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Stimulus Properties of Inhaled Substances

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Inhaled substances can modify behavior by their toxic action, or because they are discriminable events, or because they can support or suppress behavior. They can be used as discriminative stimuli at concentrations above the olfactory threshold. Inhalants can elicit unconditioned reflexes. As aversive stimuli, they can be studied in respondent conditioning experiments (e.g. conditioned suppression), in punishment paradigms, or as negative reinforcers in escape paradigms. Inhalants can also be positive reinforcers; their intoxicating properties have engendered patterns of chronic self-administration (solvent abuse). Such stimulus properties should be considered in industrial hygiene and environmental quality decisions. Laboratory techniques to study such properties abound.

Toxicology must deal with a large variety of atmospheric contaminants possessing a vast array of toxic effects. Such contaminants include gases and vapors, which may be asphyxiants, irritants, metabolic poisons or carcinogens, and aerosols in the form of dusts, fumes, smokes, mists, fogs, and smogs. The respiratory system is an efficient route of entry for such substances. The pervasive presence of atmospheric pollutants behooves us to examine the effects of representative agents that pose environmental or occupational hazards. This paper will discuss techniques suitable for characterizing the behavioral significance of airborne contaminants as stimulus events that can control behavior. It will not emphasize their role in the toxicologic impairment of behavior. Techniques used to evaluate poisons administered by other routes generally can be used to evaluate the behavioral effects of inhaled substances.

Studies of the behavioral effects and stimulus properties of inhaled agents require the investigator to master both the behavioral technology and the instrumental techniques for generating and monitoring test atmospheres. Perhaps this need for a dual apprenticeship explains the relative paucity of experimental work in this area. Fortunately, a number of good reference works are available (*1–4*). When studying the stimulus properties of inhaled substances, experimenters use smaller exposure chambers to achieve rapid and precise control of concentration. The concentrations employed consequently tend to be higher than those employed to evaluate chronic toxicity.

The experimental techniques described here will help resolve the following questions: is the odor detectable? Is the material irritating? Can odor or irritation be relied upon as adequate warning of the presence of the material? Do fatigue, adaptation, tolerance or similar processes restrict the utility of these stimuli as warning signals or as noxious events that can be relied upon to limit worker exposure? Are some substances so pleasant that they pose special hazards to workers who develop a fondness for the materials with which they work?

Odors as Discriminative Stimuli

Olfactory Psychophysics

Airborne materials can function as discriminative stimuli in behavioral experiments in much the same way as lights or tones (*5, 6*). For example, Pavlov (*7*) used camphor as a conditioned inhibitory stimulus. Allen (*8*) investigated the differential function of the olfactory and trigeminal nerves in response to a variety of olfactants with a discriminated avoidance procedure. Many methodological problems flawed the early studies. Vapor-generating equipment was crude, frequently consisting of little more than a ball of cotton soaked in

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the stimulus material. The olfactory stimuli of interest frequently were confounded with their spatial location, as in T-maze studies, by stimuli from preceding animals, by the odor of the reinforcer, or by the presence of the experimenter. A discussion of the early work is available (*9*).

A considerable improvement occurred with the adoption of operant conditioning techniques (*10–14*). Small chambers assured rapid turnover of chamber atmosphere and maintained the orientation of the subject to the air stream. For example, odorless or odorized air was delivered to the end of a Teflon cylinder closed by a perforated Teflon disk that the rat pressed with its nose (*12*). In some experiments, responding was reinforced only in the absence of odor (*10, 11, 15*). In others, rats were conditioned to discriminate between different odors (*15*).

Similar techniques have been developed for the pigeon. Michaelson (*16*) demonstrated that pigeons can discriminate between the presence and absence of olfactory stimuli. The pigeon's absolute detection threshold and thresholds for the detection of differences in stimulus intensity have now been described (*17–20*). Much of this work has been done using conditioned suppression, a technique whose application to animal psychophysics has been reviewed (*21*). With this technique, subjects are trained to respond on an intermittent reinforcement schedule. Once stable response rates are achieved, the presentation of an odor for, say, 30 sec, is followed by an unavoidable electric shock. At first, a marked decrease in responding occurs after the shock. After repeated pairings of the olfactory warning stimulus and the shock, the odor presentation produces large reductions in response rate. This is called conditioned suppression because the suppression originally seen after shock now occurs when the odor is introduced. Response suppression reflects detection of the stimulus. Thus, standard psychophysical techniques such as the descending method of limits (i.e., the presentation of successively lower concentrations of the odorant) can now be used to determine detection thresholds.

Davis (*22*) developed a conditioned suppression technique to determine the absolute and difference detection thresholds in the rat. The relevance of the difference threshold is discussed below. It was determined as follows. Two concentrations of the odorant were chosen. The lower concentration stimulus was a "safe" stimulus, not followed by shock delivery. A concentration 10 times greater was used as the warning stimulus. Presentation of the latter for 30 sec was always followed by shock to the feet. When no suppression occurred to the safe stimulus and substantial suppression followed the presentation of the high concentration warning stimulus, the subject could be said to discriminate between the two stimuli. The subject was then tested for generalization by using intermediate concentrations; the discriminability of changes in concentration could thus be estimated. The conditioned suppression technique apparently is a particularly sensitive method for psychophysical studies of olfaction. Stevens (*5*) asserts that the absolute thresholds determined by Davis are lower than those determined by other methods, both behavioral and electrophysiological.

Application of Olfactory Psychophysical Techniques

Absolute and Difference Detection Thresholds. Such techniques allow us to address several problems relevant to occupational and environmental health. One is to establish odor thresholds. Another is to compare these values with exposure limit values and with the concentrations believed to cause toxic signs. They also permit us to study olfactory fatigue and tolerance. Such studies tell us how long odors will be useful to the worker as warning stimuli, and whether chronic exposure to low concentrations elevates the olfactory threshold. These problems have been neglected. Olfactory fatigue, especially, has been considered a complication, a nuisance obstructing attempts to determine "true" olfactory thresholds.

The threshold for the detection of differences may prove to be a particularly sensitive index of adaptation, since the organism is challenged to perform refined discriminations well above the limit of detection. The procedure may be particularly useful in describing the nature of olfactory fatigue: after several hours of exposure to a volatile substance, how much of a change in concentration can be discriminated? The worker may be able to detect the substance, but be unable to report a concentration increase that he was able to detect before exposure.

Manifestations of Toxicity. Another major class of problems is the direct olfactory manifestation of toxicity. Diminished olfactory sensitivity or the total loss of sensitivity (anosmia) can ensue from exposure to agents that obstruct, destroy, or impair the function of the olfactory mucosa. For example, gross corrosion and perforation of the olfactory mucosa and the nasal septum occur following exposure to hexavalent chromium (*23*) and inorganic arsenic (*24*). Emmett (*25*) observed hyposmia and qualitative changes in olfaction (dysosmia) after solvent exposure, and cited a number of anecdotal reports of injury to the sense of smell following ex-

posure to hydrazine, carbon disulfide, benzol, oil of peppermint, solvent mixtures, sulfuric acid, hydrogen selenide, phosphorus oxychloride, pepper and cresol mixtures, nuisance dusts, and formaldehyde. Functional changes in olfactory sensitivity should precede gross morphological changes in nasal structure. Indeed, this is what the clinical evidence suggests. For example, cadmium dust exposure can produce complete loss of olfactory sensitivity (*26–29*). However, Adams and Crabtree asserted that the presence of pathological changes in the olfactory mucosa were of no value in assessing the extent of damage to the sense of smell. The onset of this loss due to cadmium may be a very gradual phenomenon occurring across a period of six months or more. Some exposed men who failed to detect very high concentrations of phenol were not aware of any significant disability (*28*). Women were more aware of the loss of functioning discriminative stimuli. They reported frequently burning food in the kitchen, and, worse, suffering from bouts of food poisoning that resulted from eating spoiled food (*27*). Such gradual losses of sensitivity could be examined carefully in the laboratory.

The mechanism by which cadmium dust produces anosmia is unknown. Anosmia has not been linked to cadmium fume exposure or oral cadmium ingestion. Impaction of dust particles on the olfactory mucosa apparently is a necessary precondition. Baader (*27*) reports recovery from anosmia in some patients with the termination of exposure. One mechanism of cadmium toxicity may be the displacement of zinc. There are two reasons for this speculation: first, some of the toxic effects of cadmium can be reversed by zinc administration (*30*); and, second, dietary zinc deficiency or zinc deficiency produced by chelation can result in disorders of smell and taste (*31*). Inorganic mercury vapor (*32*) and vanadium (*33*) have also been associated with changes in olfactory sensitivity. Basic contributions to the understanding of the role of metals in the physiology of olfaction could be made employing olfactory psychophysical techniques.

Changes in olfactory and taste sensitivity may provide early signs of toxicity. Loss of appetite and weight loss are among the earliest symptoms of systemic toxicity resulting from exposure to inorganic mercury (*34*). Weight loss or the retardation of growth are early signs of methylmercury toxicity in laboratory animals (*35*). These changes may reflect changes in the sensory qualities of food. Such findings have been observed in patients with idiopathic disorders of taste and smell (*36*). Functional disturbances of the olfactory system may also influence other behaviors, including copulation, irritability and aggression, maternal and other social behaviors, activity and exploration, regulatory behaviors and learning (*37*).

Inhalants as Aversive Events

As we know from everyday experience, inhaled substances can also be aversive events. Aversive stimuli can elicit unconditioned reflexes. An aversive stimulus can also change the frequency of a behavior. The direction and magnitude of change varies with the intensity of the stimulus and the scheduling of the onset and offset of the aversive stimulus.

Unconditioned Reflexes

Irritants (e.g., riot control agents) decrease respiratory rate and induce expiratory apnea, peripheral vasoconstriction, elevated systolic blood pressure, bradycardia, and other related physiological events. Alarie (*38–40*) has developed a preparation in which mice are restrained in a whole-body plethysmograph attached to an exposure cylinder enclosing the head. The evoked decrease in respiratory rate is useful for characterizing the effects of airborne materials at relatively high concentrations, for rank-ordering potencies, and for determining structure-activity relationships. No information, however, is provided about the behavioral significance of exposure to moderate concentrations that may not be aversive and that might elicit components of the trigeminal reflex. Consequently, examining only the respiratory reflex could spuriously identify a substance as aversive at concentrations without behavioral significance.

Respondent Conditioning

Inhaled substances have been used as unconditioned stimuli in respondent conditioning experients. Jamison (*41*) used ammonia as an unconditioned stimulus; bradycardia could be elicited by a tone paired with the delivery of ammonia. This autonomic response was used to determine auditory intensity thresholds in the rat. Alarie (*38*) has respondently conditioned to a flashing light the trigeminally-mediated respiratory reflex elicited by upper airway irritants.

Conditioned Suppression

One way to establish that an upper airway irritant is behaviorally significant (i.e., aversive) at a given concentration would be to pair a neutral stimulus with the inhaled stimulus and subsequently observe

the effects of this previously neutral stimulus on schedule-controlled behavior. As already noted, the conditioned suppression technique can be used to determine odor detection thresholds by pairing an olfactory stimulus with an aversive electrical stimulus. A psychophysical estimate of the aversiveness of an event could be made by keeping the discriminative stimulus at a fixed value and manipulating the intensity of the inhaled stimulus, choosing values that range from the ineffective to the aversive. The amount of suppression produced by the presentation of such a conditioned stimulus depends on the intensity of the unconditioned aversive stimulus (*42–44*). Conditioned suppression has also been established using an intravenously administered chemical as the unconditioned stimulus, e.g., nalorphine has been used as an aversive stimulus with morphine-dependent monkeys (*45*).

Punishment

Another way to determine if a compound is an aversive stimulus is to use it as a punishing stimulus, and see if it reduces the frequency of occurrence of the response that produces it. The punishment paradigm has yet to be examined in the laboratory with inhaled agents. However, it appears often in society. Surely this is what the mailman intends when he sprays allyl isothiocynate at the vicious dog, or the peace officer when he uses a riot control agent. Such control devices may be effective partly because they immediately generate incompatible behavior, apart from any effect on the future probability of the behavior being punished.

Negative Reinforcement

An aversive stimulus increases the frequency of any response that terminates or delays its occurrence. No one has yet conclusively demonstrated escape from an inhaled substance in a laboratory preparation. Although Weinstein (*46*) reported escape from carbon dioxide by mice and pigeons, no one has attempted to repeat this work in other laboratories, and it could be a direct rate-increasing effect of carbon dioxide on the performance. A discriminated escape procedure (e.g., two available levers, only one of which terminates the aversive stimulus) would be one way to separate the direct effects on rate from the negative reinforcing effect of stimulus termination.

Techniques established to study the aversive properties of intravenously administered drugs should facilitate work on the aversive properties of inhalants. Hoffmeister and Wuttke (*47*) trained monkeys to press a lever that turns off a light associated with the periodic delivery of shocks to the scalp. Drugs were substituted for shock delivery to determine if they would maintain escape behavior. A variety of drugs were found to maintain escape behavior in drug naive subjects, including hallucinogens (*49, 50*), major tranquilizers (*49–51*) and narcotic antagonists (*47, 48*). Saline infusion did not maintain performance. An analogous preparation could be established for the study of inhaled agents. Response latency should be related to the aversiveness of the compound and the time course of concentration change in the helmet or exposure chamber.

The establishment of such an escape performance is a prerequisite for the establishment of titration performance, a procedure which enables the continuous monitoring of aversive thresholds (*52, 53*). This procedure allows the subject to reduce the intensity of a stimulus which increases in discrete increments with time. With appropriate parameter selection, the response rate matches the interincrement interval and yields a stable aversive threshold. The principal dependent variables are measures of central tendency and variability of the aversive stimulus intensity maintained by the subject. The performance generated by this technique has been demonstrated to be sensitive to analgesic drugs.

Behavior controlled by the aversive properties of inhaled substances could be employed to study the relative aversiveness of compounds and their course of action. Acute and chronic adaptation phenomena are of special importance when considering the irritating, aversive properties of inhaled substances. Such acutely unpleasant properties are sometimes relied on to control worker exposure in industrial settings, i.e., it is assumed that the worker will flee. Nonetheless, experienced individuals will remain in environments that cannot be endured by individuals without recent exposure histories (e.g., ammonia) (*54*). Many compounds could be studied using these techniques, including corrosives, solvents, and the combustion products of industry, the automobile, and the catastrophic conflagration.

Inhalants as Positive Reinforcers

Volatile substances have been inhaled for their intoxicating central nervous system effects throughout recorded history. Apollo's priestess at Delphi inhaled vapors, producing an altered state and mystical observations (*55*). The use of nitrous oxide and ether as anesthetic agents was presaged by a long period of their use as recreational drugs. The experience of Oliver Wendell Holmes (*56*) is

instructive:

> "I once inhaled a pretty full dose of ether, with the determination to put on record, at the earliest moment of regaining consciousness, the thought I should find uppermost in my mind. The mighty music of the triumphal march into nothingness reverberated through my brain, and filled me with a sense of infinite possibilities, which made me an archangel for a moment. The veil of eternity was lifted. The one great truth which underlies all human experience and is the key to all the mysteries that philosophy has sought in vain to solve, flashed upon me in a sudden revelation. Henceforth all was clear: a few words had lifted my intelligence to the level of the knowledge of the cherubim. As my natural condition returned, I remembered my resolution; and, staggering to my desk, I wrote, in ill-shaped, straggling characters, the all embracing truth still glimmering in my consciousness. The words were these (children may smile; the wise will ponder): 'A strong smell of turpentine prevails throughout.' "

Access to the agents, of course, is a precondition of their abuse. Just as physicians and other medical personnel are more likely to develop a narcotic addiction (*57, 58*), anesthesiologists have been known to self-administer habitually ether, nitrous oxide, cyclopropane, ethyl chloride, chloroform, and halothane (*59*). Halothane abuse recently resulted in the sudden death of three hospital technicians (*60*). The abuse of gasoline by rural children may be related to its ready availability (*61, 62*). Toluene, a solvent in many household and industrial products, has an extensive history of abuse (*63–65*). The abuse by youth of toluene-containing glues and aerosol sprays is aggravated directly by the easy availability of these substances in hardware and grocery stores. In addition, occupational exposure to toluene as a degreasing agent and paint solvent has in some cases led to its chronic abuse (*66–69*).

A particularly horrifying story is the abuse of vinyl chloride in the industrial setting. Early experimental human exposures to vinyl chloride (*70*) employed concentrations that ranged up to 20,000 ppm. The authors stated that "vinyl chloride causes clearcut intoxicating symptoms which can serve as adequate warning signs of its presence." Suciu et al. noted that during exposure, workers displayed euphoria "marked by singing, whistling, and sardonic, careless laughter" (*71*). Inevitably, intoxication occurred in the workplace: one Goodrich worker observed "Some would become like alcoholics. They would breathe it again and again until they passed out" (*72*).

It is of great importance to be able to predict the abuse potential of substances (*73*). Although nonhuman primates will self-administer most CNS drugs abused by humans (*74–76*), the reinforcing properties of inhaled substances have received little attention in the laboratory. Yanagita and his coworkers (*77*) reported that macaque monkeys increased lever pressing when it produced intranasal infusions of chloroform, lacquer thinner, or ether. This study suggested that self-administration of inhalants might be examined profitably in the laboratory, and led us to undertake a systematic examination of this process with nitrous oxide (*78*). This agent is readily available, easily administered, and causes little systemic toxicity.

Squirrel monkeys were restrained in a chair with plates at the waist and neck (Fig. 1). The restraining chair faced a clear panel with a push-button. Gas was delivered through tubing to the top of a cylindrical helmet placed over the subject's head. The helmet tubing was attached via two-way valves to tanks of N_2O and O_2 so that various mixtures could be delivered.

Monkeys easily learn to self-administer nitrous oxide. After responding had stabilized under conditions in which each response produced a 15 sec delivery of 60% N_2O, an experiment was undertaken in which groups of daily sessions with N_2O available were alternated with groups of sessions during which it was not. All other conditions remained the same. Withholding N_2O from the flow of gas delivered to the helmet produced a three to four-fold reduction in reinforcement rate, demonstrating that N_2O delivery maintained the high rate of responding (Fig. 2). When N_2O delivery depended on more than a single response (on a fixed-ratio schedule) behavior was still maintained in strength. Increasing the fixed-ratio requirement increased response rates, demonstrating the similarity of N_2O delivery to the delivery of other reinforcers, such as food, water, and intravenous drug administration.

Toluene also functions as a reinforcer (*79–81*). Squirrel monkeys previously trained to self-administer N_2O readily worked for 15 sec deliveries

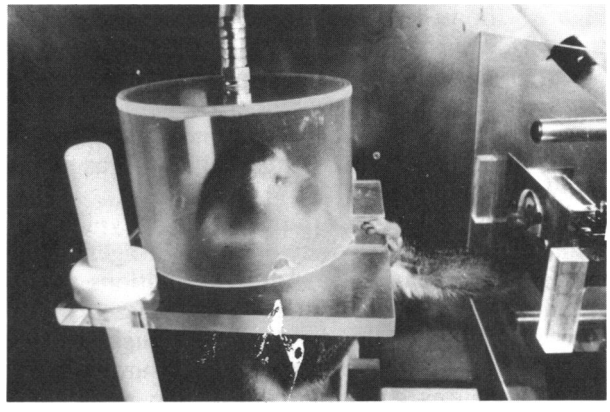

FIGURE 1. Subject 33 seated in chair pressing the manipulandum which will produce a 15 sec delivery of 60% N_2O at 8 liter/min. Blocks mounted on front of panel maintain minimum distance from manipulandum during autoshaping phase.

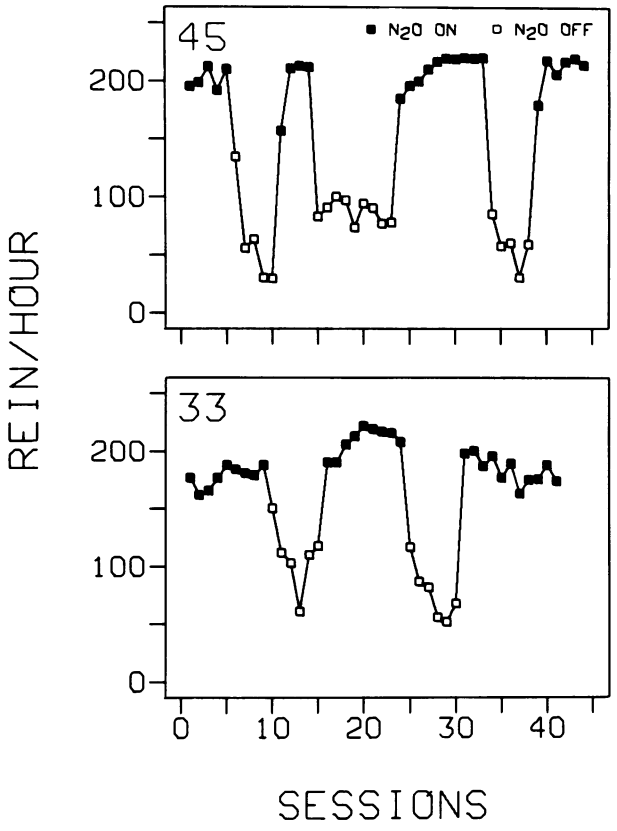

FIGURE 2. Reinforcement rates for subjects 45 (top) and 33 (bottom) under conditions where a response produced either 60% nitrous oxide (N_2O "on") or oxygen only (N_2O "off").

of toluene vapor. The frequency with which monkeys self-administered toluene vapor varied with vapor concentration (0.056 to 1.0%). The highest average rate observed at any concentration was 141/hr at 0.1%.

Figure 3 shows representative cumulative records of this performance when concentration was varied. Response rates were stable and reinforcer deliveries rather evenly spaced when toluene was delivered contingent upon a response. Responding occurred irregularly and in bursts when toluene was not available.

It should be noted that the procedures typically used in evaluating the toxicity of a volatile agent are not representative of the exposure conditions produced during the abuse of these substances. Toxicologic studies typically use either very high levels of exposure or chronic regimens of exposure to low levels. Exposures generated during the abuse of such agents typically fall between these two extremes. The consistency and chronicity of this type of spiked exposure can be remarkable. Simple measurements of concentrations in the work place cannot characterize this exposure. Knox and Nelson

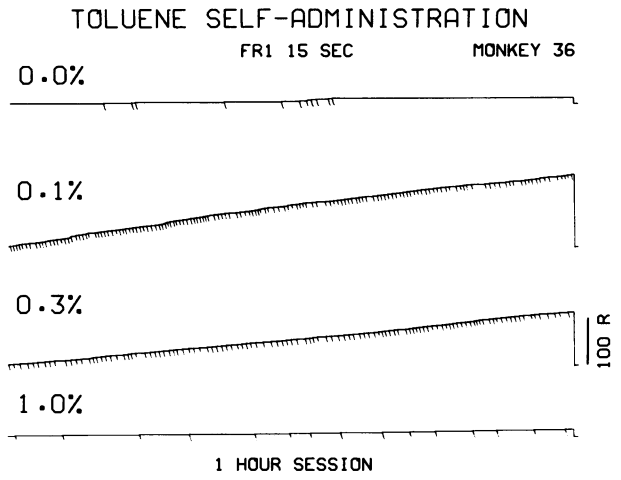

FIGURE 3. Cumulative records of monkey 36, illustrating fixed ratio 1 performance maintained by 15 sec deliveries of toluene. Paper runs with time; pen steps up with each response. Session duration was one hour. Toluene concentrations are indicated at the left of each cumulative record. Note irregular responding in the absence of toluene; response and reinforcement rates at these concentrations were inversely related to concentration.

(*67*) described a man who noticed euphoria while working with paint thinner at an aircraft manufacturing company. His habit escalated to deep inhalations of concentrated vapors from a small container more than ten times per hour throughout the day, including meal times! This behavior persisted over a 14-year period.

The abuse potential of industrial materials should be taken into consideration when short-term exposure limit values are set. Animal tests can identify positively reinforcing substances without resorting to experimental human exposures. The self-administration model described here should allow rapid determination of exposure levels sufficient to maintain self-administration of these agents. Further work should determine how this "self-administration limit value" correlates with values that affect complex learned behavior.

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