Testing the Neural Sensitization and Kindling Hypothesis for Illness from Low Levels of Environmental Chemicals

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Sensitization in the neuroscience and pharmacology literatures is defined as progressive increase in the size of a response over repeated presentations of a stimulus. Types of sensitization include stimulant drug-induced time-dependent sensitization (TDS), an animal model related to substance abuse, and limbic kindling, an animal model for temporal lobe epilepsy. Neural sensitization (primarily nonconvulsive or subconvulsive) to the adverse properties of substances has been hypothesized to underlie the initiation and subsequent elicitation of heightened sensitivity to low levels of environmental chemicals. A corollary of the sensitization model is that individuals with illness from low-level chemicals are among the more sensible members of the population. The Working Group on Sensitization and Kindling identified two primary goals for a research approach to this problem: to perform controlled experiments to determine whether or not sensitization to low-level chemical exposures occurs in multiple chemical sensitivity (MCS) patients, and to use animal preparations for kindling and TDS as nonhomologous models for the initiation and elicitation of MCS. — Environ Health Perspect 105(suppl 2):539-547 (1997)

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Background

Sensitization is the progressive increase in the size of a response over repeated presentations of a stimulus (1). Time-dependent sensitization (TDS), a term suggested by Antelman (2,3), involves sensitization by the simple passage of time between initial and later reexposures to a stimulus. Thus, intermitency is an important time-related feature of stimuli that initiate sensitization as opposed to continuous exposures that initiate tolerance (4). Pharmacologic agents, direct electrical stimulation, and physical and psychological stressors can all initiate or elicit the amplified responses in TDS (2,5,6,7). Sensitization can interact with tolerance and with conditioning (8–10), but each of these processes can be distinguished from the other by proper experimental design (8–10). The mechanisms of sensitization are not fully understood but may involve persistent changes in neurotransmitters, receptors, and basic neural cellular functions (5,6). Sensitization of immune function can occur during TDS protocols (11), but neural rather than classical immunological changes appear to mediate TDS of neurobehavioral functions (2,6,12). For example, various investigators have blocked drug-induced sensitization in the central nervous system using excitatory amino acid antagonists (13), nitric oxide synthase inhibitors (14), protein synthesis inhibitors (15), or delta-opioid receptor antagonists (16). In TDS, the subcortical, dopaminergic mesolimbic pathways also may be involved (5,6). A special type of neural sensitization is kindling, in which periodic repeated electrical or chemical stimulation of brain limbic structures such as the olfactory bulb, amygdala, and areas of the hippocampus leads to permanent susceptibility to convulsions not seen upon initial stimulation (17–22).

Because most persons with multiple chemical sensitivity (MCS) do not have clinical seizure disorders, kindling per se is not the most apt model for their condition (7). However, nonconvulsive TDS, subconvulsive kindling and/or related neural sensitization processes (7,18,20–23) could provide an explanation for a puzzling feature of MCS, i.e., susceptibility to low levels of environmental chemicals that according to classical toxicological dose–response relationships should not occur (24). Convergent lines of evidence point to this possibility. First, a subset, though not all, of MCS patients has been found to have increased lifetime histories or comorbid histories of certain psychiatric disorders, specifically major depression, anxiety disorders, and somatoform disorders (25–29). Researchers in biological psychiatry have proposed for many years that the recurrent, long-term course of these conditions follows the pattern of a sensitized response in that progressively less severe life stress or eventually...
no stress at all is required to trigger later episodes of illness (12,30). Still others have reported increased histories of childhood abuse in certain MCS patients (31). Early abuse may trigger increased rates of posttraumatic stress disorder (PTSD) (32,33). PTSD is a condition of persistent hyperreactivity to salient stimuli and other environmental stimuli (e.g., startle to noise) for which TDS is a leading model (2,34). Rather than assume that MCS is merely a misattribution of psychiatric symptoms from these conditions, an alternative view would be that the psychiatric findings and the MCS are both the result of an increased susceptibility to sensitization (7,22).

The second line of evidence that could provide an explanation for some patients' susceptibility to low levels of environmental chemicals is that other characteristics of TDS and MCS overlap (3,5,7,22,35–37). For example, females are more susceptible to both TDS and MCS (38). Both processes can be initiated by a wide range of chemically unrelated agents (3). Agents of different types can cross-sensitize with one another (2,3,5). Elicited responses can proceed in a bidirectional manner (39,40). The amplified responses can occur in multiple different bodily systems (2,3,5,17). Individuals sensitized through TDS and those with MCS can appear no different from the normal population in their responses to a given agent (a) at an initial but not later exposure (41); (b) at later exposures if insufficient time has passed since the last sensitizing exposure (6,42) (i.e., sensitization may not yet have occurred or is obscured by tolerance); (c) at later exposures if encountered under novel conditions different from those under which the original sensitization developed (8,43). An important implication of the latter points is that it will be essential to perform multiple, not one, exposure sessions separated in time to test the sensitization model for MCS (7,22,36). That is, it is necessary to initiate and elicit sensitization within the same experiment (42). Otherwise, negative findings could be explained as a lack of preexisting sensitization or as a suppression of a truly sensitized response by tolerance or by the novelty of the experimental situation at the time of a single test session.

**Experimental Design—Human Studies**

**Participant Selection**

Demographic variables important to MCS research include gender, age, education, and occupational/chemical exposure histories. The Working Group on Sensitization and Kindling concluded that research in MCS needs a generally accepted structured interview based upon common patterns of patient symptoms. Such an interview would help characterize the nosology of MCS and facilitate comparison of results between studies. It is feasible and reasonable to borrow from the precedents of mainstream psychiatry that generated the standardized Diagnostic and Statistical Manual (DSM)(44) and its associated Structured Clinical Interview for DSM Diagnosis (SCID)(45). These systematic tools for psychiatric diagnosis rely on patient self-reports of particular patterns of symptoms; determination of clinician agreement over etiological factors is not required for most diagnoses except for those related to specific drugs of abuse or organic causes such as a recognized medical condition. If and when generally accepted objective markers for MCS become available, specific test parameters can be incorporated into the overall case definition. This does not imply that MCS is or is not a psychiatric disorder. Rather, use of a phenomenologically based interview would capture the state of knowledge in the field at that time in a practical way so as to advance understanding of the problem.

Chronicity of illness would be important to establish, e.g., 6 months or longer, to eliminate persons with self-limited acute or subacute toxic reactions to accidental poisonings. The MCS interview items also should draw upon the descriptive scientific data beginning to emerge from surveys of patients (46) and the clinicians who evaluate them (47–51). For example, the number of incitant chemicals and severity of illness attributed to chemicals, regardless of the specific symptoms, may help distinguish MCS from overlapping syndromes such as chronic fatigue or fibromyalgia (47). Another important subtyping question might ask for self-identification of a defined initiating chemical exposure, including age at onset versus no clear onset date or event (51). Marked changes in lifestyle attributed to chemical sensitivity (26) are also distinguishing features of clinical MCS, including disability or change in occupation, personal hygiene products, places frequented or traveled to, home structure, and furnishings (46). Queries about specific symptoms might include the most frequent MCS complaints, e.g., feelings of unreality, memory difficulties, dizziness or lightheadedness, problems focusing eyes, muscle aches, tingling in fingers and/or toes, tiredness, irritability (46). Clinically, most MCS patients report additional intolerances to common foods and various medications (46,52).

One potentially important set of subtyping questions would be about past and/or current history of certain psychiatric disorders (51). For those items, the MCS interview might borrow the screening questions for past and current depression, anxiety disorders, and somatization disorder from the psychiatric SCID or other validated instruments [e.g., somatization screen (53); Minnesota Multiphasic Personality Inventory (MMPI) (54); Symptom Checklist 90, revised (SCL-90-R) (55)]. For instance, one could have dementia with or without comorbid depression (44). Similarly, available data indicate that one could have MCS with or without comorbid depression or anxiety disorders (49–51). Preliminary electroencephalographic studies by Bell et al. (56) indicate that the electrophysiological activation patterns of individuals with both chemical intolerance and depression differ from those of persons with only one or the other condition or neither. Thus, it may be essential to recruit subjects systematically who have or do not have specific features. Subject screening should include validated self-report and observer-rated measures of depression and anxiety, with specific cut-off scores for inclusion and exclusion criteria. Self-report measures could include instruments such as the Beck Depression Inventory (57) and the Spielberger State-Trait Anxiety Inventory (58); observer-rated measures could include the Hamilton Depression and Hamilton Anxiety Scales (59). By the same token, control/comparison groups, e.g., depressives or panic disorder patients, would have to be screened specifically to eliminate those with high levels of chemical intolerance. Preclinical or clinically mild chemical intolerance with minimal associated lifestyle changes is common in nonindustrial samples (60–67). However, previous controlled studies generally have not screened for chemical intolerance, thereby adding a major design flaw into comparisons of MCS patient groups with other groups such as medically ill patients or even some normal persons. A central tenet of experimental design is to select groups that differ on the key independent measure under consideration, e.g., degree of self-reported chemical odor intolerance.

Because of the lack of previous human studies in this area using specific outcome
measures with chemical exposures, it is difficult to predict the appropriate group sample sizes to ensure adequate statistical power with certainty. However, sample sizes in the several studies that have demonstrated significant sensitization or failure of habituation of autonomic variables in human subjects have fallen in the range of 9 to 25 subjects per group (42,68,69). The ability to detect significant group differences in these between-group studies with these small samples suggests large estimated effect sizes. Similarly, animal studies of chemical sensitization with behavioral end points have used 9 to 32 animals per group (5,20,70). A between-subjects design in human studies could risk Type II error from insufficient sample size and too low power to detect medium- or small-sized effects. Nonetheless, the high likelihood of carryover effects from one exposure condition to another in a within-subjects design favors using a between-subjects approach. If within-subjects designs are used, a counterbalanced order of exposure conditions in separate subgroups of each group, e.g., MCS and controls, would assist in clarifying any such asymmetric transfer of effects (71). It will be necessary to restrict the number of outcome measures in any given protocol to limit confounding of results of one outcome measure by a preceding outcome measure (72).

An additional consideration for experimental design is that of stimulus range effects (73). The range of stimuli or the range of responses used by the subjects may affect their responses (73). That is, sensitization studies within subjects would risk confounding by range effects if a given subject were to undergo more than one experimental condition. This problem again favors the use of separate groups for each concentration, stressor, and time factor. The nature of sensitization studies requires use of repeated sessions with the same outcome measure(s) in the same subjects, but the experimental condition (i.e., chemical vs sham exposures) and the timing of exposures must differ among subgroups of each group. Taken together, these issues point to the need for a large number of separate groups in human or animal sensitization studies to be certain of the source of a given finding. For example, Antelman et al. (74) used nine separate groups rather than the same group of animals (n = 6–10 per group) to evaluate the effects on mesolimbic dopamine status of pretreatment with a range of different intensity environmental stressors (home cage, clean cage, dirty cage, black box) interacting with a range of drug treatment conditions (no injection, saline injection alone, or 0.2 mg/kg haloperidol in saline given at three different time lags after the pretreatment: none, 2 hr, or 2 weeks). They also used entirely separate groups of animals to confirm the stressfulness of each of the pretreatment conditions with glucocorticoid measurements. It also may be necessary to consider similar separate studies and between-groups methodology in human sensitization studies (71–73).

**Experimental Conditions**

Among many potential issues in the design of human MCS/sensitization studies are the following: state of adaptation or deadaptation of subjects (24); route of sensitizing and test exposures (e.g., oral, inhalation, dermal); environmental context (novel versus familiar). For the first issue, Ashford et al. (75) and Miller (76) have presented a systematic case for the need for an environmentally controlled medical unit where human subjects could be cleared of possible masking, adaptation, and/or pharmacological cross-tolerance to multiple inhaled chemicals. The sensitization working group agreed that one design for protocols to initiate and test for sensitization in MCS patients could involve the same sensitization procedures but compare outcomes under conditions of masking and unmasking.

Related to the second issue, route of sensitization, laboratory sensitization in animals has been initiated primarily by injection with drugs or pesticides (3–6,19,20) and inhalation with solvents such as toluene (21,70). In human studies, oral alco-hol ingestion has been used successfully to initiate and demonstrate autonomic nervous system sensitization of nonalcoholics without first withdrawing them from alcohol outside the laboratory (42). The working group discussed the possibility of separate human studies involving different types of agents and routes of administration, e.g., oral ingestion of a drug such as methylphenidate or inhalation exposure to a solvent such as toluene. The advantage of testing for drug sensitization is the greater potential control over cross-sensitizing or cross-tolerant exposures outside the laboratory. From an ethical perspective, using a stimulant drug such as methylphenidate versus a placebo in humans would be a clinically appropriate trial. Current standards of practice in psychiatry indicate that low-dose stimulants may particularly benefit persons with low energy or depression related to medical conditions (77).

A test of stimulant sensitization in MCS patients and controls also would facilitate understanding of the question of the presence or absence of heightened general sensitizability in MCS patients, even though it would not directly address the involvement of specific environmental chemicals. Alternatively, the group considered other agents such as opiate drugs, substance P, or alcohol for possible tests of TDS. For example, Antelman (3) noted that human sensitization of β-endorphin to interleukin-2 has been shown in clinical populations (non-MCS) (78). Bell et al. (79) also have evidence that specific foods might induce sensitization of β-endorphin in nonclinical chemically intolerant elderly. Another important advantage of using drugs to test for TDS would be to evaluate the capacity of selected outcome measures under consideration for chemical exposure studies to exhibit sensitization. Repeated drug administrations would permit refinement of these outcome measures during administration of better studied agents at doses with known effects compared to possibly arbitrary selections of test chemicals and concentrations for initial chemical exposure studies.

In the case of inhaled volatile exposures in the laboratory as sensitizing events, one approach could mimic elements of the dose selection procedures used in Molhave et al (80). Different subgroups could receive various doses, e.g., low doses: subfactory levels of a given substance (e.g., toluene) or volatile mixture (e.g., Molhave volatile organic compound mixture found in indoor air) in an exposure test chamber; moderate doses: detectable levels of a substance or mixture similar to those measured in sick buildings; high doses: detectable levels but below Occupational Safety and Health Administration (OSHA) standards for an industrial workplace. The duration of dosing would be important. Antelman (2) emphasized that brief exposures to a sensitizing agent may be more effective at initiating just sensitization and not tolerance, whereas prolonged exposures may tend to induce both sensitization and tolerance. Thus, studies could compare exposure durations of several minutes, 1 hr, or 6 to 8 hours at a time.

With regard to the third issue in the design of human sensitization studies, environmental context, Bell et al. (36) have extensively discussed the contextual points involved in sensitization research. These are relevant to ethical concerns to avoid persistent injury to subjects’ health outside the
labouratory setting. One way to approach these concerns would be to initiate human subjects in a context-dependent rather than independent manner (9,42,81,82). That is, the protocol for initiating sensitization would require that the physical setting (e.g., distinctive laboratory appearance, color of walls, etc.), procedures, and time of day be identical for both sensitization and testing sessions. Varying the context in which sensitization occurs could induce context-independent sensitization such as may relate to MCS patients' heightened chemical reactivity in a wide range of environments different from that of the originally identified exposure event. In contrast, the proposed laboratory procedures would require that the context remain the same throughout the study in order that the risk of subjects later reacting adversely be confined to reexposures during any return visits to the laboratory situation and not to other situations in their everyday lives. Thus, while context-dependent designs would help address ethical concerns for human studies, these same issues make it imperative that full testing of the sensitization hypothesis for MCS employ animal models to permit initiation and assessment of context-independent sensitization, i.e., administer the agent in various cages and/or rooms throughout the study.

The basic protocol for initiating and testing for context-dependent sensitization in human subjects would then involve at least two and preferably three or more laboratory sessions well spaced in time. The time interval between sessions for initiating TDS could range from 1 to 14 days. Testing immediately after a daily protocol in animals often does not reveal the sensitization (6). Past research suggests that it would then be necessary to wait at least several days, preferably 7 to 14 days, after the final sensitization exposure to test for development of a sensitized response. While context-dependent designs by definition invoke elements of classical conditioning to the environment, it is still possible to design studies to differentiate sensitization from conditioning. For example, drawing from similar animal research (9), it would be possible to establish the development of an amplified response in humans to a given substance with a sensitization protocol, then repeatedly reexpose them to the same setting and procedures with sham exposures (e.g., arrowroot starch-filled capsules for drug placebo or filtered airstreams for inhalation route) until the amplified response returns to baseline, i.e., extinguishes. Then another test exposure with the active agent is conducted to see if the amplified response returns immediately. If so, then sensitization and conditioning factors have been separated; that is, the sensitized response is still present (elicitable) even though the conditioned, context-dependent component of the response is not (9,10).

Another variation of the contextual design that demonstrates the context-dependence would be to initiate laboratory sensitization to a given substance in a particular room of the laboratory and then test for TDS by reexposing half of each group to the same substance in the original exposure room and half of each group to the same substance in a distinctly different exposure room. Because novelty is expected to dampen the size of a sensitized response in context-dependent TDS (8–10), it is predicted that the sensitized group(s) would show a lesser response to the substance in the new room compared with that in the old room. However, retesting in the old room should reinitiate the amplified response promptly. Various between-groups and within-groups crossover designs (e.g., ABABBA) counterbalanced for order of test room type (new or old) could be utilized [(71–73) however, on unwanted within-subjects effects]. Another possible strategy for addressing the ability of novelty to dampen elicitation of sensitization responses would be to habituate subjects to the laboratory setting and procedures for several sessions without chemical or drug exposures before beginning the sensitization process.

**Dependent Variables**

One of the least discussed but most important methodological issues in MCS research is the selection of outcome measures. Many investigators have elected relatively insensitive designs involving subjects' dichotomous guesses about the presence or absence of a chemical and/or subtle increases in subjective symptoms. While this approach may be especially important in the clinical situation and should be included in any human study, the Sensitization Working Group considers it necessary but not sufficient for the research situation. Dependent variables that would add objectivity and sensitivity to experimental design would include neurophysiological (e.g., olfactory-evoked potentials, cognitive event-related potentials [ERPs] such as P300, quantitative electroencephalography [EEG], and polysomnography) (83–87); neuroimaging (e.g., functional MRI); autonomic (e.g., pupil response, heart rate, blood pressure, respiratory, pulmonary function tests) (68,69); cognitive (e.g., continuous performance tests, divided attention tests, information-processing tests) (88–90); behavioral (e.g., Profile of Mood States [POMS] scale, anxiety sensitivity index) (79,91); and motor activity (e.g., physical activity monitors, facial electromyography [EMG] for positive and negative affect, acoustic startle responses) (42,64).

There are several advantages to most of the above measures. First, most of the variables can detect subtle and/or rapid changes in function as well as failure to habituate upon repeated sampling (68). Second, all variables except neuroimaging are relatively inexpensive and noninvasive to obtain repeatedly once the equipment has been purchased. These measures have been and currently are in use in scientific studies of human subjects with cognitive, affective, or somatic symptoms similar to those reported in MCS, e.g., dementias, depressions, PTSD, chronic pain, migraine headache, irritable bowel. Thus, the available research literature using those same measures would offer information on the specificity of any findings in MCS compared with findings for better characterized disorders.

Finally, testing the sensitization hypothesis in human subjects involves important methodological considerations. Design issues that pertain to TDS studies can differ from those used when testing other hypotheses for MCS. For example, the seemingly reasonable approach of pretesting with open challenges (75) of possible active and placebo substances to determine current reactivity or nonreactivity in MCS is not possible from a TDS perspective. Even in animal studies, prior experience with a stimulus changes a given individual's responsivity to later reexperiences if the individual is sensitizable (2). Thus, lack of initial reactivity to a particular substance does not necessarily predict lack of subsequent reactivity (2,3,5,6,41). Indeed, many different agents and stimuli evoke no difference in the first session of TDS studies between animals that will eventually sensitize and those that will not. A placebo at the beginning of an experiment could turn into an active agent in a sensitizable subject by the end of testing.

For this reason, most animal TDS studies utilize between-group rather than within-group designs (2,5,6). For example, one of several control groups proceeds through the experiment with no exposures to the test agent. Another control group
receives the test agent only at the final testing session. In comparison, the experimental group(s) receive the test agent repeatedly at each sensitizing session and at the final testing session. In addition to designs using different initiating exposures, another design strategy is to compare groups of animals predicted to exhibit individual differences in sensitizability. Such groups would include different genetic strains (92), females versus males (93,94), or hyperreactivity versus hypo-reactivity to novelty (41). That is, half the animals are predicted to be maximally, and half to be minimally, sensitizable. For human studies, selection of control groups to compare with MCS patients might mean ensuring that such groups lack potential for sensitizability, e.g., no family histories of recurrent affective disorders or substance abuse (65), as well as no self-reported chemical odor intolerance.

In summary, the working group suggests two primary experimental approaches, one involving a shorter-term repeated measures design, the other involving longitudinal follow-up of persons who had experienced an identifiable chemical exposure event. The first study would compare MCS patients with any of various control groups for initiation and elicitation of sensitization to low-level chemical exposures. The second study would determine risk factors for developing MCS by assessing persons who later develop MCS and those who do not.

Experiment 1, Repeated Measures Study

The first study would test the hypothesis that MCS patients are more susceptible to initiation of context-dependent sensitization than control subjects. This short-term between-subjects sensitization study (over a period of 6 weeks, one session per week) would involve three sessions of habituation to the laboratory and procedures but without chemical exposures followed by three test sessions (active or placebo). Pilot studies should include pretesting the sensitivity of proposed outcome measures to sensitization in normals (who then would not participate in any other part of the research) to an agent such as methylphenidate; and determination of olfactory thresholds in MCS patients and controls (who then would not participate in any other part of the research) for active chemical agents used in the study. For the primary study, participants would include MCS patients with and without depression and nonchemically sensitive controls with and without major depression. The study will purposely oversample women to approximate the reported gender distribution among MCS sufferers (24). In view of the animal evidence that a high estrogen-to-progestosterone ratio might favor sensitization in females (93) and that testosterone might lessen sensitization in males (94), an adjunctive exploratory measure for risk of sensitization in this human study might be blood levels of estrogen and progesterone at specified times in the menstrual cycle as well as blood levels of testosterone.

From the above list of possible dependent variables, an initial selection might include physiological measures considered most likely to detect group differences, i.e., stabilometer (general motor activity level), respiration, heart rate, pupil, EEG and cognitive event-related potentials (auditory odd-ball paradigm), and facial EMG (an objective and sensitive correlate of mood state). For mood changes and cognitive dysfunction respectively, the POMS and specific neuropsychological tests previously found to show differences from those of controls in studies of chemically intolerant or solvent-exposed persons (e.g., divided attention, continuous performance test) would be appropriate (85,89,95). All participants would undergo initial baseline sessions on filtered room air delivered by an olfactometer similar to that used by Kobal and Hummel (83) to facilitate habituation to the novelty of the laboratory and procedures. For subsequent sessions in this study, an olfactometer would deliver brief exposures to filtered room air (the placebo) and test chemicals (e.g., subolfactory and supraolfactory threshold levels of toluene in air stream) (below and above threshold). Half the participants in each group would get filtered room air during the entire experiment and half of each group would get the chemical (split-plot design). The exposure would occur as either intermittent bursts (1-min exposure, 3-min wait) or continuous exposures for at least 10 to 15 min. Additional sessions would occur at 1-, 2-, and 3-week intervals at the same time of day.

While studies designed to elicit acute adverse reactions in MCS patients raise ethical concerns, the need for systematic understanding of this illness and its mechanisms is pressing. Lack of data has severely hampered research on possible preventive and treatment interventions. At the present stage of knowledge about MCS, the potential benefits outweigh the risks. That is, acute reactions in chemically sensitive individuals typically resolve within minutes to hours after conclusion of a low-level chemical exposure. Most patients do not experience life-threatening symptoms during such reactions, and those with disorders such as asthma or epilepsy can be screened out of the studies. However, even in standard clinical practice, diagnostic testing for conditions with episodic rather than continuous clinical manifestations, e.g., methacholine challenge in asthma or hyperventilation during EEG recording in epilepsy, often involves deliberate provocation of acute exacerbations as part of a workup. The laboratory context-dependent design of the present proposed experiments would minimize the risk of persistent worsening of a patient’s long-term course, as discussed above. Thus, it is reasonable to proceed with acute chemical exposure research in MCS at this time. The emergence of new data in the area may or may not necessitate reassessment of the ethics of additional challenge studies in the future.

Experiment 2, Longitudinal Study

In addition to acute studies, longitudinal studies with repeated measures would permit evaluation of fluctuations over time in MCS, which is inherently a chronic condition (48). As indicated above, studies of sensitization require repeated measure designs. Ethical concerns in human research obviously preclude any experimental effort to initiate MCS in healthy persons. Rather, participant samples for a longitudinal study would include individuals either with pre-existing MCS or with a history of an acute identifiable toxicant exposure (cohort of persons who proceed over time to develop or not develop MCS). This approach takes advantage of preexisting conditions in affected persons, and involves repeated evaluations of symptoms, mood, electrophysiological and autonomic status, and cognitive performance. The use of these outcome measures does not appear to raise any ethical concerns, as they would monitor but not alter the course of MCS patients’ illnesses. Nonetheless, these measures might reveal evidence of a sensitized state in MCS patients [compare Morrow and Steinhauser (68)]. In addition to descriptive data on the course of MCS, a longitudinal study would test the hypothesis that MCS patients but not healthy similarly exposed individuals show maintenance and/or progression of sensitization in measures of nervous system dysfunction over extended periods of time, following induction by an initial toxic exposure or other event.
Periodic laboratory reevaluations would permit assessment of progressive change (e.g., worsening, improvement, plateau) or persistence of change over extended blocks of time [e.g., seven or eight times on an every-6-months basis during a 5-year study, compare Morrow and Steinhauser (68)]. Monthly laboratory evaluations would entail excessive subject burden and risk; however, the working group recommends monthly telephone follow-up data collection. Outcome variables on which the telephone component could focus include a POMS, an individualized symptom-rating scale for frequency and severity, updates on medical/psychiatric diagnoses and treatments, and a quality-of-life questionnaire. Six-month laboratory follow-ups could include specific variables such as cognitive, affective (POMS, MMPI), and physiological (ERPs in response to the challenge). If a component of the study assessed MCS in its adapted versus nonadapted state to obtain continuous physiological recordings, an inpatient study in an environmental medical unit would be necessary.

Overall, this model encompasses both the possibility of individual differences between MCS patients and normal patients in general sensitizability and cross-sensitizability to different agents and classes of stimuli and the possibility of differences between chemical agents in their abilities to initiate and elicit sensitization in persons with equivalent degrees of sensitizability. Studies designed to evaluate each of these areas may be needed to provide a complete test of the model.

**Animal Studies**

**Rationale**

If a kindlinglike process or neural time-dependent sensitization is a mechanism that underlies MCS, direct olfactory stimulation probably represents the most likely route of exposure (21,96–98). Although inhalation exposures through the lung obviously occur simultaneously with olfactory system stimulation, and although the inhalation route may play some role in modulation of neural sensitization, the concentration of inhaled chemicals reaching the brain from nonolfactory routes of administration probably is not sufficient to cause the kinds of neural activation necessary to support a kindlinglike process (98). Accordingly, although bloodborne chemical contaminants may contribute to some systemic chemical kindlinglike effects, if a neural sensitization process is involved in the development of MCS, it is more probable that the process involves the output from stimulation of the olfactory apparatus (96–101).

Olfactory pathways, specifically the olfactory bulbs, are particularly sensitive to electrical and chemical kindling (21). Additionally, the receptors in the olfactory epithelium form a direct access pathway to limbic structures in the central nervous system. It is reasonable, therefore, to assume that strong activation of the olfactory epithelium cells can provide sufficient input into CNS limbic circuits to induce sensitization. It probably is possible to design studies that indirectly test this hypothesis using human subjects, but the specific role of olfactory stimulation in the ontogeny of MCS can be directly evaluated using standard neurophysiological assessments of central olfactory and limbic structures in response to stimulation of the olfactory epithelia of laboratory animals (21).

**Experimental Procedures**

The following procedures test the hypothesis that repeated olfactory exposures to chemicals can modulate neurophysiological activity in the olfactory–limbic axis or that neurophysiological activity in the olfactory–limbic axis can be modulated using techniques such as footshock-induced stress, partial limbic kindling, or psychostimulant sensitization, which have been implicated in physiological or behavioral sensitization.

**Experiment 1.** The most direct test of an olfactory system-mediated sensitization process involves the monitoring of olfactory–limbic neural activity during and after repeated stimulations of the olfactory epithelium with compounds implicated in the initiation of MCS. Although it is probable that CNS olfactory activity has been assessed after chemical stimulation of the olfactory epithelium, it is improbable that structures other than the olfactory bulb have been studied, and that the olfactory bulb recording studies that have been conducted have assessed long-term changes in neural functioning after systematic repetitive chemical stimulations.

**Paradigm.** Microelectrode bundles will be chronically implanted into the olfactory bulbs, the piriform cortex, the hippocampus, the entorhinal cortex, the amygdala, the medial hypothalamus, or the ventral tegmental area. The olfactory epithelium will be stimulated with vapors from chemicals believed to initiate MCS, vapors from chemicals not usually reported to initiate MCS, or distilled water vapor six times in a 2-hr testing session at equally spaced 20-min intervals. Exposure procedures for inhaled vapor generation will be adapted from Wood et al. (102–103). Unit firing patterns will be assessed from each of the microelectrode bundles during stimulation for a period of 15 min following cessation of stimulation. Testing sessions will be conducted daily for 15 days. In addition, to test for changes that may occur after the passage of time, animals will be tested 30 and/or 60 days later.

**Experiment 2.** Genetic or other predisposing variables may account for an innate predisposition for induction of sensitization in persons who present with symptoms of MCS. If this is true, it is possible that sensitization arising from direct olfactory stimulation may not specifically induce limbic sensitivity in normal (i.e., nonsensitivity-primed) rats. The following experiment tests the hypothesis that exposures to initiating chemicals can modulate neurophysiological activity in the olfactory–limbic axis in rats that have undergone experimental manipulations previously demonstrated to result in neural sensitization.

**Paradigm.** Rats will be implanted with microelectrode bundles and groups of animals evaluated for baseline chemically induced firing patterns using the same procedure as in Experiment 1. The animals will be sensitized by one of the following procedures: footshock stress-induced sensitization; partial amygdala kindling; or psychostimulant sensitization. Neural responses to chemical olfactory stimulation will be reassessed following induction of sensitization.

**Experiment 3.** It is possible that an interaction exists between repeated olfactory stimulation and other sensitization induction processes in which sensitization induced by some other physiological process (e.g., stress) is exacerbated by prior repeated olfactory stimulation. The following experiments test the hypothesis that repeated exposure to chemicals can alter sensitization parameters in experimental manipulations previously demonstrated to result in neural sensitization.

**Paradigm.** Groups of rats will be exposed to chemicals as in Experiment 1 over 15 trial days. Following the olfactory stimulation procedure, the rats will be sensitized by the procedures described in Experiment 2. Latency or number of trials required to induce sensitization are then compared.
Conclusions

The Working Group on Sensitization and Kindling agreed that a neural sensitization hypothesis for initiation and escalation of MCS is testable in both human and animal experiments. Both kinds of experiments are essential to provide a full test of the hypothesis and, in animal research, to permit further elucidation of underlying mechanisms. The public health implications of chemical intolerance or chemical sensitivity are potentially extensive. A problem such as chemical odor intolerance, reported at subclinical degrees by at least 15% of American nonindustrial populations, e.g., young adults (61,64,65) and active community elderly (62,63) as well as by 30% of office workers (67) and of a rural community-based population (66), merits systematic investigation of its phenomenology, course, and possible mechanisms.

REFERENCES

1. Groves PM, Thompson RF. Habituation: a dual-process theory. Psychol Rev 77:419–450 (1970).
2. Antelman SM. Time-dependent sensitization as the cornerstone for a new approach to pharmacotherapy: drugs as foreign/stressful stimuli. Drug Devel Res 14:1–30 (1988).
3. Antelman SM. Time-dependent sensitization in animals: a possible model of multiple chemical sensitivity in humans. Toxicol Ind Health 10:335–342 (1994).
4. Post RM. Intermittent versus continuous stimulation: effect of the interval on the development of sensitization or tolerance. Life Sci 26:1275–1282 (1980).
5. Sorg BA, Willis JR, Nowatka TC, Ulibarri C, See RE, Westberg HH. A proposed animal neurosensitization model for multiple chemical sensitivity in studies with formalin. Toxicology 111:135–145 (1995).
6. Kalivas PW, Sorg BA, Hooks MS. The pharmacology and neural circuitry of sensitization to psychostimulants. Behav Pharmacol 4:315–334 (1993).
7. Bell IR. Neuropsychiatric aspects of sensitivity to low level chemicals: a neural sensitization model. Toxicol Ind Health 10:277–312 (1994).
8. Stewart J, Badiani A. Tolerance and sensitization to the behavioral effects of drugs. Behav Pharmacol 4:289–312 (1993).
9. Stewart J, Vezina P. Extinction procedures abolish conditioned stimulus control but spare sensitized responding to amphetamine. Behav Pharmacol 2:65–71 (1991).
10. Jodogne C, Marinelli M, LeMoal M, Piazza PV. Animals predisposed to develop amphetamine self-administration show higher susceptibility to develop contextual conditioning of both amphetamine-induced hyperlocomotion and sensitization. Brain Res 657:236–244 (1994).
11. Antelman SM, Cunnick JE, Lysle DT, Caggiula AR, Knopf S, Kocan DJ, Rabin BS, Edwards JR, Dunbar HH. Sensitization in rats to repeated administration of dopamine agonists: differential effects on amphetamine sensitization. Pharmacol Biochem Behav 35:419–450 (1990).
12. Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am J Psychiatry 149:999–1010 (1992).
13. Altsdatter JE, Kalivas PW. Involvement of N-methyl-D-aspartate receptor stimulation in the ventral tegmental area and amygdala in behavioral sensitization to cocaine. J Pharmacol Exp Ther 267:486–495 (1993).
14. Inthak Y. Blockade of sensitization to the toxic effects of cocaine in mice by nitric oxide synthase inhibitors. Pharmacol Toxicol 74:162–166 (1994).
15. Karler R, Finnegan KT, Calder LD. Blockade of behavioral sensitization to cocaine and amphetamine by inhibitors of protein synthesis. Brain Res 603:19–24 (1993).
16. Heidbreder C, Goldberg SR, Shippenberg TS. Inhibition of cocaine-induced sensitization by the delta-opioid receptor antagonist naltrindole. Eur J Pharmacol 243:123–127 (1993).
17. Goddard GV. Development of epileptic seizures through brain stimulation at low intensity. Nature 214:1020–1021 (1967).
18. Rossi J. Sensitization induced by kindling and kindling-related phenomena as a model for multiple chemical sensitivity. Toxicology 111:87–100 (1996).
19. Gilbert ME. Neurotoxicants and limbic kindling. In: The Vulnerable Brain and Environmental Risks. Vol 1: Malnutrition and Hazard Assessment (Isaacson RL, Jensen KF, eds). New York: Plenum Press, 1992:173–193.
20. Gilbert, ME. Repeated exposure to lindane leads to behavioral sensitization and facilitates electrical kindling. Neurotoxicol Teratol 17:131–141 (1995).
21. Kay LM. Support for the kindling hypothesis in multiple chemical sensitivity syndrome (MCSS). Induction. Society for Neuroscience 22:1825 (1996).
22. Bell IR, Miller CS, Schwartz GE. An olfactory–limbic model of multiple chemical sensitivity syndrome: possible relationships to kindling and affective spectrum disorders. Biol Psychiatry 32:18–24 (1992).
23. Adams RE. Does kindling model anything clinically relevant? Biol Psychiatry 27:249–279 (1990).
24. Ashford NA, Miller CS. Chemical Exposures. Low Levels and High Stakes. New York: Van Nostrand Reinhold, 1991.
25. Black DW, Rathe A, Goldstein RB. Environmental illness. A controlled study of 26 subjects with 20th century disease. JAMA 264:3166–3170 (1990).
26. Simon GE, Katon WJ, Sparks PJ. Allergic to life: psychological factors in environmental illness. Am J Psychiatry 147:901–906 (1990).
27. Simon GE, Daniell W, Stockbridge H, Claypoole K, Rosenstock I, Immuno logical, psychological, and neuropsychological factors in multiple chemical sensitivity. A controlled study. Ann Int Med 19:97–103 (1993).
28. Dager SR, Holland JP, Cowley DS, Dunner DL. Panic disorder precipitated by exposure to organic solvents in the work place. Am J Psychiatry 144:1056–1058 (1987).
29. Sparks PJ, Daniell W, Black DW, Kipen HM, Altman LC, Simon GE. Terr AL. Multiple chemical sensitivity syndrome: a clinical perspective. I: Case definition, theories of pathogenesis, and research needs. J Occup Med 36:18–730 (1994).
30. Leyton, M, Belanger C, Martial J, Beaulieu S, Corin E, Pecknold J, Kin NMK, Meaney M, Thavundayil J, Larue S, Nair NPV, Cardiovascular, neuroendocrine, and monoaminergic responses to psychological stressors: possible differences between remitted panic disorder patients and healthy controls. Biol Psychiatry 40:353–360 (1996).
31. Staudenmayer H, Selner ME, Selner JC. Adult sequelae of childhood abuse presenting as environmental illness. Ann Allergy 71:538–546 (1993).
32. Lemieux AM, Coe CL. Abuse-related posttraumatic stress disorders: evidence for chronic neuroendocrine activation in women. Psychosom Med 57:105–115 (1995).
33. Teicher MH, Glod CA, Sarey J, Swett C. Early childhood abuse and limbic system ratings in adult psychiatric outpatients. J Neuropsychiatry Clin Neurosci 5:301–306 (1993).
34. Yehuda R, Antelman SM. Criteria for rationally evaluating animal models of posttraumatic stress disorder. Biol Psychiatry 33:479–486 (1993).
35. Bell IR. Clinically relevant EEG studies and psychophysiological findings: possible neural mechanisms for multiple chemical sensitivity. Toxicology 111:101–117 (1996).
Bell IR, Schwartz GE, Baldwin CM, Hardin EE, Klimas NG, Kline JP, Pataca R, Song ZY. Individual differences in neural sensitization and the role of context in illness from low level environmental chemical exposures. Environ Health Perspect 105(Suppl 2):457–466 (1997).

Bell IR, Schwartz GE, Baldwin CM, Hardin EE. Neural sensitization and physiological markers in multiple chemical sensitivity. Regul Toxiciol Pharmacol 24:S39–S47 (1996).

Camp DM, Robinson TE. Susceptibility to sensitization. I: Sex differences in the enduring effects of chronic D-amphetamine treatment on locomotion, stereotyped behavior and brain monoamines. Behav Brain Res 30:55–68 (1988).

Antelman SM, Caggiula AR, Kocan D, Knopf S, Meyer D, Edwards DJ, Barry H. One experience with lower or higher intensity stressors, respectively enhances or diminishes responsiveness to haloperidol weeks later: implications for understanding drug variability. Brain Res 566:276–283 (1993).

Antelman SM, Caggiula AR, Kiss S, Edwards DJ, Kocan D, Stillier R. Neurochemical and physiological effects of cocaine oscillate with sequential drug treatment: possibly a major factor in drug variability. Neuropharmacol 12:297–306 (1995).

Hooke J, Jones GH, Neuf DB, Justice JB. Individual differences in amphetamine sensitization: dose-dependent effects. Pharmacol Biochem Behav 41:203–210 (1992).

Newlin DB, Thomson JB. Chronic tolerance and sensitization to alcohol in sons of alcoholics. Alcohol Clin Exp Res 15:399–405 (1991).

Badani A, Brown KE, Robinson TE. Influence of novelty versus home environments on sensitization to the psychomotor stimulant effects of cocaine and amphetamine. Brain Res 674:291–298 (1995).

Diagnostic and Statistical Manual of Mental Disorders (DSM–IV). 4th ed. Washington:American Psychiatric Press, Inc. 1994.

First MB, Gibbon M, Spitzer RL, Williams JBW. Structured Clinical Interview for DSM–IV Axis I Disorders: Clinician Version. Washington:American Psychiatric Press, Inc, 1996.

Miller CS, Mitzel HC. Chemical sensitivity attributed to pesticide exposure versus remodeling. Arch Environ Health 50:119–129 (1995).

Buchwald D, Garry D. Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. Arch Intern Med 154:2049–2053 (1994).

Nethercott JR, Davidoff LL, Curbow B, Abbey H. Multiple chemical sensitivities syndrome: toward a working case definition. Arch Environ Health 48:19–26 (1993).

Fiechter N, Kipen H. Evaluation of chemically sensitive patients. J Occup Med 34:529–536 (1992).

Fiedler N, Kipen H, DeLuca J, Kelly-McNeil K, Natelson B. Neuropsychology and psychology of MCS. Toxicol Ind Health 10:545–554 (1994).

Fiedler N, Kipen HM, DeLuca J, Kelly-McNeil K, Natelson B. A controlled comparison of multiple chemical sensitivities and chronic fatigue syndrome. Psychosom Med 58:38–49 (1996).

Bell IR, Peterson JM, Schwartz GE. Medical histories and psychological profiles of middle-aged women with and without self-reported illness from environmental chemicals. J Clin Psychiatry 56:151–160 (1995).

Smith GR, Brown FW. Screening indexes in DSM-III-R somatization disorder. Gen Hosp Psychiatry 12:148–152 (1990).

Dahlstrom WG, Welsh GS, Dahlstrom LE. An MMPI Handbook. Minneapolis:University of Minnesota Press, 1972.

Symptom Checklist 90 (revised). Towson: MD:Clinical Psychometric Research, 1983.

Bell IR, Schwartz GE, Baldwin CM, Hardin EE, Kline JP. Unpublished data.

Beck AT, Ward CH, Mendelson M, Mock JE, Erbaugh J. An inventory measuring depression. Arch Gen Psychiatry 4:561–571 (1961).

Spielberger CD. State-Trait Anxiety Inventory. Odessa, FL: Psychological Assessment Resources, 1996.

Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 6:278–296 (1967).

Bell IR, Walsh ME, Goss A, Gersmeyer J, Schwartz GE, Kanof P. Unpublished data.

Bell IR, Schwartz GE, Peterson JM, Amend D. Self-reported illness from chemical odors in young adults without clinical syndromes or occupational exposures. Arch Environ Health 48:6–13 (1993).

Bell IR, Schwartz GE, Peterson JM, Amend D, Stini WA. Possible time-dependent sensitization to xenobiotics: self-reported illness from chemical odors, foods, and opiate drugs in an older adult population. Arch Environ Health 48:315–327 (1993).

Bell IR, Schwartz GE, Amend D, Peterson JM, Stini WA. Sensitization to early life stress and response to chemical odors in older adults. Biol Psychiatry 35:857–863 (1994).

Bell IR, Miller CS, Schwartz GE, Peterson JM, Amend D. Neuropsychiatric and somatic characteristics of young adults with and without self-reported chemical odor intolerance and chemical sensitivity. Arch Environ Health 51:9–21 (1996).

Bell IR, Hardin EE, Baldwin CM, Schwartz GE. Increased limbic system symptomatology and sensitizability of young adults with chemical and noise sensitivities. Environ Res 70:84–97 (1995).

Meggis WJ, Dunn KA, Bloch RM, Goodman PE, Davidoff AL. Prevalence and nature of allergy and chemical sensitivity in a general population. Arch Environ Health 51:275–282 (1996).

Wallace L, Nelson CJ, Kollander M, Leaderer B, Bascom R, Dunteman G. Indoor Air Quality and Work Environment Study. Multivariate Statistical Analysis of Health, Comfort, and Odor Perceptions As Related to Personal and Workplace Characteristics. Vol 4. Research Triangle Park, NC:U.S. Environmental Protection Agency, 1991.

Morrow LA, Steinshauer SR. Alterations in heart rate and pupillary response in persons with organic solvent exposure. Biol Psychiatry 37:721–730 (1995).

Bell IR, Schwartz GE, Bootzin RR, Wyatt JK. Time-dependent sensitization of heart rate and blood pressure over multiple laboratory sessions in elderly individuals with chemical odor intolerance. Arch Environ Health (in press).

Stoll EA, Euler G, Ogren S, Eneroth P, Puxe K, Gustafsson J. Persistent effects of 80 ppm toluene on dopamine-regulated locomotor activity and prolactin secretion in the male rat. Neurotoxicology 15:621–624 (1994).

Poulton EC, Freeman PR. Unwanted asymmetrical transfer effects with balanced experimental designs. Psychol Bull 66:1–8 (1969).

Poulton EC. Range effects in experiments on people. Am J Psychol 88:3–32 (1975).

Poulton EC. Unwanted range effects from using within-subject experimental designs. Psychol Bull 80:113–121 (1973).

Antelman SM, Kocan D, Knopf S, Edwards DJ, Caggiula AR. One brief exposure to a psychological stressor induces long-lasting, time-dependent sensitization of both the catecholamine and neurochemical responses to haloperidol. Life Sci 51:261–266 (1992).

Miller C, Ashford N, Doty R, Lamille M, Otto D, Rahill A, Wallace L. Working Group Report 1: Empirical approaches for the investigation of toxicant-induced loss of tolerance. Environ Health Perspect 105(Suppl 2):515–519 (1997).

Miller CS. Chemical sensitivity: history and phenomenology. Toxicol Ind Health 10:253–276 (1994).

Katon W, Raskind M. Treatment of depression in the medically ill elderly with mirtazapine. Am J Psychiatry 137:963–965 (1980).

Denicoff KD, Durkin TM, Lorze MT, Quinlan PE, Davis CL, Listailk SJ, Rosenberg SA, Rubinow DR. The neuroendocrine effects of interleukin-2 treatment. J Clin Endocrinol Metab 69:402–410 (1989).

Bell IR, Bootzin RR, Davis T, Hau V, Ritenbaugh C, Johnson KA, Schwartz GE. Time-dependent sensitization of plasma beta-endorphin in community elderly with self-reported environmental chemical odor intolerance. Biol Psychiatry 40:134–143 (1996).
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80. Molhave L, Jensen JG, Larsen S. Subjective reactions to volatile organic compounds as air pollutants. Atmos Environ 25a:1283–1293 (1991).
81. van de Kar LD, Peichowski RA, Rittenhouse, PA, Gray TD. Amygdaloid lesions: differential effect on conditioned stress and immunoblotting-induced increases in corticosterone and renin secretion. Neuroendocrinology 54:89–95 (1991).
82. Brown EE, Robertson GS, Flibiger HC. Evidence for conditioned neuronal activation following exposure to a cocaine-paired environment: role of forebrain limbic structures. J Neurosci 12:4112–4121 (1992).
83. Kobal G, Hummel T. Olfactory (chemosensory) event-related potentials. Toxicol Ind Health 10:587–596 (1994).
84. Morrow LA, Steinhauser SR, Hodgson MJ. Delay in P300 latency in patients with organic solvent exposure. Arch Neurol 49:315–320 (1992).
85. Morrow LA, Steinhauser SR, Condray R. Differential associations of P300 amplitude and latency with cognitive and psychiatric function in solvent-exposed adults. J Neuropsychiatry Clin Neurosci 8:446–449 (1996).
86. Lorig TS, Huffman E, DeMartino A, DeMarco J. The effects of low concentration odors on EEG activity and behavior. J Psychophysiol 5:67–77 (1991).
87. Bell IR, Bootzin RR, Ritenbaugh C, Wyatt JK, DeGiovanni G, Kulinovich T, Anthony JL, Kuo TF, Rider SP, Peterson JM, Schwartz GE, Johnson KA. A polysomnographic study of sleep disturbance in community elderly with self-reported environmental chemical odor intolerance. Biol Psychiatry 40:123–133 (1996).
88. Ryan CM, Morrow LA, Hodgson M. Cacosmia and neurobehavioral dysfunction associated with occupational exposure to mixtures of organic solvents. Am J Psychiatry 145:1442–1445 (1988).
89. Morrow LA, Robin N, Hodgson, MJ, Kamis H. Assessment of attention and memory efficiency in persons with solvent neurotoxicity. Neuropsychologia 30:911–922 (1992).
90. Morrow LA, Ryan CM, Hodgson MJ, Robin N. Alterations in cognitive and psychological functioning after organic solvent exposure. J Occup Med 32:444–450 (1990).
91. Morrow LA, Kamis H, Hodgson MJ. Psychiatric symptomatology in persons with organic solvent exposure. J Consult Clin Psychol 61:171–174 (1993).
92. Tolliver BK, Belknap JK, Woods WE, Carney JM. Genetic analysis of sensitization and tolerance to cocaine. J Pharmacol Exp Ther 270:1230–1238 (1994).
93. Peris J, Decambre N, Coleman-Hardee ML, Simkins JW. Estradiol enhances behavioral sensitization to cocaine and amphetamine-stimulated striatal \(^{3}H\) dopamine release. Brain Res 566:255–264 (1991).
94. Robinson TE, Becker JB, Presty SK. Long-term facilitation of amphetamine-induced rotational behavior and striatal dopamine release produced by a single exposure to amphetamine: sex differences. Brain Res 253:231–241 (1982).
95. Bell IR, Wyatt JK, Bootzin RR, Schwartz GE. Slowed reaction time performance on a divided attention task in elderly with environmental chemical odor intolerance. Int J Neurosci 84:127–134 (1995).
96. Wang HW, Wysocki CJ, Gold GH. Induction of olfactory receptor sensitivity in mice. Science 260:998–1000 (1993).
97. Stevens DA, O'Connell RJ. Enhanced sensitivity to androsterone following regular exposure to pemenone. Chemical Senses 20:413–419 (1995).
98. Evans J, Hastings L. Accumulation of CD(II) in the CNS depending on the route of administration: intraperitoneal, intratracheal, or intranasal. Fundam Appl Toxicol 19:275–278 (1992).
99. Ghantous H, Dencker L, Gabrielson J, Danielsson BRG, Bergman K. Accumulation and turnover of metabolites of tolune and xylene in nasal mucoa and olfactory bulb in the mouse. Pharmacol Toxicol 66:87–92 (1990).
100. Britto EB. Metabolism of xenobiotics in the nasal olfactory mucoa: implications for local toxicity. Pharmacol Toxicol 72 (Suppl 3):50–52 (1993).
101. Berliner DL, Monti-Bloch L, Jennings-White C, Diaz-Sanchez V. The functionality of the human vomeronasal organ (VNO): evidence for steroid receptors. J Steroid Biochem Molec Biol 58:259–265 (1996).
102. Wood RW. Determinants of irritant termination behavior. Toxicol Appl Pharmacol 61:260–268 (1981).
103. Wood RW, Coleman JB. Behavioral evaluation of irritant properties of formaldehyde. Toxicol Appl Pharmacol 130:67–72 (1995).