I have read this consent form. I understand the information about this study. This study has been explained to me and all my questions have been answered. I voluntarily consent to participate. I understand that this consent form will be filed with my study records and that I will receive a signed and dated copy.

I authorize the release of my study records for research or regulatory purposes to the sponsor and WIRB®.

APPROVED
Aug 07, 2000
WIRB®
Olympia, WA

By signing this consent form, I have not waived any of the legal rights which I otherwise would have as a subject in a research study.

Subject's Name (print)

Subject's Signature

Date

Witness' Signature

Date

Signature of Person Conducting
Informed Consent Discussion

Date

Investigators Signature (if different from above)

Date

wirb/humanpher/20001294/08-07-2000/gkk/cmj



Joe Lynch 205-951-1434
Woodruff-Sawyer & Co.
Insurance Services

220 Bush Street, 7th Floor
San Francisco, CA 94104-3509
License No. 0329598
Telephone 415 391 2141
Fax 415 989.9923

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fax

TO FAX #:	510-226-6431	DATE:	11/02/00
NAME:	Bill Horgan	FROM:	Linda Rebenstorf For Jerry Sullivan
COMPANY:	HPSI	# OF PAGES:	2
CC:	Andrea Pugh, Phenn Pharmaceuticals (Fax: 650-903-7101)		
RE:	Evidence of Insurance RE: Clinical Trials Insured: Phenn Pharmaceuticals		

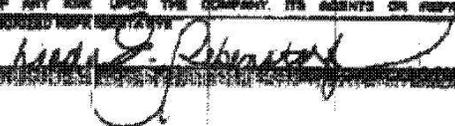
Dear Bill,

Attached is a copy of the captioned Evidence of Insurance.

The original will follow via regular mail.

Regards,

Linda Rebenstorf

ACORD		DATE (MM/DD/YY) 11/02/00			
PRODUCER WSS Woodruff-Sawyer & Co. 220 Bush Street, 7th Floor San Francisco, CA 94104-0000 415-391-2141		THIS CERTIFICATE IS ISSUED AS A MATTER OF INFORMATION ONLY AND CONFERS NO RIGHTS UPON THE CERTIFICATE HOLDER. THIS CERTIFICATE DOES NOT AMEND, EXTEND OR ALTER THE COVERAGE AFFORDED BY THE POLICIES BELOW.			
INSURED 009006 Pharis Pharmaceuticals, Inc. 235 Middlefield Road, Suite 240 Menlo Park, CA 94025-3444		COMPANIES AFFORDING COVERAGE COMPANY A General Star Indemnity Company COMPANY B COMPANY C COMPANY D			
THIS IS TO CERTIFY THAT THE POLICIES OF INSURANCE LISTED BELOW HAVE BEEN ISSUED TO THE INSURED NAMED ABOVE FOR THE POLICY PERIOD INDICATED, NOTWITHSTANDING ANY REQUIREMENT, TERM OR CONDITION OF ANY CONTRACT OR OTHER DOCUMENT WITH RESPECT TO WHICH THIS CERTIFICATE MAY BE ISSUED OR MAY PERTAIN. THE INSURANCE AFFORDED BY THE POLICIES DESCRIBED HEREIN IS SUBJECT TO ALL THE TERMS, EXCLUSIONS AND CONDITIONS OF SUCH POLICIES. LIMITS SHOWN MAY HAVE BEEN REDUCED BY PAID CLAIMS.					
CO LTR	TYPE OF INSURANCE	POLICY NUMBER	POLICY EFFECTIVE DATE (MM/DD/YY)	POLICY EXPIRATION DATE (MM/DD/YY)	LIMITS
A	GENERAL LIABILITY <input checked="" type="checkbox"/> COMMERCIAL GENERAL LIABILITY <input checked="" type="checkbox"/> CLAIMS MADE <input type="checkbox"/> OCCUR <input type="checkbox"/> OWNER'S & CONTRACTOR'S PROT	IYG3569978	03/13/00	03/13/01	GENERAL AGGREGATE \$ 1,000,000 PRODUCTS - COMMER AGG \$ 1,000,000 PERSONAL & ADV INJURY \$ 1,000,000 EACH OCCURRENCE \$ 1,000,000 FIRE DAMAGE (Any one fire) \$ 50,000 MED EXP (Any one person) \$
	AUTOMOBILE LIABILITY <input type="checkbox"/> ANY AUTO <input type="checkbox"/> ALL OWNED AUTOS <input type="checkbox"/> SCHEDULED AUTOS <input type="checkbox"/> HIRED AUTOS <input type="checkbox"/> NON-OWNED AUTOS				COMBINED SINGLE LIMIT \$ BODILY INJURY (Per person) \$ BODILY INJURY (Per accident) \$ PROPERTY DAMAGE \$
	DAMAGE LIABILITY <input type="checkbox"/> ANY AUTO				AUTO ONLY - EA ACCIDENT \$ OTHER THAN AUTO ONLY EACH ACCIDENT \$ AGGREGATE \$
A	EXCESS LIABILITY <input checked="" type="checkbox"/> UMBRELLA FORM <input type="checkbox"/> OTHER THAN UMBRELLA FORM	EXG573436	10/02/00	03/13/01	EACH OCCURRENCE \$ 2,000,000 AGGREGATE \$ 2,000,000
	WORKERS COMPENSATION AND EMPLOYERS LIABILITY THE PROPRIETOR, PARTNER/EXECUTIVE OFFICERS ARE <input type="checkbox"/> INCL. <input type="checkbox"/> EXCL. OTHER				TOTAL LIMITS PER YEAR EL EACH ACCIDENT \$ EL DISEASE - POLICY LIMIT \$ EL DISEASE - EA EMPLOYEE \$
DESCRIPTION OF OPERATIONS, OCCASIONS OR SPECIAL ITEMS RE: Clinical Trial #1195 WIRB-Aroclor and/or wake patients associated with pharmaceuticals administered in the anaesthetic environment during sleep-20 patients. Evidence Only.					
MPSI Attn: Bill Morgan 46750 Fremont Boulevard Fremont, CA 94538		10 Day Notice For Non-Payment of Premium SHOULD ANY OF THE ABOVE DESCRIBED POLICIES BE CANCELLED BEFORE THE EXPIRATION DATE THEREOF, THE ISSUING COMPANY WILL endeavor to MAIL 30 DAYS WRITTEN NOTICE TO THE CERTIFICATE HOLDER NAMED TO THE LEFT. BUT FAILURE TO MAIL SUCH NOTICE SHALL IMPOSE NO OBLIGATION OR LIABILITY OF ANY KIND UPON THE COMPANY, ITS AGENTS OR REPRESENTATIVES. AUTHORIZED REPRESENTATIVE 			

Appendix E Photographs of the Sleep Study



E1--a picture of the screening process.



Figure E2--a picture of the nebulizer.



Figure E3--a picture of the ceiling discharge.

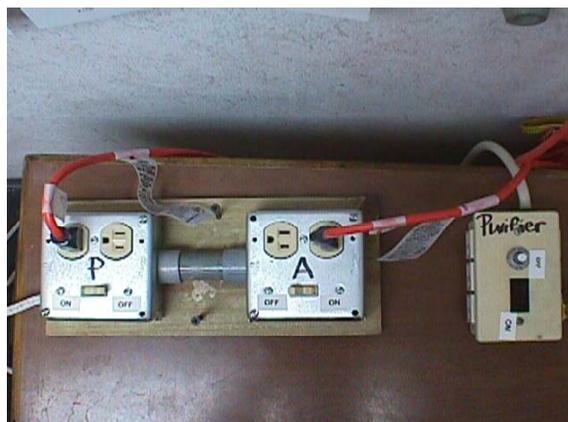
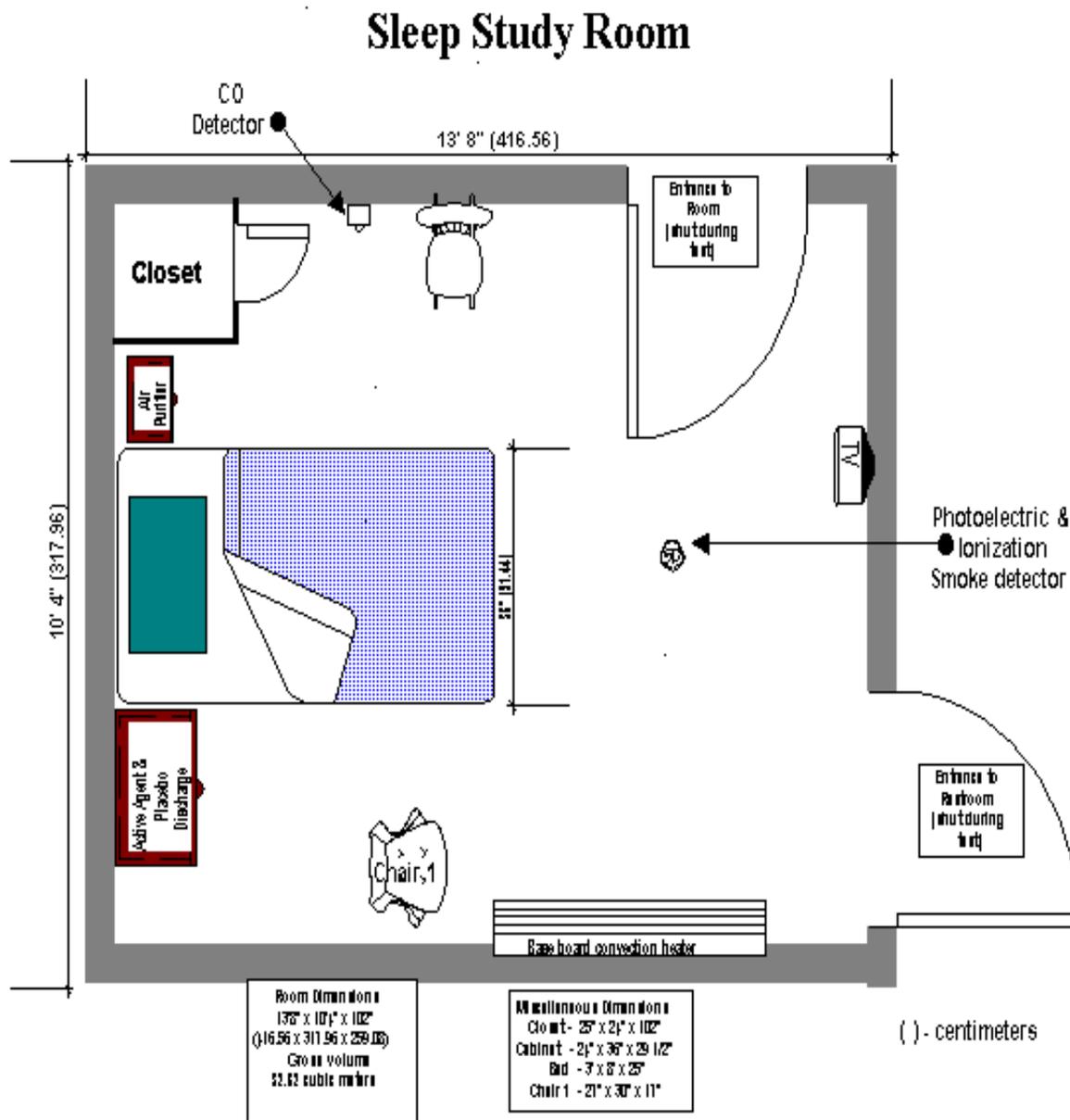


Figure E4--a picture of the various controls.

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Appendix F Room Diagram



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Appendix G Results Chart

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RESULTS CHART--PHEROMONE TESTS

Subjects	Active			Placebo			Comments
	2	3/4	REM	2	3/4	REM	
#1 30 C,F Shellie March 5 th	N	2 arousals		N	N		
#2 50 C,M Chuck March 6 th	N left	N left		1 Awakening left			
#3 42 C,M Allen March 7 th	N right	N left	3 arousals right	N left	1 arousal left		
#4 31 C,F Karen March 13	N right	1 arousal right		N back	1 arousal right	N right	
#5 34 C,M Charles March 14 th	1 arousal right	N left	3 arousals right		1 arousal right	N left	
#6 21 C,M Mark March 19	N left	N left	N Back	N left	N left	N back	
#7 37 C,M Robert March 22	4 arousals back	N back	1 arousal back				

Sheet Notes: N=15: 10 males, 5 females- Ages: Male Mean=35.40, Female Mean=31.80, Group Mean=34.20 .

Active and Placebo: The administration was either the active agent or placebo agent. Active and Placebo were two of the variables of the study.

2, 3/4 , REM: The stage of sleep that the active agent or the placebo agent was administered in. Referred to as NUMCOND, the sleep stages were variables of the study. Information about subjects that is located in the first column: subject's number, first name, age, race, gender, and date they were tested (all dates were in 2001). Arousal=Awakening, Each Arousal or Awakening=1 , N=No Reaction

Back, Right, Left, & Supine (This indicates the patient's actual position during administration of active or placebo agent.)

Blank Field=No Opportunity For Presentation (The subjects never reached that stage of sleep or pasted through it too quickly to administer test segment).

RESULTS CHART--PHEROMONE TESTS

Subjects	Active			Placebo			Comments
	2	3/4	REM	2	3/4	REM	
#8 32 C,M Larry March 23		N right	5 arousals supine/right 1 Awakening	N supine	1 arousal right	1 arousals left	
#9 39 C,M Harold March 26		N left	1 Awakening back				
#10 33 C,M Mike March 27 th	1 arousal 1 Awakening right	N left	1 Awakening right	N right		1 arousal left	
#11 35 C,F Angela March 28	4 arousals back	1 arousal left	2 arousals left	N left	N Back		
#12 35 C,M Joseph March 29	N right	N right	4 arousals right		N right		
#13 27 C,F Jania April 1	N left	N back		N left	N right	2 arousals back	

Sheet Notes: N=15: 10 males, 5 females- Ages: Male Mean=35.40, Female Mean=31.80, Group Mean=34.20 .

Active and Placebo: The administration was either the active agent or placebo agent. Active and Placebo were two of the variables of the study.

2, 3/4, REM: The stage of sleep that the active agent or the placebo agent was administered in. Referred to as NUMCOND, the sleep stages were variables of the study. Information about subjects that is located in the first column: subject's number, first name, age, race, gender, and date they were tested (all dates were in 2001). Arousal=Awakening, Each Arousal or Awakening=1, N=No Reaction

Back, Right, Left, & Supine (This indicates the patient's actual position during administration of active or placebo agent.)

Blank Field=No Opportunity For Presentation (The subjects never reached that stage of sleep or passed through it too quickly to administer test segment).

RESULTS CHART--PHEROMONE TESTS

Subjects	Active			Placebo			Comments
	2	3/4	REM	2	3/4	REM	
14 31 C,M Brad April 3	N left		3 arousals left				
15 36 C,F Allison April 4	3 arousals left, back	N	2 arousals right	2 arousals right			

Arousals By Category of Sex

Male	7	0	22	1	3	2
Total For Males		29	—		6	—
Female	7	4	4	2	1	2
Total For Females		15			5	

Note: Arousals or awakenings were a minimum of .00 and no maximum. N=15 for overall, N=10 for males, and N=5 for females. The number of presentations (conditions) were as follows: Overall 38 active, 25 placebo; males 26 active, 14 placebo; females 12 active, 11 placebo. Proportional results were established by reporting the number of arousals/awakenings occurring in the overall, male, and female test population for placebo and active agent presentations. Overall test population Chi-square response significance (with standard deviations in parentheses) for Active Agent was .919 (2.251), and Placebo Agent was .449 (.799). Male test population Chi-square response significance (with standard deviations in parentheses) for Active Agent was .849 (2.025), and Placebo Agent was .273 (.699). Female test population Chi-square response significance (with standard deviations in parentheses) for Active Agent was 1.00 (2.915), and Placebo Agent was .819 (1.000).

Sheet Notes: N=15: 10 males, 5 females- Ages: Male Mean=35.40, Female Mean=31.80, Group Mean=34.20 .

Active and Placebo: The administration was either the active agent or placebo agent. Active and Placebo were two of the variables of the study.

2, 3/4, REM: The stage of sleep that the active agent or the placebo agent was administered in. Referred to as NUMCOND, the sleep stages were variables of the study. Information about subjects that is located in the first column: subject's number, first name, age, race, gender, and date they were tested (all dates were in 2001). Arousal=Awakening, Each Arousal or Awakening=1, N=No Reaction

Back, Right, Left, & Supine (This indicates the patient's actual position during administration of active or placebo agent.)

Blank Field=No Opportunity For Presentation (The subjects never reached that stage of sleep or passed through it too quickly to administer test segment).

Format changes have been made to facilitate reproduction. While these research projects have been selected as outstanding, other NFA EFOP and APA format, style, and procedural issues may exist.

Appendix H
Sleep Technologist's Guidelines

Pheromone Sciences Research Study
Technologist's Guidelines

Active Agent Nebulizer on **20 seconds**
Wait One Full Minute

Air Purifier on **2 minutes**

Placebo Nebulizer on **20 seconds**
Wait One Full Minute

Air Purifier on **2 minutes**

Always allow **30 minutes between** Active and
Placebo Nebulizers

Attempt to deliver Active and Placebo agents in
Stage 2, Delta (3or4) & REM a minimum of twice
throughout the night

Please document body position when Agent or
Placebo is delivered

Air Purifier must run after both Active and Placebo

Format changes have been made to facilitate reproduction. While these research projects have been selected as outstanding, other NFA EFOP and APA format, style, and procedural issues may exist.

Format changes have been made to facilitate reproduction. While these research projects have been selected as outstanding, other NFA EFOP and APA format, style, and procedural issues may exist.

Appendix I SPSS Report

Format changes have been made to facilitate reproduction. While these research projects have been selected as outstanding, other NFA EFOP and APA format, style, and procedural issues may exist.

Var Lab Subject "Name of Subject" Sex "Sex of Subject"
 NumCond "Number of Conditions" Active "Active agent responses"
 Placebo "Placebo agent responses" ActResp "Active Agent Responses"
 PlacResp "Placebo Agent Responses".
 Val Lab Subject 1 "Shellie" 2 "Chuck" 3 "Allen" 4 "Karen" 5 "Charles" 6
 "Mark"
 7 "Robert" 8 "Larry" 9 "Harold" 10 "Mike" 11 "Angela" 12 "Joseph" 13
 "Jania"
 14 "Brad" 15 "Allison".
 Val Lab Sex 1 "Male" 2 "Female".
 Val Lab ActResp 1 "Response" 0 "No Response".
 Val Lab PlacResp 1 "Response" 0 "No Response".
 display all.

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 4/20/ 1

Variable: SUBJECT Label: Name of Subject
 Value labels follow Type: Number Width: 2 Dec: 0 Missing: *
 None *
 1.00 Shellie 2.00 Chuck
 3.00 Allen 4.00 Karen
 5.00 Charles 6.00 Mark
 7.00 Robert 8.00 Larry
 9.00 Harold 10.00 Mike
 11.00 Angela 12.00 Joseph
 13.00 Jania 14.00 Brad
 15.00 Allison

Variable: SEX Label: Sex of Subject
 Value labels follow Type: Number Width: 1 Dec: 0 Missing:
 * None *
 1.00 Male 2.00 Female

Variable: NUMCOND Label: Number of Conditions
 No value labels Type: Number Width: 1 Dec: 0 Missing: *
 None *

Variable: ACTIVE Label: Active agent responses
 No value labels Type: Number Width: 1 Dec: 0 Missing: *
 None *

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 4/20/ 1

Variable: PLACEBO Label: Placebo agent responses
 No value labels Type: Number Width: 1 Dec: 0 Missing: *
 None *

Variable: ACTRESP Label: Active Agent Responses
 Value labels follow Type: Number Width: 1 Dec: 0 Missing: *
 None *
 1.00 Response .00 No Response

Format changes have been made to facilitate reproduction. While these research projects have been selected as outstanding, other NFA EFOP and APA format, style, and procedural issues may exist.

Karen	4	1	6.7	6.7	26.7
Charles	5	1	6.7	6.7	33.3
Mark	6	1	6.7	6.7	40.0
Robert	7	1	6.7	6.7	46.7
Larry	8	1	6.7	6.7	53.3
Harold	9	1	6.7	6.7	60.0
Mike	10	1	6.7	6.7	66.7
Angela	11	1	6.7	6.7	73.3
Joseph	12	1	6.7	6.7	80.0
Jania	13	1	6.7	6.7	86.7
Brad	14	1	6.7	6.7	93.3
Allison	15	1	6.7	6.7	100.0
Total		15	100.0	100.0	

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4/20/ 1

SUBJECT Name of Subject

Mean 8.000 Std dev 4.472 Minimum 1.000
Maximum 15.000

Valid cases 15 Missing cases 0

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4/20/ 1

SEX Sex of Subject

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
Male	1	10	66.7	66.7	66.7
Female	2	5	33.3	33.3	100.0
Total		15	100.0	100.0	

Mean 1.333 Std dev .488 Minimum 1.000
Maximum 2.000

Valid cases 15 Missing cases 0

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4/20/ 1

NUMCOND Number of Conditions

Valid Cum

Format changes have been made to facilitate reproduction. While these research projects have been selected as outstanding, other NFA EFOP and APA format, style, and procedural issues may exist.

Value Label	Value	Frequency	Percent	Percent	Percent
	2	2	13.3	13.3	13.3
	3	2	13.3	13.3	26.7
	4	3	20.0	20.0	46.7
	5	7	46.7	46.7	93.3
	6	1	6.7	6.7	100.0
	Total	15	100.0	100.0	
Mean	4.200	Std dev	1.207	Minimum	2.000
Maximum	6.000				

Valid cases 15 Missing cases 0

 Page 13 Effect of agents on the sleeping person
 4/20/ 1

ACTIVE Active agent responses

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
	0	3	20.0	20.0	20.0
	1	2	13.3	13.3	33.3
	2	1	6.7	6.7	40.0
	3	3	20.0	20.0	60.0
	4	2	13.3	13.3	73.3
	5	2	13.3	13.3	86.7
	6	1	6.7	6.7	93.3
	7	1	6.7	6.7	100.0
	Total	15	100.0	100.0	
Mean	2.933	Std dev	2.251	Minimum	.000
Maximum	7.000				

Valid cases 15 Missing cases 0

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 4/20/ 1

PLACEBO Placebo agent responses

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
	0	7	46.7	46.7	46.7
	1	5	33.3	33.3	80.0
	2	3	20.0	20.0	100.0
	Total	15	100.0	100.0	

Format changes have been made to facilitate reproduction. While these research projects have been selected as outstanding, other NFA EFOP and APA format, style, and procedural issues may exist.

		Total	15	100.0	100.0
Mean	.733	Std dev	.799	Minimum	.000
Maximum	2.000				

Valid cases 15 Missing cases 0

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 4/20/ 1

ACTRESP Active Agent Responses

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
No Response	0	3	20.0	20.0	20.0
Response	1	12	80.0	80.0	100.0
	Total	15	100.0	100.0	

Mean	.800	Std dev	.414	Minimum	.000
Maximum	1.000				

Valid cases 15 Missing cases 0

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 4/20/ 1

PLACRESP Placebo Agent Responses

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
No Response	0	7	46.7	46.7	46.7
Response	1	8	53.3	53.3	100.0
	Total	15	100.0	100.0	

Mean	.533	Std dev	.516	Minimum	.000
Maximum	1.000				

Valid cases 15 Missing cases 0

 Page 17 Effect of agents on the sleeping person
 4/20/ 1

This procedure was completed at 10:54:55
 descriptives all.

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Number of Valid Observations (Listwise) = 15.00

Variable	Mean	Std Dev	Minimum	Maximum	N	Label
SUBJECT	8.00	4.47	1	15	15	Name of Subject
SEX	1.33	.49	1	2	15	Sex of Subject
NUMCOND	4.20	1.21	2	6	15	Number of Conditions
ACTIVE	2.93	2.25	0	7	15	Active agent respons
PLACEBO	.73	.80	0	2	15	Placebo agent respon
ACTRESP	.80	.41	0	1	15	Active Agent Respons
PLACRESP	.53	.52	0	1	15	Placebo Agent Respon

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 4/20/ 1

This procedure was completed at 10:54:55
 npar tests /chisquare sex numcond active placebo.

***** WORKSPACE allows for 13416 cases for NPAR TESTS *****

 Page 20 Effect of agents on the sleeping person
 4/20/ 1

- - - - - Chi-square Test

SEX	Sex of Subject	Category	Cases Observed	Expected	Residual
Male		1	10	7.50	2.50
Female		2	5	7.50	-2.50
			--		
		Total	15		

Chi-Square	D.F.	Significance
1.667	1	.197

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4/20/ 1

- - - - - Chi-square Test

NUMCOND		Number of Conditions		
Category	Cases			
	Observed	Expected	Residual	
2	2	3.00	-1.00	
3	2	3.00	-1.00	
4	3	3.00	.00	
5	7	3.00	4.00	
6	1	3.00	-2.00	
	--			
Total	15			

WARNING - Chi-Square statistic is questionable here.
5 Cells have expected frequencies less than 5.
Minimum expected cell frequency is 3.0

Chi-Square	D.F.	Significance
7.333	4	.119

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4/20/ 1

- - - - - Chi-square Test

ACTIVE		Active agent responses		
Category	Cases			
	Observed	Expected	Residual	
0	3	1.88	1.13	
1	2	1.88	.13	
2	1	1.88	-.88	
3	3	1.88	1.13	
4	2	1.88	.13	
5	2	1.88	.13	
6	1	1.88	-.88	
7	1	1.88	-.88	
	--			
Total	15			

WARNING - Chi-Square statistic is questionable here.
8 Cells have expected frequencies less than 5.
Minimum expected cell frequency is 1.9

Chi-Square	D.F.	Significance
2.600	7	.919

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4/20/ 1

- - - - - Chi-square Test

PLACEBO Placebo agent responses

Category	Cases		
	Observed	Expected	Residual
0	7	5.00	2.00
1	5	5.00	.00
2	3	5.00	-2.00
	--		
Total	15		

Chi-Square	D.F.	Significance
1.600	2	.449

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4/20/ 1

This procedure was completed at 10:55:01
npar tests /chisquare ActResp.

***** WORKSPACE allows for 22890 cases for NPAR TESTS *****

Page 25 Effect of agents on the sleeping person
4/20/ 1

- - - - - Chi-square Test

ACTRESP Active Agent Responses

	Category	Cases		
		Observed	Expected	Residual
No Response	0	3	7.50	-4.50
Response	1	12	7.50	4.50
		--		
	Total	15		

Chi-Square	D.F.	Significance
5.400	1	.020

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4/20/ 1

This procedure was completed at 10:55:04
npar tests /chisquare PlacResp.

***** WORKSPACE allows for 22890 cases for NPAR TESTS *****

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 4/20/ 1

- - - - - Chi-square Test

PLACRESP Placebo Agent Responses

	Category	Cases Observed	Expected	Residual
No Response	0	7	7.50	-.50
Response	1	8	7.50	.50
		--		
	Total	15		

Chi-Square	D.F.	Significance
.067	1	.796

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 4/20/ 1

This procedure was completed at 10:55:05
 frequencies active placebo /STATISTICS SUM.

***** Memory allows a total of 17873 Values, accumulated across all Variables.
 There also may be up to 2234 Value Labels for each Variable.

 Page 29 Effect of agents on the sleeping person
 4/20/ 1

ACTIVE Active agent responses

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
	0	3	20.0	20.0	20.0
	1	2	13.3	13.3	33.3
	2	1	6.7	6.7	40.0
	3	3	20.0	20.0	60.0
	4	2	13.3	13.3	73.3
	5	2	13.3	13.3	86.7
	6	1	6.7	6.7	93.3
	7	1	6.7	6.7	100.0
	Total	15	100.0	100.0	

Sum 44.000

Valid cases 15 Missing cases 0

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4/20/ 1

PLACEBO Placebo agent responses

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
	0	7	46.7	46.7	46.7
	1	5	33.3	33.3	80.0
	2	3	20.0	20.0	100.0
	Total	15	100.0	100.0	

Sum 11.000

Valid cases 15 Missing cases 0

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4/20/ 1

This procedure was completed at 10:55:06
T-TEST /pairs active with placebo.
T-TEST requires 64 BYTES of workspace for execution.

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4/20/ 1

- - - t-tests for paired samples - - -

Variable	Number of pairs	Corr	2-tail Sig	Mean	SD	SE of Mean
ACTIVE Active agent responses				2.9333	2.251	.581
PLACEBO Placebo agent responses	15	.029	.918	.7333	.799	.206

Mean	Paired Differences SD	SE of Mean	t-value	df	2-tail Sig
------	-----------------------	------------	---------	----	------------

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4/20/ 1

SEX Sex of Subject

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
Male	1	10	100.0	100.0	100.0
	Total	10	100.0	100.0	
Mean	1.000	Std dev	.000	Minimum	1.000
Maximum	1.000				

Valid cases 10 Missing cases 0

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4/20/ 1

NUMCOND Number of Conditions

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
	2	2	20.0	20.0	20.0
	3	2	20.0	20.0	40.0
	4	1	10.0	10.0	50.0
	5	4	40.0	40.0	90.0
	6	1	10.0	10.0	100.0
	Total	10	100.0	100.0	
Mean	4.000	Std dev	1.414	Minimum	2.000
Maximum	6.000				

Valid cases 10 Missing cases 0

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4/20/ 1

ACTIVE Active agent responses

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
	0	2	20.0	20.0	20.0
	1	1	10.0	10.0	30.0
	3	3	30.0	30.0	60.0
	4	2	20.0	20.0	80.0

Format changes have been made to facilitate reproduction. While these research projects have been selected as outstanding, other NFA EFOP and APA format, style, and procedural issues may exist.

			5	1	10.0	10.0	90.0
			6	1	10.0	10.0	100.0
					-----	-----	-----
		Total		10	100.0	100.0	
Mean	2.900	Std dev		2.025	Minimum		.000
Maximum	6.000						

Valid cases 10 Missing cases 0

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 4/20/ 1

PLACEBO Placebo agent responses

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
	0	5	50.0	50.0	50.0
	1	4	40.0	40.0	90.0
	2	1	10.0	10.0	100.0
		-----	-----	-----	
	Total	10	100.0	100.0	

Mean	.600	Std dev	.699	Minimum	.000
Maximum	2.000				

Valid cases 10 Missing cases 0

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 4/20/ 1

ACTRESP Active Agent Responses

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
No Response	0	2	20.0	20.0	20.0
Response	1	8	80.0	80.0	100.0
		-----	-----	-----	
	Total	10	100.0	100.0	

Mean	.800	Std dev	.422	Minimum	.000
Maximum	1.000				

Valid cases 10 Missing cases 0

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4/20/ 1

PLACRESP Placebo Agent Responses

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
No Response	0	5	50.0	50.0	50.0
Response	1	5	50.0	50.0	100.0
		-----	-----	-----	
Total		10	100.0	100.0	
Mean	.500	Std dev	.527	Minimum	.000
Maximum	1.000				

Valid cases 10 Missing cases 0

Page 42 Effect of agents on the sleeping person
4/20/ 1

This procedure was completed at 10:55:13
process if sex=1.
NPAR tests /CHISQUARE SEX Numcond ACTIVE PLACEBO.

***** WORKSPACE allows for 13416 cases for NPAR TESTS *****

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4/20/ 1

- - - - - Chi-square Test

SEX	Sex of Subject	Cases		
	Category	Observed	Expected	Residual
Male	1	10	10.00	.00
		--		
Total		10		

Only one cell generated. Test abandoned.

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4/20/ 1

- - - - - Chi-square Test

NUMCOND	Number of Conditions	Cases		
	Category	Observed	Expected	Residual

Format changes have been made to facilitate reproduction. While these research projects have been selected as outstanding, other NFA EFOP and APA format, style, and procedural issues may exist.

2	2	2.00	.00
3	2	2.00	.00
4	1	2.00	-1.00
5	4	2.00	2.00
6	1	2.00	-1.00
	--		
Total	10		

WARNING - Chi-Square statistic is questionable here.
 5 Cells have expected frequencies less than 5.
 Minimum expected cell frequency is 2.0

Chi-Square	D.F.	Significance
3.000	4	.558

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- - - - - Chi-square Test

ACTIVE Active agent responses

		Cases	
Category	Observed	Expected	Residual
0	2	1.67	.33
1	1	1.67	-.67
3	3	1.67	1.33
4	2	1.67	.33
5	1	1.67	-.67
6	1	1.67	-.67
	--		
Total	10		

WARNING - Chi-Square statistic is questionable here.
 6 Cells have expected frequencies less than 5.
 Minimum expected cell frequency is 1.7

Chi-Square	D.F.	Significance
2.000	5	.849

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- - - - - Chi-square Test

PLACEBO Placebo agent responses

		Cases	
Category	Observed	Expected	Residual
0	5	3.33	1.67

1	4	3.33	.67
2	1	3.33	-2.33
	--		
Total	10		

WARNING - Chi-Square statistic is questionable here.
 3 Cells have expected frequencies less than 5.
 Minimum expected cell frequency is 3.3

Chi-Square	D.F.	Significance
2.600	2	.273

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 4/20/ 1

This procedure was completed at 10:55:15
 process if sex=2.
 NPAR TESTS /CHISQUARE sex NumCond active placebo.

***** WORKSPACE allows for 13416 cases for NPAR TESTS *****

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 4/20/ 1

- - - - - Chi-square Test

SEX	Sex of Subject				
		Category	Cases Observed	Expected	Residual
Female		2	5	5.00	.00
			-		
		Total	5		

Only one cell generated. Test abandoned.

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- - - - - Chi-square Test

NUMCOND	Number of Conditions				
		Category	Cases Observed	Expected	Residual
		4	2	2.50	-.50
		5	3	2.50	.50
			-		
		Total	5		

WARNING - Chi-Square statistic is questionable here.
2 Cells have expected frequencies less than 5.
Minimum expected cell frequency is 2.5

Chi-Square	D.F.	Significance
.200	1	.655

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4/20/ 1

- - - - - Chi-square Test

ACTIVE Active agent responses

Category	Cases		
	Observed	Expected	Residual
0	1	1.00	.00
1	1	1.00	.00
2	1	1.00	.00
5	1	1.00	.00
7	1	1.00	.00
	-		
Total	5		

WARNING - Chi-Square statistic is questionable here.
5 Cells have expected frequencies less than 5.
Minimum expected cell frequency is 1.0

Chi-Square	D.F.	Significance
.000	4	1.000

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- - - - - Chi-square Test

PLACEBO Placebo agent responses

Category	Cases		
	Observed	Expected	Residual
0	2	1.67	.33
1	1	1.67	-.67
2	2	1.67	.33
	-		
Total	5		

WARNING - Chi-Square statistic is questionable here.
3 Cells have expected frequencies less than 5.
Minimum expected cell frequency is 1.7

Chi-Square D.F. Significance
 .400 2 .819

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This procedure was completed at 10:55:18
 process if sex=2.
 frequencies all /statistics.

***** Memory allows a total of 17873 Values, accumulated across all
 Variables.
 There also may be up to 2234 Value Labels for each Variable.

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 4/20/ 1

SUBJECT Name of Subject

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
Shellie	1	1	20.0	20.0	20.0
Karen	4	1	20.0	20.0	40.0
Angela	11	1	20.0	20.0	60.0
Jania	13	1	20.0	20.0	80.0
Allison	15	1	20.0	20.0	100.0
	Total	5	100.0	100.0	

Mean 8.800 Std dev 6.017 Minimum 1.000
 Maximum 15.000

Valid cases 5 Missing cases 0

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 4/20/ 1

SEX Sex of Subject

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
Female	2	5	100.0	100.0	100.0
	Total	5	100.0	100.0	

Mean 2.000 Std dev .000 Minimum 2.000
 Maximum 2.000

Valid cases 5 Missing cases 0

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4/20/ 1

NUMCOND Number of Conditions

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
	4	2	40.0	40.0	40.0
	5	3	60.0	60.0	100.0
	Total	5	100.0	100.0	
Mean	4.600	Std dev	.548	Minimum	4.000
Maximum	5.000				

Valid cases 5 Missing cases 0

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4/20/ 1

ACTIVE Active agent responses

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
	0	1	20.0	20.0	20.0
	1	1	20.0	20.0	40.0
	2	1	20.0	20.0	60.0
	5	1	20.0	20.0	80.0
	7	1	20.0	20.0	100.0
	Total	5	100.0	100.0	
Mean	3.000	Std dev	2.915	Minimum	.000
Maximum	7.000				

Valid cases 5 Missing cases 0

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4/20/ 1

PLACEBO Placebo agent responses

Valid Cum

Format changes have been made to facilitate reproduction. While these research projects have been selected as outstanding, other NFA EFOP and APA format, style, and procedural issues may exist.

Value Label	Value	Frequency	Percent	Percent	Percent
	0	2	40.0	40.0	40.0
	1	1	20.0	20.0	60.0
	2	2	40.0	40.0	100.0
	Total	5	100.0	100.0	

Mean 1.000 Std dev 1.000 Minimum .000
 Maximum 2.000

Valid cases 5 Missing cases 0

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 4/20/ 1

ACTRESP Active Agent Responses

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
No Response	0	1	20.0	20.0	20.0
Response	1	4	80.0	80.0	100.0
	Total	5	100.0	100.0	

Mean .800 Std dev .447 Minimum .000
 Maximum 1.000

Valid cases 5 Missing cases 0

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 4/20/ 1

PLACRESP Placebo Agent Responses

Value Label	Value	Frequency	Percent	Valid Percent	Cum Percent
No Response	0	2	40.0	40.0	40.0
Response	1	3	60.0	60.0	100.0
	Total	5	100.0	100.0	

Mean .600 Std dev .548 Minimum .000
 Maximum 1.000

Valid cases 5 Missing cases 0

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4/20/ 1

This procedure was completed at 10:55:22
correlations /variables sex, numcond, active, placebo.

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4/20/ 1

Correlations:	SEX	NUMCOND	ACTIVE	PLACEBO
SEX	1.0000	.2425	.0217	.2443
NUMCOND	.2425	1.0000	.0578	.3556
ACTIVE	.0217	.0578	1.0000	.0291
PLACEBO	.2443	.3556	.0291	1.0000

N of cases: 15 2-tailed Signif: * - .01 ** - .001

" . " is printed if a coefficient cannot be computed

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4/20/ 1

This procedure was completed at 10:55:25
process if sex=1.
correlations /variables sex, active, placebo.

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Correlations:	SEX	ACTIVE	PLACEBO
SEX	1.0000	.	.
ACTIVE	.	1.0000	.3610
PLACEBO	.	.3610	1.0000

N of cases: 10 2-tailed Signif: * - .01 ** - .001

" . " is printed if a coefficient cannot be computed

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This procedure was completed at 10:55:25
process if sex=2.
correlations /variables sex, active, placebo.

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Correlations:	SEX	ACTIVE	PLACEBO
---------------	-----	--------	---------

Format changes have been made to facilitate reproduction. While these research projects have been selected as outstanding, other NFA EFOP and APA format, style, and procedural issues may exist.

SEX	1.0000	.	.
ACTIVE	.	1.0000	-.3430
PLACEBO	.	-.3430	1.0000

N of cases: 5 2-tailed Signif: * - .01 ** - .001

" . " is printed if a coefficient cannot be computed

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This procedure was completed at 10:55:26
fin.

End of Include file.