
We investigated the effects of a combined exposure to restraint stress and low doses of chemicals pyridostigmine bromide (PB), N, N-diethyl-m-toluamide (DEET), and permethrin in adult male rats, a model of Gulf-War syndrome. Animals were exposed daily to one of the following for 28 days: (i) a combination of stress and chemicals (PB, 1.3 mg/kg/day; DEET, 40 mg/kg/day; and permethrin, 0.13 mg/kg/day); (ii) stress and vehicle; (iii) chemicals alone; and (iv) vehicle alone. All animals were evaluated for: (i) the disruption of the blood-brain barrier (BBB) using intravenous horseradish peroxidase (HRP) injections and endothelial barrier antigen (EBA) immunostaining; (ii) neuronal cell death using H&E staining, silver staining, and glial fibrillary acidic protein (GFAP) immunostaining; and (iii) acetylcholinesterase (AChE) activity and m2-muscarinic acetylcholine receptors (m2-AChR). Animals subjected to stress and chemicals exhibited both disruption of the BBB and neuronal cell death in the cingulate cortex, the dentate gyrus, the thalamus, and the hypothalamus. Other regions of the brain, although they demonstrated some neuronal cell death, did not exhibit disruption of the BBB. The neuropathological changes in the above four brain regions were highly conspicuous and revealed by a large number of HRP-positive neurons (21-40% of total neurons), a decreased EBA immunostaining (42-51% reduction), a decreased number of surviving neurons (27-40% reduction), the presence of dying neurons (4-10% of total neurons), and an increased GFAP immunostaining (45-51% increase). These changes were also associated with decreased forebrain AChE activity and m2-AchR (19-25% reduction). In contrast, in animals exposed to stress and vehicle or chemicals alone, the above indices were mostly comparable to that of animals exposed to vehicle alone. Thus, a combined exposure to stress and low doses of PB, DEET, and permethrin leads to significant brain injury. The various neurological symptoms reported by Gulf-War veterans could be linked to this kind of brain injury incurred during the war.

Exposure to a combination of stress and low doses of the chemicals pyridostigmine bromide (PB), DEET, and permethrin in adult rats, a model of Gulf War exposure, produces blood-brain barrier (BBB) disruption and neuronal cell death in the cingulate cortex, dentate gyrus, thalamus, and hypothalamus. In this study, neuropathological alterations in other areas of the brain where no apparent BBB disruption was observed was studied following such exposure. Animals exposed to both stress and chemical exhibited decreased brain acetylcholinesterase (AChE) activity in the midbrain, brainstem, and cerebellum and decreased m2 muscarinic acetylcholine (ACh) receptor ligand binding in the midbrain and cerebellum. These alterations were associated with significant neuronal cell death, reduced microtubule-associated protein (MAP-2) expression, and increased glial fibrillary acidic protein (GFAP) expression in the cerebral cortex and the hippocampal subfields CA1 and CA3. In the cerebellum, the neurochemical alterations were associated with Purkinje cell loss and increased GFAP immunoreactivity in the white matter. However, animals subjected to either stress or chemicals alone did not show any of these changes in comparison to vehicle-treated controls. Collectively, these results suggest that prolonged exposure to a combination of stress and the chemicals PB, DEET, and permethrin can produce significant damage to the cerebral cortex, hippocampus, and cerebellum, even in the absence of apparent BBB damage. As these areas of the brain are respectively important for the maintenance of motor and sensory functions, learning and memory, and gait and coordination of movements, such alterations could lead to many physiological, pharmacological, and behavioral abnormalities, particularly motor deficits and learning and memory dysfunction.


Malathion (O,O-dimethyl-S-[1,2-carbethoxyethyl]phosphorodithionate), DEET (N,N-diethyl-m-toluamide), and permethrin [(+/-)-cis/trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane carboxylic acid (3-phenoxyphenyl) methyl ester] are commonly used pesticides. To determine the effects of the dermal application of these chemicals, alone or in combination, the sensorimotor behavior, central cholinergic system, and histopathological alterations were studied in adult male Sprague-Dawley rats following a daily dermal dose of 44.4 mg/kg malathion, 40 mg/kg DEET, and 0.13 mg/kg permethrin, alone and in combination for 30 d. Neurobehavioral evaluations of sensorimotor functions included beam-walking score, beam walk time, inclined plane, and grip response assessments. Twenty-four hours after the last treatment with each chemical alone or in combination all behavioral measures were impaired. The combination of DEET and permethrin, malathion and permethrin, or the three chemicals together resulted in greater impairments in inclined performance than permethrin alone. Only animals treated with a combination of DEET and malathion or with DEET and permethrin exhibited significant increases in plasma butyrylcholinesterase (BChE) activity. Treatment with DEET or permethrin alone, malathion and permethrin, or DEET and permethrin produced significant increases in
cortical acetylcholinesterase (AChE) activity. Combinations of malathion and permethrin or of DEET and permethrin produced significant decreases in midbrain AChE activity. Animals treated with DEET alone exhibited a significant increase in cortical m2 muscarinic ACh receptor binding. Quantification of neuron density in the dentate gyrus, CA1 and CA3 subfields of the hippocampus, midbrain, brainstem, and cerebellum revealed significant reductions in the density of surviving neurons with various treatments. These results suggest that exposure to real-life doses of malathion, DEET, and permethrin, alone or in combination, produce no overt signs of neurotoxicity but induce significant neurobehavioral deficits and neuronal degeneration in brain.


Organophosphorus compounds are potent neurotoxic chemicals that are widely used in medicine, industry, and agriculture. The neurotoxicity of these chemicals has been documented in accidental human poisoning, epidemiological studies, and animal models. Organophosphorus compounds have 3 distinct neurotoxic actions. The primary action is the irreversible inhibition of acetylcholinesterase, resulting in the accumulation of acetylcholine and subsequent overstimulation of the nicotinic and muscarinic acetylcholine receptors, resulting in cholinergic effects. Another action of some of these compounds, arising from single or repeated exposure, is a delayed onset of ataxia, accompanied by a Wallerian-type degeneration of the axon and myelin in the most distal portion of the longest tracts in both the central and peripheral nervous systems, and is known as organophosphorus ester-induced delayed neurotoxicity (OPIDN). In addition, since the introduction and extensive use of synthetic organophosphorus compounds in agriculture and industry half a century ago, many studies have reported long-term, persistent, chronic neurotoxicity symptoms in individuals as a result of acute exposure to high doses that cause acute cholinergic toxicity, or from long-term, low-level, subclinical doses of these chemicals. The author attempts to define the neuronal disorder that results from organophosphorus ester-induced chronic neurotoxicity (OPICN), which leads to long-term neurological and neurobehavioral deficits. Although the mechanisms of this neurodegenerative disorder have yet to be established, the sparse available data suggest that large toxic doses of organophosphorus compounds cause acute necrotic neuronal cell death in the brain, whereas sublethal or subclinical doses produce apoptotic neuronal cell death and involve oxidative stress degeneration in brain.


The operating environment of the service personnel during the Persian Gulf War involved psychological, biological, and chemical elements including exposure to pesticides such as the insect repellent DEET (\(N,N\)-diethyl-\(m\)-toluamide) and the insecticide chlorpyrifos (\(O,O\)-diethyl\(O\)-3,5,6-trichloropyridinyl phosphorothioate) and to pyridostigmine bromide (PB, 3-dimethylaminocarbonyloxy-\(N\)-methylpyridinium bromide) that was administered as a prophylactic agent against possible nerve gas attack. The present study was designed to determine the toxicity produced by individual or coexposure of hens 5 days/week for 2 months to 5 mg PB/kg/day in water, by gavage; 500 mg DEET/kg/day, neat, sc; and 10 mg chlorpyrifos kg/day in corn oil, sc. Coexposure to various binary treatments produced greater neurotoxicity
that caused by individual exposures and was characterized by severe neurologic deficit and neuropathological alterations. Also, neurotoxicity was further enhanced following concurrent administration of the three chemicals. Severe inhibition of plasma butyrylcholinesterase (BuChE) activity was produced in hens treated with PB (activity 17% of control) compared to those treated with chlorpyrifos (activity 51% of control) or DEET (activity 83% of control). BuChE inhibition was further increased in binary and tertiary treatment groups compared to individual treatment groups. In contrast, a significant inhibition of brain acetylcholinesterase (AChE) was produced in hens administered chlorpyrifos alone (activity 67% of control), while those given chlorpyrifos in combination with other compounds exhibited a significant inhibition of brain AChE activity ranging from 43 to 76%. Brain neurotoxicity target esterase (NTE) was not inhibited in any of the individual treatment groups or PB/DEET, but was significantly inhibited and had activity expressed as a percentage of control in groups administered combined chlorpyrifos with PB of 73% or DEET of 74% and in the tertiary treatment group of 71%. We hypothesize that test compounds may compete for xenobiotic metabolizing enzymes in the liver and blood and may also compromise the integrity of the blood–brain barrier, leading to an increase in their “effective concentrations” in the nervous system to levels equivalent to the toxic doses of individual compounds. This is consistent with the present observation of increases in (1) the inhibition of brain AChE and NTE, (2) the extent of neurologic dysfunction, and (3) the severity and frequency of neuropathologic lesions in the combined treatment groups compared to those administered individual compounds.


We investigated the effects of uranyl acetate on sensorimotor behavior, generation of nitric oxide and the central cholinergic system of rats. Male Sprague-Dawley rats were treated with intramuscular injection of 0.1 and 1 mg/kg uranyl acetate in water, daily for 7 days. Control animals received equivalent amount of water. The treatment was stopped after the seventh injection because the animals in the 1-mg/kg group appeared lethargic. The animals were maintained for an additional observation period of 30 days. The study was initiated as a dose-finding study that covered doses of 10 and 100 mg/kg, as well. However, all the animals in the 100-mg/kg treatment group died after the third and fourth injections, and all animals given 10 mg/kg died after the fifth and sixth injections. On day 30 following the cessation of treatment, the sensorimotor functions of the animals in the 0.1- and 1-mg/kg treatment groups were evaluated using a battery of tests that included measurements of postural reflexes, limb placing, orientation to vibrissae touch, grip time, beam walking and inclined plane performance. The animals were sacrificed the same day and the cerebral cortex, brainstem, cerebellum and midbrain were dissected. The levels of nitric oxide as marker for increased oxidative stress, and the integrity of the cholinergic system as reflected in acetylcholinesterase (AChE) activity and m2 muscarinic acetylcholine receptors ligand binding, were determined. The data from behavioral observations show that there was a dose-related deficit at the 0.1- and 1-mg/kg treatment groups for inclined plane performance. Both doses reduced grip time, but there was no significant difference between the two doses. Similarly, both beam-walk score and beam-walk time were impaired at both doses as compared with the controls. A significant increase in nitric oxide was seen at 0.1 mg/kg dose in cortex and midbrain, whereas brainstem and cerebellum...
showed an insignificant decrease at both the doses. Similarly, there was no significant change in nitric oxide levels in kidneys and liver of the treated animals as compared with the controls. There was a significant increase in AChE activity in the cortex of the animals treated with 1 mg/kg uranyl acetate, but not in other brain regions. Ligand binding densities for the m2 muscarinic receptor did not show any change. These results show that low-dose, multiple exposure to uranyl acetate caused prolonged neurobehavioral deficits after the initial exposure has ceased.


Military personnel deployed in the Persian Gulf War (PGW) were exposed to a combination of chemicals, including pyridostigmine bromide (PB), DEET, and permethrin. We investigated the dose-response effects of these chemicals, alone or in combination, on the sensorimotor performance and cholinergic system of male Sprague-Dawley rats. Animals were treated with a daily dermal dose of DEET and/or permethrin for 60 days and/or PB (gavage) during the last 15 days. Neurobehavioral performance was assessed on day 60 following the beginning of the treatment with DEET and permethrin. The rats were sacrificed 24 h after the last treatment for biochemical evaluations. PB alone, or in combination with DEET, or DEET and permethrin resulted in deficits in beam-walk score and longer beam-walk times compared to controls. PB alone, or in combination with DEET, permethrin, or DEET and permethrin caused impairment in incline plane performance and forepaw grip strength. PB alone at all doses slightly inhibited plasma butyrylcholinesterase activity, whereas combination of PB with DEET or permethrin increased its activity. Brainstem acetylcholinesterase (AChE) activity significantly increased following treatment with combinations of either DEET or permethrin at all doses, whereas the cerebellum showed a significant increase in AChE activity following treatment with a combination of PB/DEET/permethrin. Co-exposure to PB, DEET, and permethrin resulted in significant inhibition in AChE in midbrain. PB alone or in combination with DEET and permethrin at all doses increased ligand binding for m2 muscarinic acetylcholine receptor in the cortex. In addition, PB and DEET together or a combination of PB, DEET, and permethrin significantly increased ligand binding for nicotinic acetylcholine receptor. These results suggest that exposure to various doses of PB, alone and in combination with DEET and permethrin, leads to sensorimotor deficits and differential alterations of the cholinergic system in the CNS.


In this study concentrations of markers of oxidative stress 3-nitrotyrosine and 8-hydroxy-2’-deoxyguanosine (8-OhdG) were determined in rat urine following a single oral dose of pyridostigmine bromide (PB) 13 mg/kg and a single intramuscular dose of sarin 80 microg/kg alone or in combination. Urine samples were collected 16, 24, 48, 72, and 96 h following dosing. Control urine samples of five rats treated with normal saline were also collected at the same time intervals. A combined dose of PB and sarin significantly increased levels of 3-nitrotyrosine and (8-OhdG) starting 48 h after dosing. An increase in the concentration of these markers was not
detected following a single dose of PB or sarin alone. Maximal increase in 3-nitrotyrosine and 8-OhdG was detected 48 h after administration of a combination PB and sarin. The results indicate that concurrent exposure to PB and sarin could generate free radical species that may cause oxidative stress in rats. The results may have significant impact if veterans were expose to sarin following an oral dose of PB.


Biomarkers rely on biochemical, histological, morphological, and physiological changes in whole organisms. Their use is becoming an important tool to examine changes at cellular and molecular levels, especially in nucleic acids and proteins. Biomarkers are used to measure exposure to a toxic agent, to detect severity of any toxic response, and to predict the possible outcome. Information on the mechanisms of action of toxicants can allow the development of potential biomarkers of effect and thus improvement of the risk assessment processes. Use of biomarkers as a tool to predict induction of apoptosis allows identification of biological signs that may indicate increased risk for disease. In cells undergoing apoptosis, the release of cytochrome c from the mitochondria to the cytoplasm and the activation of caspase-3, a key enzyme to execution stage of apoptotic pathway, have been studied as biomarkers of cell death (apoptosis). Products of DNA fragmentation that either accumulate in the cellular tissues or are excreted in the urine are useful markers of DNA damage. The induction level of urinary or cellular level of 8-hydroxy-2-deoxyguanosine and 3-nitrotyrosine has been used as a marker to measure extent of DNA oxidative damage. Furthermore, alteration or overexpression of the p53 gene was considered an indication of apoptosis. This article reviews some of the aspects of biomarkers of apoptosis, indicating relevance of their uses to predict apoptosis following exposure to environmental toxicants.


The in vitro human plasma activity and liver microsomal metabolism of pyridostigmine bromide (PB), a prophylactic treatment against organophosphate nerve agent attack, N,N-diethyl-m-toluamide (DEET), an insect repellent, and permethrin, a pyrethroid insecticide, either alone or in combination were investigated. 2. The three chemicals disappeared from plasma in the following order: permethrin > PB > DEET. The combined incubation of DEET with either permethrin or PB had no effect on permethrin or PB. Binary incubation with permethrin decreased the metabolism of PB and its disappearance from plasma and binary incubation with PB decreased the metabolism of permethrin and its clearance from plasma. Incubation with PB and/or permethrin shortened the DEET terminal half-life in plasma. These agents behaved similarly when studied in liver microsomal assays. The combined incubation of DEET with PB or permethrin (alone or in combination) diminished DEET metabolism in microsomal systems. 3. The present study evidences that PB and permethrin are metabolized by both human plasma and liver microsomal enzymes and that DEET is mainly metabolized by liver oxidase enzymes.
Combined exposure to test chemicals increases their neurotoxicity by impeding the body's ability to eliminate them because of the competition for detoxifying enzymes.


Many of the symptoms described in Sick Building Syndrome (SBS) and multiple chemical sensitivity (MCS) resemble the symptoms known to be elicited by airborne irritant chemicals. Irritation of the eye, nose, and throat is common to SBS, MCS, and sensory irritation (SI). Difficulty of breathing is often seen with SBS, MCS, and pulmonary irritation (PI). We therefore asked the question: can indoor air pollutants cause SI and/or PI? In laboratory testing in which mice breathed the dilute volatile emissions of air fresheners, fabric softeners, colognes, and mattresses for 1 h, we measured various combinations of SI and PI as well as airflow decreases (analogous to asthma attacks). Air samples taken from sites associated with repeated human complaints of poor air quality also caused SI, PI, and airflow limitation (AFL) in the mice. In previous publications, we have documented numerous behavior changes in mice (which we formally studied with a functional observational battery) after exposure to product emissions or complaint site air; neurological complaints are a prominent part of SBS and MCS. All together, these data suggest that many symptoms of SBS and MCS can be described as SI, PI, AFL, and neurotoxicity. All these problems can be caused by airborne irritant chemicals such as those emitted by common commercial products and found in polluted indoor air. With some chemical mixtures (e.g., emissions of some fabric softeners, disposable diapers, and vinyl mattress covers) but not others (e.g., emissions of a solid air freshener), the SI response became larger (2- to 4-fold) when we administered a series of two or three 1-h exposures over a 24-h period. Since with each exposure the intensity of the stimulus was constant yet the magnitude of the response increased, we concluded that there was a change in the sensitivity of the mice to these chemicals. The response was not a generalized stress response because it occurred with only some mixtures of irritants and not others; it is a specific response to certain mixtures of airborne chemicals. This is one of the few times in MCS research that one can actually measure both the intensity of the stimulus and the magnitude of the response and thus be allowed to discuss sensitivity changes. The changing SI response of the mice might serve as a model of how people develop increasing sensitivity to environmental pollutants. Intensive study of this system should teach us much about how people respond to and change sensitivity to airborne irritant chemicals.


There is increasing evidence that human exposure to levels of chemicals once thought to be safe—or presenting insignificant risk—are, in fact, harmful. So-called low-level exposures are now known to be associated with adverse biological effects including cancer, endocrine disruption, and chemical sensitivity. This requires that we change both (1) the way we design research linking chemicals and health, and (2) the solutions we devise to address chemically caused injury. The new and emerging science of low-level exposure to chemicals requires appropriate social policy responses which include regulation of toxic substances, notification of those exposed, and compensation and reasonable accommodation to those affected. Research and social policy need to be focused towards two distinct groups: (1) those individuals who could
become chemically intolerant as a result of an initiating exposure, and (2) those individuals who have already become chemically intolerant and are now sensitive to chemicals at low levels.


Chemical intolerance, or reported illness from odors of common environmental chemicals (e.g., car exhaust, pesticides), is emerging as an important environmental and public health-care issue. Epidemiologic methods provide relevant heuristic devices for studies of complex disorders, such as chemical intolerance. The authors examined personal and reported parental cardiopulmonary disease prevalence rates in a community sample of chemically intolerant and control individuals. A county government (Tucson, Arizona) employee and kin subset (N = 181; 113 households) completed standard health questionnaires. Investigators determined chemical intolerance (n = 41/181) from self-reports of individuals who felt "moderately" to "severely" ill from exposure to at least three of five chemicals (i.e., car exhaust, pesticides, paint, new carpet, and perfume) on a Chemical Odor Intolerance Index. The authors chose the control group (n = 57/181) on the basis of self-reports of "never" feeling ill on the Chemical Odor Intolerance Index. The chemically intolerant group, which primarily comprised women (78% versus 51% of controls, p < .05), was significantly more likely to report-and to have sought--medical attention for heart problems, bronchitis, asthma, and pneumonia. Reports of heart problems in the chemically intolerant index cases and the occurrence of heart disease in both of their parents were significant (Fisher's p < .05). The chemically intolerant individuals were also significantly more likely to report maternal histories of chest problems (e.g., inhalant allergens, tuberculosis) than controls. The findings of the study suggested that the chemically intolerant individuals (a preponderance of whom were women [sex-related risk]) were more likely to have (a) reported cardiopulmonary problems (i.e., greater health risk); (b) actively sought medical care for these problems (i.e., increased medical utilization); and (c) reported more parental illnesses-particularly heart disease, asthma, and diabetes (i.e., genetic risk). Additional community-based studies of chemical intolerance are needed.


This is a community-based study of odor sensitivity and respiratory complaints for persons reporting asthma (n=14/141), hay fever (n=72/140), and chemical odor intolerance (CI) (n=41/181). CI, a symptom of multiple chemical sensitivity (MCS), was determined from self-ratings of feeling `moderately' to `severely' ill using the Chemical Odor Intolerance Index (CII). Index odors included perfume, pesticide, drying paint, new carpet odor, and car exhaust. Six additional odors [natural gas, disinfectants, chlorinated water, room deodorizers, and environmental tobacco smoke (ETS)] were also assessed in the health and environment survey. Asthmatics reported feeling `frequently' to `almost always' ill from the CII index odors of drying paint, new carpet odor, perfume, and cleaning agents compared to nonasthmatics. People with hay fever documented feeling 'frequently' to 'almost always' ill from pesticides, drying paint, and car exhaust compared to individuals without hay fever. The CI cited illness from air freshener,
natural gas and chlorinated water, in addition to the index odors of perfume, paint, pesticides, new carpeting and auto exhaust. All three groups were significantly more likely to report feeling ill from ETS. People with asthma were significantly more likely to report lower lung complaints, such as wheeze and dyspnea. People with hay fever cited more chest tightness. The CI were significantly more likely to report upper and lower respiratory symptoms. Given this overlap in respiratory complaints, it could be that CI may serve to amplify these traditional immune-related disorders and/or suggest that having asthma or hay fever could make one more vulnerable to CI.


The Working Group on Neurogenic Inflammation proposed 11 testable hypotheses in the three domains of neurogenic inflammation, perceptual and central integration, and nonneurogenic inflammation. The working group selected the term people reporting chemical sensitivity (PRCS) to identify the primary subject group. In the domain of neurogenic inflammation, testable hypotheses included: PRCS have an increased density of c-fiber neurons in symptomatic tissues; PRCS produce greater quantities of neuropeptides and prostanooids than nonsensitive subjects in response to exposure to low-level capsaicin or irritant chemicals; PRCS have an increased and prolonged response to exogenously administered c-fiber activators such as capsaicin; PRCS demonstrate augmentation of central autonomic reflexes following exposure to agents that produce c-fiber stimulation; PRCS have decreased quantities of neutral endopeptidase in their mucosa; exogenous neuropeptide challenge reproduces symptoms of PRCS. In the domain of perceptual and central integration, testable hypotheses included: PRCS have alterations in adaptation, habituation, cortical representation, perception, cognition, and hedonics compared to controls; the qualitative and quantitative interactions between trigeminal and olfactory systems are altered in PRCS; higher integration of sensory inputs is altered in PRCS. In the domain of nonneurogenic inflammation, testable hypotheses included: increased inflammation is present in PRCS in symptomatic tissues and is associated with a heightened neurosensory response; PRCS show an augmented inflammatory response to chemical exposure. The working group recommended that studies be initiated in these areas.


This paper reviews the clinical and experimental literature on patients with multiple adverse responses to chemicals (Multiple Chemical Sensitivity Syndrome-MCS) and develops a model for MCS based on olfactory-limbic system dysfunction that overlaps in part with Post's kindling model for affective disorders. MCS encompasses a broad range of chronic polysymptomatic conditions and complaints whose triggers are reported to include low levels of common indoor and outdoor environmental chemicals, such as pesticides and solvents. Other investigators have found evidence of increased prevalence of depression, anxiety, and somatization disorders in MCS patients and have concluded that their psychiatric conditions account for the clinical picture. However, none of these studies has presented any data on the effects of chemicals on
symptoms or on objective measures of nervous system function. Synthesis of the MCS literature with large bodies of research in neurotoxicology, occupational medicine, and biological psychiatry, suggests that the phenomenology of MCS patients overlaps that of affective spectrum disorders and that both involve dysfunction of the limbic pathways. Animal studies demonstrate that intermittent repeated low level environmental chemical exposures, including pesticides, cause limbic kindling. Kindling (full or partial) is one central nervous system mechanism that could amplify reactivity to low levels of inhaled and ingested chemicals and initiate persistent affective, cognitive, and somatic symptomatology in both occupational and nonoccupational settings. As in animal studies, inescapable and novel stressors could cross-sensitize with chemical exposures in some individuals to generate adverse responses on a neurochemical basis. The olfactory-limbic model raises testable neurobiological hypotheses that could increase understanding of the multifactorial etiology of MCS and of certain overlapping affective spectrum disorders.


This cross-sectional telephone survey study assessed prevalence rates of current chemical sensitivity, frequency of chemical odor intolerance, and self-reported Persian Gulf chemical exposures among 41 randomly sampled Department of Veterans Affairs outpatients who were Persian Gulf War (PGW) and PGW-era veterans. The participants were drawn from an initial random list of 100 veterans, of whom 28 PGW and 20 era veterans had correct telephone data on file. Of those contacted, 86% of PGW veterans (24/28) and 85% of era veterans (17/20) agreed to participate. Significantly more PGW veterans with poorer global health after military service reported considering themselves now "especially sensitive to certain chemicals" (86%, 12/14) than did the PGW veterans or era veterans in stable health (both comparison groups 30%, 3/10). Among PGW veterans, the subset with worse health associated with marked increases in chemical odor intolerance since their military service had a significantly higher odds ratio for exposure to multiple chemicals, notably wartime pesticides and insect repellent, than did comparison groups. The high rate of chemical sensitivity of PGW veterans with deteriorated health is almost three times that in PGW-era veterans and in elderly primary care outpatient veterans at the same Department of Veterans Affairs medical center and in community-based civilian samples (i.e., 30%). These preliminary findings suggest the need for further study of chemical sensitivity, including tests for acquired increases in neural sensitizability to multiple low-level chemicals, in ill PGW veterans.


The present survey of young adult college students investigated the prevalence of self-reported illness from the smell of the five following common environmental chemicals (cacosmia): (1) pesticide, (2) automobile exhaust, (3) paint, (4) new carpet, and (5) perfume. Sixty-six percent of 643 students reported feeling ill from one or more of the five chemicals; 15% identified the smell of at least four chemicals as making them ill. Ratings of illness from pesticide correlated weakly
but significantly with ratings for the largest number of individual symptoms (9 of 11); daytime tiredness and daytime grogginess both correlated at high levels of significance with illness ratings (on a 5-point scale) for four of the five chemicals. The most cacosmic group (CS) included significantly more women (79%) than the noncacosmic group (NS) (49%); women overall were more cacosmic than men (p < .001), even with the significant covariate of depression. Ratings of cacosmia correlated only weakly with scores for depression (r = 0.16), anxiety (r = 0.08), and trait shyness (r = 0.18) in the total sample. On stepwise multiple regression with cacosmia score as the dependent measure, shyness accounted for 5.8% of the variance, while depression, anxiety, sense of mastery, and repression did not enter the equation. Histories of physician-diagnosed hay fever, but not asthma, were more frequent in the CS (16%) than in the NS group (5%). Without the confounds of chronic illness or specific treatment programs, these data are similar to patterns described clinically for a subset of patients with multiple chemical sensitivities (MCS), including previous data on increased nasal resistance in MCS. The findings also suggest a limited relationship between degree of self-reported cacosmia and trait shyness, possibly on the basis of limbic hyper-reactivity. Psychological variables did not otherwise account for any of the variance in self-rated illness from chemical odors in this nonclinical sample.


This paper summarizes the key features of the olfactory-limbic, neural sensitization model for multiple chemical sensitivity (MCS) and presents relevant data on chemically intolerant human subjects from laboratory studies using quantitative electroencephalography, polysomnography, neuropsychological tests, cardiovascular measurements, and blood markers. MCS is a poorly understood chronic, polysymptomatic condition in which some prior controlled research studies have failed to find evidence to differentiate active from placebo tests. Closer examination of past MCS research, however, reveals that studies have failed to incorporate the design and methodological approaches necessary to test for nonimmunological sensitization. Time-dependent sensitization (TDS) is a well-documented phenomenon in the pharmacology literature involving the progressive increase in a given response by the passage of time between the initial and subsequent exposures to a substance or a stressor. As in MCS, multiple, chemically unrelated agents can trigger TDS. Females time-sensitize more readily than do males. Pharmacological and nonpharmacological (stress) stimuli can cross-sensitize. Dopaminergic pathways in the brain and the hypothalamic–pituitary–adrenal axis are likely involved in TDS. Data on the symptomatology of MCS point to central nervous system involvement, including limbic regions that receive input from both olfactory (odor) and trigeminal (irritant) pathways. Limbic and mesolimbic brain regions are among the most sensitizable to repeated, intermittent environmental stimuli. Sensitizable individuals can show no difference or lesser responses to a test substance on initial exposure, but later exhibit much greater increases in responsivity on the next exposure after a period of days. For future research, it is essential to distinguish chemical intolerance symptoms such as derealization, sudden mood changes, musculoskeletal pain, menstrual dysfunction, and uncontrollable sleepiness from chemical phobia and avoidance behaviors. This model permits hypothesis-driven research on MCS and has major implications.
for interpretation of apparently positive and negative tests for “true” as opposed to “perceived” sensitivity to low levels of environmental chemicals.


Chemical intolerance (CI) is an individual difference trait in which persons report feeling ill in multiple physiological systems from low levels of a wide range of chemically unrelated environmental substances. This paper discusses the neural sensitization model for progressive host amplification of polysymptomatic responses elicited by chemical exposures following an initiating event. The sensitization model accommodates hypotheses for initiating and eliciting CI in human populations that involve both environmental chemicals and physical or psychological stressors. Recent studies in this laboratory have demonstrated sensitization in individuals with CI over repeated sessions for dependent variables such as electroencephalographic (EEG) activity and diastolic blood pressure. Psychological distress variables alone do not explain these findings. Individuals with CI and/or vulnerability to sensitization share specific characteristics, for example, female gender, certain genetic background (offspring of alcohol-prefering parents), and personal preference for high sugar/carbohydrate intake. Overall, the data suggest that the 15-30% of the general population who report heightened CI are highly sensitizable. Sensitizability may serve an adaptive, sentinel function in threatening environments with poor signal-to-noise ratios. However, as sensitization gradually shifts operating set points of physiological systems out of the normal range in response to allostatic load, this process may contribute to the development of chronic, polysymptomatic health conditions such as multiple chemical sensitivity and/or fibromyalgia. Individual response specificity and stereotypy rather than toxicant properties may determine which types of central, autonomic, and/or peripheral nervous system dysfunctions manifest at subclinical and clinical levels.


An outbreak of complaints consisting primarily of eye and respiratory tract irritation accompanied by headache, dizziness, fatigue, and nausea occurred among the operating room personnel of a large metropolitan hospital. This initially was attributed to infiltration of diesel exhaust emissions into the ventilation system. However, following correction of this problem and subsequent unrevealing air monitoring, symptoms persisted and were noted in personnel in adjacent areas of the hospital as well. An industrial hygiene and medical evaluation was undertaken. Monitoring for carbon monoxide, formaldehyde, and anesthetic gases and review of medical records and patient examinations were unrevealing, and the problem resolved gradually over several weeks. This outbreak represents a case of building-associated illness among health professionals in a hospital setting that was triggered by a single, identifiable noxious exposure but was sustained despite any apparent ongoing noxious exposures.

The current principles of toxicology, immunology and allergy do not provide a coherent explanation of a chemical sensitivity lacking reproducible and measurable physiologic or biochemical changes. A new paradigm is needed as a scientific model for multiple chemical sensitivities.


Two individuals developed an asthma-like illness after a single exposure to high levels of an irritating aerosol, vapor, fume, or smoke. Symptoms developed within a few hours. A consistent physiologic accompaniment was airways hyperreactivity, with the two subjects showing positive methacholine challenge tests. No documented preexisting respiratory illness was identified, nor did subjects relate past respiratory complaints. Respiratory symptoms and airways hyperreactivity persisted for at least four years after the incident. The incriminated etiologic agents all shared a common characteristic of being irritant in nature. Bronchial biopsy specimens showed an airways inflammatory response. This report suggests that acute high-level irritant exposures may produce an asthma-like syndrome in some individuals, with long-term sequelae and chronic airways disease. Nonimmunologic mechanisms seems to be operative in the pathogenesis of this syndrome.


Thus far, no neuropsychological study has examined the cognitive profile of multiple chemical sensitivity (MCS) within the framework of Bell's Olfactory-Limbic Model. It predicts that cognitive weaknesses will be associated more with limbic (i.e., frontal and/or temporal lobe) than with non-limbic (i.e., posterior cortex) brain regions. Matched MCS, asthma, and healthy control groups (n = 63) were tested on cognitive measures with localizing value. Between-group comparisons found that the MCS group performed as well as controls on all cognitive tasks. Within-group comparisons found that both the MCS and asthma groups performed significantly more poorly on tasks that were sensitive to frontal and temporal regions than to posterior regions. Additional research is needed before concluding that the Olfactory-Limbic Model adequately describes the cognitive strengths and weaknesses of MCS. Confounding factors such as medication use and chronic illness need to be considered.


Chronic fatigue syndrome (CFS), fibromyalgia (FM), and multiple chemical sensitivities (MCS) are conditions associated with fatigue and a variety of other symptoms that appear to share many clinical and demographic features. Our objectives were to describe the similarities and differences among patients with CFS, FM, and MCS. Additional objectives were to determine
how frequently patients with MCS and FM met the criteria for CFS and if they differed in their health locus of control. METHODS: Demographic, clinical, and psychosocial measures were prospectively collected in 90 patients, 30 each with CFS, FM, and MCS. Patients were recruited from a university-based referral clinic devoted to the evaluation and treatment of chronic fatigue and three private practices. Variables included demographic features, symptoms characteristic of each condition, psychological complaints, a measure of health locus of control, and information on health care use. RESULTS: Overall, the three patient groups were remarkably similar in demographic characteristics and the presence of specific symptoms. Patients with CFS and FM frequently reported symptoms compatible with MCS. Likewise, 70% of patients with FM and 30% of those with MCS met the criteria for CFS. Health care use was substantial among patients with CFS, FM, and MCS, with an average of 22.1, 39.7, and 23.3 visits, respectively, to a medical provider during the prior year. Health locus of control did not differ among the three populations. CONCLUSIONS: In general, demographic and clinical factors and health locus of control do not clearly distinguish patients with CFS, FM, and MCS. Symptoms typical of each disorder are prevalent in the other two conditions.


Summarizes the findings of a two-phase study of the prevalence and etiology of multiple chemical sensitivities (MCS). Exploration of the lifestyle alterations produced by MCS; potential linkage between MCS and other disorders; estimation of the number of people who have MCS.


We examined the prevalence of multiple chemical sensitivities (MCS), a hypersensitivity to common chemical substances. We used a randomly selected sample of 1582 respondents from the Atlanta, GA, standard metropolitan statistical area. We found that 12.6% of our sample reported the hypersensitivity and that, while the hypersensitivity is more common in women, it is experienced by both men and women of a variety of ages and educational levels. Our prevalence for MCS is similar to that (15.9%) found by the California Department of Health Services in California and suggests that the national prevalence may be similar.


This study determined the percentages of individuals who report adverse effects from exposure to fragranced products in the U.S. population and in subpopulations of those with asthma or chemical sensitivity. Data were collected through telephone interviews from two geographically weighted, random samples of the continental U.S. in two surveys during 2002-2003 and 2005-2006 (1,057 and 1,058 cases, respectively). Respondents were asked if they find being next to someone wearing a scented product irritating or appealing; if they have headaches, breathing difficulties, or other problems when exposed to air fresheners or deodorizers; and if they are irritated by the scent from laundry products, fabric softeners, or dryer sheets that are vented outside. Results aggregated from both surveys found that 30.5% of the general population reported scented products on others irritating, 19% reported adverse health effects from air
fresheners, and 10.9% reported irritation by scented laundry products vented outside. This study reveals that a considerable percentage of the U.S. population reports adverse health effects or irritation from fragranced products, with higher percentages among those with asthma and chemical sensitivity.


This study investigates asthma’s national prevalence and potential overlap with chemical hypersensitivity. It also examines asthma’s etiology, age of onset, and demographic characteristics. Data were collected from a geographically weighted random sample of the continental U.S. (1058 cases), in four seasonal cohorts (2005–2006). The study found that 12.9% of the sample report asthma, 11.6% report chemical hypersensitivity, and 31.4% of those with asthma report chemical hypersensitivity. Among asthmatics, 38% report irritation from scented products, 37.2% report health problems from air fresheners, and 13.6% report their asthma was caused by toxic exposure. Asthma cases affected each racial/ethnic group in roughly the same proportion, with nearly 50% classified as childhood onset.


The article presents information on the findings of a telephone survey conducted to find the prevalence of hypersensitivity to low levels of common chemicals in the American population. Chemical hypersensitivity--often called multiple chemical sensitivity (MCS)--is also referred to as toxicant-induced loss of tolerance or environmental illness. It is typically acknowledged to be a condition characterized by acute reactions that occur after exposure to even low levels of common chemical products such as fragrances, household cleaners, fresh paints, newsprint, pesticides and other products that contain petrochemicals. MCS can produce a wide range of symptoms, and individuals with the hypersensitivity can encounter great difficulty functioning in normal working and living environments. Although a limited number of epidemiological studies have investigated the regional prevalence of chemical hypersensitivity in the U.S., its national prevalence is speculative. The National Academy of Sciences estimated that up to 15% of the U.S. population experiences some degree of hypersensitivity to common chemicals.


Objective: The objective of this study was to investigate the linkage between asthma and chemical hypersensitivity.

Methods: The authors conducted a population study with a random sample of 1057 geographically weighted cases to determine the prevalence of both asthma and chemical hypersensitivity in the American population and to explore their co-occurrence.

Results: A total of 14.1% of the respondents reported being diagnosed with asthma and 11.2% reported a hypersensitivity to chemicals. Of those with asthma, 27.2% also reported being hypersensitive to chemicals and 7.4% reported also being diagnosed with multiple chemical
sensitivities (MCS). Of those diagnosed with MCS, 42% reported also being diagnosed with asthma. Additionally, 29.7% of those with asthma said air fresheners caused breathing difficulties, and 37.2% found scented products irritating.

Conclusions: The results indicate that there is significant overlap between some forms of asthma and chemical hypersensitivity.


A questionnaire was administered to individuals who had reported a hypersensitivity to common chemical products in an earlier epidemiological study in the Atlanta, Georgia, metropolitan area. The questionnaire investigated the nature of the symptoms and factors that potentially initiated hypersensitivity and subsequently triggered reactions. Also examined were associated lifestyle modifications and the relationships of hypersensitivity with other illnesses. The authors found that a majority of hypersensitive individuals (52.2%) experienced either "severe" or "somewhat severe" symptoms. The most common triggers of symptoms were cleaning products (88.4%), tobacco smoke (82.6%), perfume (81.2%), pesticides (81.2%), and car exhaust (72.5%). Only 1.4% of the subjects had a prior history of emotional problems, whereas 37.7% developed such problems after the emergence of their hypersensitivity. Lifestyle modifications varied; 76.8% changed their household cleaning/personal hygiene products, 47.8% began using water and/or air filtration systems, and 13% found it necessary to change residence. Although hypersensitivity was more common in females than males, the condition affects individuals in all categories of race/ethnicity, age, household income, and educational level.


Reports on the presence and nature of chemical sensitivities and other indices of illness in a cohort of workers excavating a subway tunnel located under a former gasoline station. Chemical sensitivities among the gasoline over-exposed sample; Abnormal findings after the tunnel shut down; Characteristics of tunnel workers with increased sensitivities and reference multiple chemical sensitivities syndrome and general population sample.


In the United States, some 80,000 commercial and industrial chemicals are now in use of which over 30,000 are produced or used in the Great Lakes region. Thus, the environmental quality within the Great Lakes basin has been compromised particularly with respect to persistent toxic substances (PTS). Information derived from wildlife studies, prospective epidemiological and toxicological studies, databases, demographics, and Geographical Information Systems (GIS) demonstrate significant public health implications. Studies of human populations indicate: (a) elevated body burden levels of PTSs, (b) decrease in gestational age, (c) low birth weight (LBW), (d) greater risk of male children with birth defects (OR = 3.01), (e) developmental and
neurological deficits, (f) increased risk of infertility, (g) changes in sex ratio, and (h) fluctuations in thyroid hormones. These findings have been identified in vulnerable populations, such as the developing fetus, children, minorities, and men and women of reproductive age who are more susceptible because of their physiologic sensitivity and/or elevated exposure to toxic chemicals. Typically such health effects are assessed on a chemical specific basis; however, most human populations are exposed to hazardous chemicals as mixtures in air, water, soil, and biota. In this article we present an assessment of the potential for joint toxic action of these substances in combinations in which they are typically found. These evaluations represent an integration of all available scientific evidence in accordance with the "NAS paradigm" for risk assessment. In aggregate, our evaluations have demonstrated a need for community-based frameworks and computational techniques to track patterns of environmentally related exposures and associated health effects.


The history of chemical sensitivity in America is reviewed from the first description published by Edgar Allan Poe in 1839, to its first medical definition as a symptom of neurasthenia in 1869, its rediscovery as allergic toxemia in 1945, its redefinition in 1987 as multiple chemical sensitivity (MCS), and its overlap in the 1990s with chronic fatigue syndrome, fibromyalgia syndrome, and Gulf War syndrome (GWS). More than half of the over 500 peer-reviewed articles on MCS support an organic basis for MCS, whereas less than one-quarter support a psychiatric basis. The same 2:1 difference is seen in the numbers of MCS researchers writing these articles and the number of journals publishing them. A psychogenic interpretation of MCS also is specifically rejected in the latest formal position statement on the subject, a 1994 consensus of the American Lung Association, American Medical Association (AMA), U.S. Environmental Protection Agency (US EPA), and U.S. Consumer Product Safety Commission (US CPSC) (U.S. Government Printing Office 1994-523-217/81322). This and other government recognition of MCS in policy, research, and scientific conferences are summarized. Dozens of federal, state, and local authorities accept MCS as a legitimate disease and/or disability that deserves reasonable accommodation in housing, employment, and public facilities. Official recognition is expected later in 1999 when the U.S. Centers for Disease Control and Prevention (CDC) announces a formal definition of MCS and the federal Interagency Workgroup on MCS releases its long-awaited final report, 4 years in the making. Given that epidemiological data from three states puts the prevalence of chemical sensitivity at 16 to 33% of the general population, 2 to 6% of whom have already been diagnosed with MCS, this truly is a hidden epidemic that deserves the priority attention of public health researchers and policy makers. Industrial toxicologists are encouraged to work on reducing and eliminating the use of synthetic fragrances, chemical sensitizers, and other irritants in consumer products and occupational settings.

Background: Exposure to perfume and fragrance products may, in some individuals, cause symptoms from the eyes and airways. The localization, character and risk factors of such symptoms in the general population are unknown.

Objective: To investigate both the localization and character of symptoms from the eyes and airways elicited by fragrance products, and the associations between such symptoms and skin prick test reactivity (atopy), methacholine bronchial hyper-reactivity (BHR), allergic rhinitis and asthma.

Methods: A questionnaire on mucosal symptoms elicited by fragrance products was posted to 1189 persons who had participated in a Danish population-based study of allergic diseases in 1997/1998. The study included measurement of BHR, atopy, forced expiratory volume in 1 s (FEV1), and serum eosinophilic cationic protein (serum ECP).

Results: The response rate was 79.6%. Symptoms from the eyes or airways elicited by fragrance products were reported by 42%. BHR (adjusted odds ratio 2.3, 95% confidence interval 1.5–3.5) was independently associated with symptoms from the eyes and airways elicited by fragrance products. There were no significant associations between these symptoms and atopy, FEV1 or serum ECP.

Conclusions: Mucosal symptoms from the eyes and airways were common in this population. BHR was a significant and independent predictor of these symptoms. The lack of association with atopy suggested that IgE-mediated allergic mechanisms do not play a major role in the development of these symptoms.


The authors sought to determine whether reported symptoms of mothers and infants were associated significantly with the use of household products that raised indoor levels of total volatile organic compounds (TVOCs). Data collected from 170 homes within the Avon Longitudinal Study of Parents and Children (ALSPAC: a large birth cohort of more than 10,000) had determined which household products were associated with the highest levels of TVOCs. The latter data were collected over a period that approximated 6 mo of pregnancy and the infants' first 6 mo of life. This paper presents (a) the mothers' self-reports of the use of these products in their homes and (b) self-reported medical symptoms of mothers and infants postnatally. Higher TVOC levels were associated with air freshener and aerosol use. Infant diarrhea and earache were statistically significantly associated with air freshener use, and diarrhea and vomiting were significantly associated with aerosol use. Headache experienced by mothers 8 mo after birth was significantly associated with the use of air fresheners and aerosols; maternal depression was significantly associated with the use of air fresheners. The results of the study suggest a link between the use of products that raise indoor levels of TVOCs and an increased risk of certain symptoms among infants and their mothers.

This study tested the sensitization model proposed by Bell et al. [Bell I.R., Miller C.S. and Schwartz G.E. An olfactory-limbic model of multiple chemical sensitivity syndrome: possible relationship to kindling and affective spectrum disorders. Biol. Psychiatry 1992: 32: 218-242] to study chemical sensitivity. The sensitization model indicates that a pharmacological stimulus or a traumatic event which elicits a strong response can sensitize limbic and/or mesolimbic pathways; and subsequent less intense trauma or stimuli, in the same or different modality, can elicit an amplified response. Three groups of subjects were tested: (1) women who reported chemical sensitivity and no sexual abuse (chemically sensitive, CS); (2) sexually abused (SA) women without chemical sensitivity; and (3) healthy women without chemical sensitivity or sexual abuse history (normal, N). All subjects were exposed to odorant and nonodorous control stimuli once a week for 3 weeks. Electroencephalographic activity was recorded while subjects sniffed the odorant and control stimuli. Results of the study revealed that both the CS and the SA group showed electroencephalogram (EEG) alpha sensitization across experimental sessions, while the N group showed little change over time. Additionally, EEG findings revealed that the CS group generated significantly greater alpha activity than the other two groups. Finally, while the groups were different on measures of psychological distress, these differences did not diminish the EEG findings. In summary, these findings suggest that intermittent exposure to chemicals elicits sensitization in CS and SA women without chemical sensitivity, supporting our expectations that chemical sensitivity is, in part, a manifestation of time-dependent sensitization (TDS). Additionally, these EEG findings indicate that CS women are unlike SA and healthy women in the amount of EEG alpha activity they generate. Finally, these findings indicate that psychological factors as assessed in this study do not explain electrophysiological differences between chemically and non-chemically-sensitive women.


Provides some information about the perceptions of multiple chemical sensitivities patients regarding a large number of interventions. Examination of the types of the perceived efficacy of the treatments used by people with MCS; Analysis of the lengths of helpful and harmful effects of time-limited therapies.


Repeated intermittent exposure to some chemicals produces behavioral sensitization and seizure induction through a kindling mechanism. Although many pesticides are convulsant at high dosages, the persistent neurological effects of chronic low level exposure are unclear. The impact of intermittent exposure to lindane on behavioral seizure development and subsequent electrical kindling was assessed in the present study. Rats were administered lindane (0 or 10 mg/kg, po) for 30 days, or 3 times/week for 10 weeks. Enhanced behavioral responsiveness to lindane
(myoclonic jerks, clonic seizures) emerged over the course of dosing and persisted 2 to 4 weeks after the last dose. The incidence of generalized convulsions was increased from 0% to 15% between the first and final day of dosing. In addition, electrographic recordings from the amygdala revealed brief rhythmic bursts and isolated interictal spike and wave discharge in the absence of overt behavioral seizures. Electrical kindling of the amygdala, beginning 4 to 6 weeks after the final dose, was facilitated. In contrast, prior administration of a single convulsive dose of lindane (20 mg/kg) was without effect on kindling development. These data indicate that repeated exposure to subconvulsant doses of lindane produces a persistent alteration in the central nervous system as evidenced by an enhanced susceptibility to kindled seizures. The pattern of behavioral development whereby the sensitivity is built up gradually over time is suggestive of a chemical kindling mechanism. Savings in the number of stimulation sessions required to induce electrical kindling following a history of lindane treatment provides further evidence that prior lindane exposure may lead to a state of partial kindling. Thus, intermittent subconvulsive lindane treatment induces alterations in limbic excitability that persist for at least 1 month.


Environmental exposures to very low levels of airborne chemicals are associated with adverse symptoms, often affecting multiple organ systems, in the phenomenon of chemical sensitivity (CS). Recent surveys suggest a significant prevalence of chemically sensitive subjects in the United States, but the mechanism linking exposure to symptoms remains unclear, despite the advancement of a variety of theoretical models. In many of these models, exposure of the nasal respiratory system to an airborne agent is the first step in the pathway leading to symptoms. In this article, we advance the hypothesis that interactions between environmental chemicals and the vomeronasal organ (VNO) may play a role in the etiology of CS. The VNO, a bilateral, tubular organ located in the nose, serves in animals as part of a sensitive chemosensory system; however, evidence suggesting that the VNO retains a functional role in the adult human is controversial. Reported characteristics of the human VNO relevant to CS, including location, prevalence, selective sensitivity to airborne chemical exposure, and capacity to produce systemic effects, are discussed within the context of this ongoing debate. Beyond relevance to CS, the demonstration of an active, adult VNO could have significant impact on environmental toxicology.


Previously Haley et al. described six possible syndromes identified by factor analysis of symptoms in Gulf War veterans and demonstrated that veterans with these symptom complexes were more neurologically impaired than age-sex-education-matched well controls. They also uncovered strong associations (relative risks 4-8) suggesting that these symptom complexes were related to wartime exposure to combinations of organophosphate pesticides, chemical nerve agents, high concentration DEET insect repellent, and symptoms of advanced acute toxicity after taking pyridostigmine. Here we have shown that compared to controls, ill veterans with the
neurologic symptom complexes were more likely to have the R allele (heterozygous QR or homozygous R) than to be homozygous Q for the paraoxonase/arylesterase 1 (PON1) gene. Moreover, low activity of the PON1 type Q (Gln192, formerly designated type A) arylesterase allozyme distinguished ill veterans from controls better than just the PON1 genotype or the activity levels of the type R (Arg192, formerly designated type B) arylesterase allozyme, total arylesterase, total paraoxonase, or butyrylcholinesterase. A history of advanced acute toxicity after taking pyridostigmine was also correlated with low PON1 type Q arylesterase activity. Type Q is the allozyme of paraoxonase/arylesterase that most efficiently hydrolyzes several organophosphates including sarin, soman, and diazinon. These findings further support the proposal that neurologic symptoms in some Gulf War veterans were caused by environmental chemical exposures.


Exposures to neurotoxic chemicals such as pesticides, glues, solvents, etc. are known to induce neurologic and psychiatric symptomatology. We report on 41 patients--16 young patients (6 males, 10 females, age 34 +/- 8 yrs.) and 25 elderly patients (9 males, 16 females, age 55 +/- 7 yrs). Fifteen of them were exposed to pesticides, and 29 to solvents. They were studied with quantitative and qualitative analysis of regional cerebral blood flow (rCBF), performed with 30 mCi of Xe-133 by inhalation, followed by 30 mCi of Tc-HMPAO given intravenously. Imaging was performed with a brain dedicated system, distribution of rCBF was assessed with automatic ROI definition, and HMPAO was normalized to maximal pixel activity in the brain. Results of Xe rCBF are expressed as mean and S.D. in ml/min/100g, and HMPAO as mean and S.D. uptake per ROI, and compared with age-matched controls--10 young and 20 elderly individuals. Table: see text] We conclude that patients exposed to chemicals present with diminished CBF, worse in the right hemisphere, with random presentation of areas of hypoperfusion, more prevalent in the dorsal frontal and parietal lobes. These findings are significantly different from observations in patients with chronic fatigue and depression, suggesting primary cortical effect, possibly due to a vasculitis process.


The authors studied the association between long-term exposure (i.e., > 10 y) to outdoor air pollution and the severity of obstructive pulmonary disease and prevalence of bronchial hyperreactivity to Beta 2 agonists in two groups of adult patients who were of similar ages and who had similar smoking habits. The subjects lived in downtown districts or in the outer suburbs of Marseilles, the neighborhood that contained air samplers. The regions were similar with respect to sulfur dioxide levels, but levels of nitric oxides and particulate matter (10 millimeters or less) were higher in the downtown area than the suburbs. The authors assessed airway obstruction, as determined by a decrease in forced expiratory volume in 1 s, mean forced expiratory flow measured between 25% and 75% of vital capacity, and an elevated value of central airway resistance. The authors tested the changes in these variables induced by inhalation
of a Beta 2 agonist. Baseline lung function was altered more significantly in both male and female patients who lived in downtown Marseilles than in those who resided in the suburbs, and the differences persisted regardless of the season during which the study occurred. Prevalence of bronchial hyperreactivity and symptoms of asthma (but not of rhinitis) were higher in the downtown than suburban male subjects. The results of this study suggest that an association exists between actual environmental exposure to outdoor air pollution (i.e., nitrogen oxides and/or particulate matter of 10 millimeters or less) and respiratory effects in sensitive adults represented by patients with chronic obstructive pulmonary disease or asthma.


Patients with upper and lower airway symptoms and with pronounced sensitivity to chemical odours, such as perfumes, flower scents and tobacco smoke, have been suggested to have sensory hyperreactivity (SHR). The symptoms have been difficult to identify with physiological measurements and the effects of various medications are doubtful. However, these patients have been found to be more sensitive to inhalation of capsaicin than healthy people. The aim of this study was to establish limit values with the capsaicin inhalation test in patients with SHR.

**METHODS:** Ninety-five consecutive patients with upper and lower airway problems, who were admitted for allergy testing, underwent a capsaicin inhalation test with three different concentrations. The number of coughs was registered during each challenge. Score systems were used for symptoms and influence on social life of sensitivity to odours. In relation to scored symptoms, the patients were grouped as SHR or not, and compared with 73 healthy controls.

**RESULTS:** All patients and controls coughed on capsaicin in a dose-dependent manner. Symptom score of odour sensitivity in patients was positively correlated to the response of the test. Out of 95 patients, 15 (16%) were scored to SHR. Patients with SHR reacted more to the capsaicin inhalation test than the other patients and the healthy controls. The limit values for a positive capsaicin inhalation test for the SHR were determined to be 10, 35 and 55 coughs at 0.4, 2.0 and 10 microM capsaicin, respectively. **CONCLUSION:** The capsaicin inhalation test well reflects the degree of airway sensitivity to chemicals and to what extent the social life is influenced. The cut-off values of the test can distinguish patients with pronounced sensitivity to odours.


We conducted a pilot study using a randomized, single-blind, placebo-controlled exposure among 10 individuals with and 7 without reported chemical sensitivities in a dedicated testing chamber. Objectives of the study were to explore the length of the adaptation period to obtain stable readings, evaluate responses to different substances, and measure the level and type of symptomatic and physiologic reactions to low-level exposures. Reported and observed symptoms, electrodermal response, heart rate, skin temperature, surface electromyogram, respiratory rate, contrast sensitivity, and the Brown-Peterson cognitive test were used and compared between cases and controls and between test substances (glue, body wash solution, dryer sheet) and control substances (unscented shampoo and clean air). Subjects with chemical
sensitivities (cases) took longer to adapt to baseline protocols than did controls. After adaptation, despite small study numbers, cases displayed statistically significant responses (all measures, \( p < 0.02 \)) in tonic electrodermal response to test substances compared with controls and compared with the control substance. Symptoms were also higher in cases than in controls for the body wash solution (\( p = 0.05 \)) and dryer sheets (\( p = 0.02 \)). Test-retest showed good agreement for both symptoms and tonic electrodermal responses (McNemar's test, \( p = 0.32 \) and \( p = 0.33 \), respectively). Outside of skin conductance, other measures had no consistent patterns between test and control substances and between cases and controls. This study shows the importance of using an adaptation period in testing individuals with reported chemical sensitivities and, despite small numbers, raises questions about underlying mechanisms and level of reactivity to low-level chemical exposures in sensitive individuals.


Background: The collapse of the World Trade Center (WTC) on September 11, 2001 created a large-scale disaster site in a dense urban environment. In the days and months thereafter, thousands of rescue/recovery workers, volunteers, and residents were exposed to a complex mixture of airborne pollutants.

Methods: We review current knowledge of aerodigestive inhalation lung injuries resulting from this complex exposure and present new data on the persistence of nonspecific bronchial hyperreactivity (methacholine PC20 \( < 8 \) mg/mL) in a representative sample of 179 Fire Department of the City of New York (FDNY) rescue workers stratified by exposure intensity (according to arrival time) who underwent challenge testing at 1, 3, 6, and 12 months post-collapse.

Results: Aerodigestive tract inflammatory injuries, such as declines in pulmonary function, reactive airways dysfunction syndrome (RADS), asthma, reactive upper airways dysfunction syndrome (RUDS), gastroesophageal reflux disease (GERD), and rare cases of inflammatory pulmonary parenchymal diseases, have been documented in WTC rescue/recovery workers and volunteers. In FDNY rescue workers, we found persistent hyperreactivity associated with exposure intensity, independent of airflow obstruction. One year post-collapse, 23% of highly exposed subjects were hyperreactive as compared with only 11% of moderately exposed and 4% of controls. At 1 yr, 16% met the criteria for RADS.

Conclusions: While it is too early to ascertain all of the long-term effects of WTC exposures, continued medical monitoring and treatment is needed to help those exposed and to improve our prevention, diagnosis, and treatment protocols for future disasters.


In the 19th century, deaths from acute exposure to hydrogen sulfide (H2S) portended permanent brain injury from nonlethal doses. The neurobehavioral effects of H2S exposures lasting from moments to years were compared in 16 subjects, 2 years to 22 years afterward. METHODS: Neurophysiologic and psychologic tests were used to appraise mood status and frequencies of 35 symptoms. Functions and frequencies, described as percent predicted adjusted for age, sex, educational achievement, and other factors, were compared with those in an unexposed
population. RESULTS: Frequencies were elevated for 31 of 33 symptoms. Balance was impaired (246% predicted with eyes closed, 159% predicted with eyes open), and simple and choice reaction times were prolonged (151% and 130% predicted, respectively). Visual fields performance was decreased to 72% predicted (right) and 55% predicted (left), color discrimination was abnormal, and hearing was decreased. Psychologic domains showed cognitive disability, reduced perceptual motor speed, impaired verbal recall and remote memory, and abnormal mood status. CONCLUSIONS: Exposure to H2S must be avoided.


( Editorial) Discusses issues on the effects of chemicals on the brain. Result of the comparison measurements of group of individuals who had been exposed to chemicals; Implication of the widespread use of chemicals and the repetitive patterns of exposure; Practical and safe strategy of preventing the effects of chemicals on the brain.


In today's complex environment, with an increasing number of chemicals and environmental contamination, some individuals have developed sensitivities to their surroundings. Surgical intervention for environmentally sensitive patients provides an opportunity to reach beyond the boundaries of the OR. These patients require highly individualized perioperative nursing assessments and care planning on a multidisciplinary level. Presbyterian Hospital of Dallas has developed a protocol to initiate collaborative planning for these patients and has had the opportunity to successfully care for these patients.


Thirty-five people with work-related Multiple Chemical Sensitivities were studied to learn about the onset and progression of illness. The subjects were selected from patients at an occupational health clinic. Individuals were identified as subjects if they fulfilled a seven-point case definition for Multiple Chemical Sensitivities and if onset of symptoms was related to workplace exposures. Three occupational exposures to solvents, poor indoor-air quality, and remodeling were associated with onset of Multiple Chemical Sensitivities in 63% of the subjects. Symptoms indicative of a nervous-system disorder topped the list of the most frequently reported symptoms. Commonalities in exposures and symptoms suggest that Multiple Chemical Sensitivities represents a distinct diagnostic category. Even with an incomplete understanding of etiology, it may be possible to limit the onset of work-related Multiple Chemical Sensitivities.

In this study, the authors describe a new “reactive syndrome,” Reactive Intestinal Dysfunction Syndrome (RIDS), which has similarities to the previously described clinical syndromes Reactive Airway Dysfunction Syndrome (RADS) and Reactive Upper Airway Dysfunction Syndrome (RUDS). Given that at least 5 neuropeptides are common to both the respiratory tract and digestive tract, the authors propose that the abnormal secretion of these neuropeptides or the abnormal numbers of their receptors play a role in what is perceived clinically as RADS, RUDS, and RIDS. The relatively large surface areas of both the lungs and gut render them especially vulnerable to the environment to which they are exposed constantly.


Intentional hydrocarbon inhalation can be fatal. Death can be secondary to hydrocarbon's cardiopulmonary effects. We present a case of a patient who survived ventricular fibrillation after inhalation of Glade Air Freshener(TM), which contains short chain aliphatic hydrocarbons (butane and isobutane). Unlike our case, myocardial sensitization and hypoxia are more commonly described with aromatic, halogenated or longer chain hydrocarbons.


Exposure to organophosphate (OP's) insecticides and nerve gases during the Persian Gulf War has been implicated in the development of Gulf War Syndrome. Paraoxonase (PON1) present in human serum detoxifies OP's. We determined the levels of PON1 in the serum of Gulf War Veterans and compared these to those found in a control population. One hundred fifty-two Gulf War Veterans from the UK who self-reported the presence of Gulf War Syndrome via a questionnaire and 152 age and gender matched controls were studied. PON1 activity, concentration, and genotype were determined. In the Gulf War Veterans, paraoxon hydrolysis was less than 50% of that found in the controls (100.3 (14.8-233.8) vs 214.6 (50.3-516.2) nmol/min/ml, P < 0.001). This low activity was independent of the effect of PON1 genotype. The serum PON1 concentration was also lower in the Gulf War Veterans (75.7 (18.1-351.3) vs 88.2 (34.5-527.4) microg/ml, P < 0.00025), which was again independent of PON1 genotype. There was no difference in the rate of diazoxon hydrolysis between the groups (10.2 +/- 4.1 micromol/min/ml vs 9.86 +/- 4.4, P = NS). A decreased capacity to detoxify OP insecticides resulting from low serum PON1 activity may have contributed to the development of Gulf War Syndrome.
Episodic exposures refer to intermittent acute exposures to chemicals that ordinarily have a rapid onset and short duration of effect. There has been a long tradition in preclinical behavioral pharmacology of using episodic-exposure paradigms in order to establish dose-response functions in individual organisms. In these experiments, stable baselines of behavior are first established and then followed by administering varying doses of a drug intermittently, for example, once or twice a week. The power of this approach is well established; the within-subjects design reduces error variance, allows exploration of the entire range of effective doses, and can be used to identify individual differences in drug sensitivity. Of course, the approach is only applicable to reversibly acting compounds, and checks need to be included to insure effects of one dose are not influenced by prior exposure to another dose. We have used baseline approaches to evaluate the effects of pesticides and solvents on the behavior of adult male rats and mice. Moreover, a novel probabilistic dose-tolerance analysis applied to the data suggests substantial individual differences in chemical sensitivity, often spanning orders of magnitude. These results suggest that individual differences in chemical sensitivity may be much greater than previously acknowledged.


*Background:* Impaired metabolism of toxic chemicals is a postulated mechanism underlying multiple chemical sensitivity (MCS). Because genetic variation alters the rate of chemical metabolism, this study was designed to determine if MCS cases differed from controls for genetic polymorphisms in drug-metabolizing enzymes.
Methods: Female Caucasian participants (203 cases and 162 controls) were drawn from a larger case-control study based on a reproducible and validated case definition. Common polymorphisms for CYP2D6, NAT1, NAT2, PON1, and PON2 were genotyped. Results: Comparing cases and controls, significant differences were found in genotype distributions for CYP2D6 (P = 0.02) and NAT2 (P = 0.03). Compared with the referent homozygous inactive (CYP2D6) or slow (NAT2) metabolizers, the odds for being CYP2D6 homozygous active (OR = 3.36, P = 0.01) and NAT2 rapid (OR = 4.14, P = 0.01) were significantly higher in cases than controls. The odds for being heterozygous for PON1-55 (OR = 2.05, P = 0.04) and PON1-192 (OR = 1.57, P = 0.04) were also significantly higher in cases. Conclusions: A genetic predisposition for MCS may involve altered biotransformation of environmental chemicals. The CYP2D6 enzyme activates and inactivates toxins; the NAT2 enzyme bioactivates arylamines to protein-binding metabolites. A gene–gene interaction between CYP2D6 and NAT2 suggested that rapid metabolism for both enzymes may confer substantially elevated risk (OR = 18.7, P = 0.002). Our finding parallels others’ observation of a link between PON1 heterozygosity and neurological symptoms in Gulf War syndrome. This first demonstration of genetic variation in drug-metabolizing enzymes in association with MCS requires replication. However, it suggests new research directions on genetically variable toxin pathways that might be important in MCS.


In this study, the authors used the University of Toronto's Health Survey self-administered questionnaire to determine discriminant validity of multiple chemical sensitivity definitions. The authors distributed a total of 4,126 questionnaires to adults who attended general, allergy, occupational, and environmental health practices. The authors then matched responses to features selected from existing case definitions posited by Thomson et al.; the National Research Council; Cullen; Ashford and Miller; Randolph; Nethercott et al.; and the 1999 Consensus (references 4–7, 2, 9, and 10, respectively, herein). The overall response rate was 61.7%. The prevalence of reported symptoms was lowest in general practices, was intermediate in occupational health and allergy practices, and was highest in environmental health practices. Features from the definitions presented by Nethercott et al. and the 1999 Consensus (references 9 and 10, respectively, herein) correctly identified more than 80% of environmental health practice patients and more than 70% of general practice patients. Combinations of 4 symptoms (i.e., having a stronger sense of smell than others, feeling dull/groggy, feeling “spacey,” and having difficulty concentrating) also discriminated successfully. In summary, features from 2 of 7 case definitions assessed by the University of Toronto Health Survey achieved good discrimination and identified patients with an increased likelihood of multiple chemical sensitivity.


Ten patients who met the Cullen case definition for the multiple chemical sensitivity syndrome were evaluated; a history was taken, and physical examination and fiberoptic rhinolaryngoscopy were performed. All patients had an initial chemical exposure, which was followed by multiple
physical and mental complaints in response to subsequent exposure to a variety of odorous organic chemicals. Rhinitis was a prominent complaint in nine patients, but one patient denied any nasal symptoms. Rhinolaryngoscopic findings were abnormal in all patients; edema, excessive mucus, a cobblestone appearance of the posterior pharynx and base of the tongue, and mucosal injection were observed frequently. A particularly striking finding was focal areas of blanched mucosa that surrounded a prominent vessel. These results suggest that nasal pathology may be a prominent feature of this disorder.


The objectives of this study were (a) to determine the self-reported prevalence of allergy and chemical sensitivity in a rural population of eastern North Carolina, (b) to determine the type and frequency of symptoms for each condition, and (c) to determine the demographic groups affected. A random general telephone survey was conducted during the period May 14, 1993, to September 10, 1993, and questions about allergy and chemical sensitivity were asked. Of the 1 446 households contacted, 1 027 (71%) individuals agreed to participate. Allergies were reported by 365 (35%) individuals. Thirty percent of allergic individuals reported that symptoms occurred once or more each week, whereas 61% reported that symptoms occurred, at most, once each month. Allergic symptoms that occurred daily were reported by 5.3% of the total population. Chemical sensitivity was reported by 336 (33%) individuals. Thirty-five per cent of chemically sensitive individuals reported symptoms at least once each week, whereas 53% reported that symptoms occurred once (or less) each month. Symptoms of chemical sensitivity that occurred daily were reported by 3.9% of the total population. Both allergy and chemical sensitivity were distributed widely across age, income, race, and educational groups. Simultaneous allergy and chemical sensitivity were reported by 16.9% of the population, allergy without chemical sensitivity by 16.0%, chemical sensitivity without allergy by 18.2%, and neither condition by 48.9%. If the prevalence of sensitivity to chemical irritants is, in fact, equivalent to that of allergy, as was found in this study, then support for the scientific investigation of chemical sensitivity is justified.


Neurogenic inflammation as a pathway distinct from antigen-driven, immune-mediated inflammation may play a pivotal role in understanding a broad class of environmental health problems resulting from chemical exposures. Recent progress in understanding the mediators, triggers, and regulation of neurogenic inflammation is reviewed. Evidence for and speculations about a role for neurogenic inflammation in established disorders such as asthma, rhinitis, contact dermatitis, migraine headache, and rheumatoid arthritis are presented. The sick building syndrome and multiple chemical sensitivity syndrome have been defined as clinical entities in which exposure to chemical inhalants gives rise to disease. Current data on the existence of chemical irritant receptors in the airway and skin are discussed; neurogenic inflammation arising from stimulation of chemical irritant receptors is a possible model to explain many of the aspects of chemical sensitivities.
Neurogenic switching is proposed as a hypothesis for a mechanism by which a stimulus at one site can lead to inflammation at a distant site. Neurogenic inflammation occurs when substance P and other neuropeptides released from sensory neurons produce an inflammatory response, whereas immunogenic inflammation results from the binding of antigen to antibody or leukocyte receptors. There is a crossover mechanism between these two forms of inflammation.

Neurogenic switching is proposed to result when a sensory impulse from a site of activation is rerouted via the central nervous system to a distant location to produce neurogenic inflammation at the second location. Neurogenic switching is a possible explanation for systemic anaphylaxis, in which inoculation of the skin or gut with antigen produces systemic symptoms involving the respiratory and circulatory systems, and an experimental model of anaphylaxis is consistent with this hypothesis. Food-allergy-inducing asthma, urticaria, arthritis, and fibromyalgia are other possible examples of neurogenic switching. Neurogenic switching provides a mechanism to explain how allergens, infectious agents, irritants, and possibly emotional stress can exacerbate conditions such as migraine, asthma, and arthritis. Because neurogenic inflammation is known to be triggered by chemical exposures, it may play a role in the sick building syndrome and the multiple chemical sensitivity syndrome. Thus neurogenic switching would explain how the respiratory irritants lead to symptoms at other sites in these disorders.

Allergy and chemical sensitivity are closely related disorders in which environmental exposures produce inflammatory reactions. For allergy, environmental proteins bind to IgE antibody on mast cells leading to the release of inflammatory mediators. In chemical sensitivity, low molecular weight chemicals bind to chemoreceptors on sensory nerve C-fibers leading to the release of inflammatory mediators. Clinical manifestations are similar in the two conditions. The overlap between the two conditions has a basis in mechanism, so the similarity of clinical manifestations and high percentage of individuals with both conditions may have a biological basis. Chronic exposures can lead to adaptation phenomena. Depression has been associated with both allergy and chemical sensitivity. Both the allergic and chemical irritant responses may be subjected to conditioning so that the response is triggered by other stimuli. Evidence for conditioning is strongest for allergy. Both allergy and chemical sensitivity can be acquired in association with irritant exposures.

The reactive airways dysfunction syndrome (RADS), the reactive upper airways dysfunction syndrome (RUDS), the sick building syndrome (SBS), and the multiple chemical sensitivity syndrome (MCS) are overlapping disorders in which there is an intolerance to environmental chemicals. The onset of these illnesses is often associated with an initial acute chemical exposure. To understand the pathophysiology of these conditions, a study of the nasal pathology of individuals experiencing these syndromes was undertaken. Preliminary data indicate that the
nasal pathology of these disorders is characterized by defects in tight junctions between cells, desquamation of the respiratory epithelium, glandular hyperplasia, lymphocytic infiltrates, and peripheral nerve fiber proliferation. These findings suggest a model for a relationship between the chronic inflammation seen in these conditions and an individual's sensitivity to chemicals. A positive feedback loop is set up: the inflammatory response to low levels of chemical irritants is enhanced due to the observed changes in the epithelium, and the epithelial changes are propagated by the inflammatory response to the chemicals. This model, combined with the concept of neurogenic switching, has the potential to explain many aspects of RADS, RUDS, SBS, and MCS in a unified way.


Inhalation exposures can produce asthma and rhinitis by several mechanisms. Sensitization with the production of IgE specific for a substance can lead to symptoms on reexposure via mast cell degranulation and the release of inflammatory mediators. Some substances, known as environmental adjuvants, enhance the immune response to concomitant exposures with the environmental adjuvant. Respiratory irritants can lead to asthma and rhinitis through interaction with chemical irritant receptors in the airway, leading to release of substance P from sensory nerves and neurogenic inflammation. The reactive airways dysfunction syndrome is a chronic asthma-like syndrome resulting from a single acute exposure to a respiratory irritant, while the reactive upper-airways dysfunction syndrome is chronic rhinitis stemming from an irritant exposure. The dysregulation of neurogenic inflammation by chemical exposures may be an important mechanism in the toxic induction of reactive airways dysfunction syndrome and reactive upper-airways dysfunction syndrome and may play a role in understanding the sick building syndrome and the multiple chemical sensitivity syndrome.


The term multiple chemical sensitivity confuses etiology with diagnosis. Chemical sensitivity is a symptom expressed by patients. The symptoms complex is also expressed by the majority of patients with asthma reactive airway dysfunction syndrome or rhinitis following a single acute exposure, called reactive upper airway dysfunction syndrome. The chemically sensitivity patient merits evaluation for upper airway and bronchial reactivity that may cause extra-airway symptomatology.


We report exacerbation of symptoms and chemical intolerances in three of four self-described chemically sensitive women following relocation to a newly constructed office building. Levels of total volatile organic compounds (TVOCs) in this building prior to occupancy were approximately 200 µg/m³ (toluene equivalent units) with a myriad of individual components present. By day 50 after occupancy, the concentration of TVOCs in the building dropped to approximately 50 µg/m³. Nevertheless, three women reported significant worsening of their
symptoms with spreading of their sensitivities to previously tolerated chemical exposures. One woman relocated to another building, while the other two managed their symptoms by reducing time spent in the building or by using a room air cleaner. By day 600 following occupancy, although TVOCs had increased significantly (perhaps due to cleaning agents), there were fewer individual VOCs present in the air, and some of the women were able to tolerate the air in the building. We conclude that complex mixtures of VOCs at very low levels tolerated by the majority of building occupants may pose problems for persons who report pre-existing chemical sensitivities. TVOC measurements may not correlate with symptoms in these individuals. Reasonable accommodations by an employer can reduce problem exposures, making it possible for some affected individuals to continue productive employment.


It has been hypothesized that sensitivity to low-level chemical exposures develops in two steps: initiation by an acute or chronic chemical exposure, followed by triggering of symptoms by low levels of previously tolerated chemical inhalants, foods, or drugs. The Working Group on Toxicant-induced Loss of Tolerance has formulated a series of research questions to test this hypothesis: Do some individuals experience sensitivity to chemicals at levels of exposure unexplained by classical toxicological thresholds and dose-response relationships, and outside normally expected variation in the population? Do chemically sensitive subjects exhibit masking that may interfere with the reproducibility of their responses to chemical challenges? Does chemical sensitivity develop because of acute, intermittent, or continuous exposure to certain substances? If so, what substances are most likely to initiate this process? An experimental approach for testing directly the relationship between patients' reported symptoms and specific exposures was outlined in response to the first question, which was felt to be a key question. Double-blind, placebo-controlled challenges performed in an environmentally controlled hospital facility (environmental medical unit) coupled with rigorous documentation of both objective and subjective responses are necessary to answer this question and to help elucidate the nature and origins of chemical sensitivity.


One hundred twelve individuals who reported onset of multiple chemical sensitivity following well-documented exposure to either (1) a cholinesterase-inhibiting organophosphate or carbamate pesticide or (2) remodeling of a building completed mail-out/mail-back questionnaires concerning their exposure, symptoms, sensitivity to ingesta and inhalants, utilization of health-care resources, and impact of their illness on lifestyle. It was hypothesized that if multiple chemical sensitivity resulted from neurotoxic exposure, then organophosphate-exposed respondents should report greater severity of illness resulting from the relatively greater neurotoxicity of this class of chemicals. Pesticide-exposed and remodeling-exposed multiple chemical sensitivity groups reported similar patterns of symptoms and identified similar inhalants and ingesta as triggers for their symptoms; these results suggested a common mechanism (biological and/or psychological) for their conditions. The pesticide-exposed group,
however, reported significantly greater symptom severity than did the remodeling-exposed group, especially for neuromuscular, affective, airway, gastrointestinal, and cardiac symptoms. These findings provide evidence for (1) a possible biological basis for multiple chemical sensitivity and (2) a distinct pathophysiology or final common pathway for the condition that, while as yet undefined, appears to be shared by these two groups. Although subjective multisystem health complaints characterize both multiple chemical sensitivity and somatoform disorder, features of this multiple chemical sensitivity sample were inconsistent with somatoform disorder, i.e., onset after 30 y of age in 83%, the predominance of severe cognitive symptoms, and attributions of environmental causation. No group differences were found with respect to lifestyle impact. Eighty-one percent of respondents said they had been working full-time at the time they were exposed, yet at the time of the survey (on average, 7.7 y post exposure) only 12.5% were working full-time. The majority said they had quit their jobs, changed jobs, or changed careers because of their illness. Approximately 40% reported that they had consulted 10 or more medical practitioners. The persistent, disabling neuropsychological symptoms reported by these multiple chemical sensitivity groups are strikingly similar to those reported among individuals exposed occupationally to pesticides and solvents. These parallel findings suggest that the types and levels of exposures associated with extermination and remodeling may not be inconsequential, at least for a subset of the population. Further studies from a variety of perspectives, including human challenge studies and the development of animal models, are needed to define the pathophysiological and psychological mechanisms underlying this costly condition.


The lack of a generally accepted case definition for multiple chemical sensitivity (MCS) and the absence of a standardized approach for measuring salient aspects of chemical sensitivity that would permit cross-comparison of findings by different investigators have hindered progress in this area. Based upon findings from an earlier study of 112 persons with self-reported chemical sensitivity who attributed their chemical sensitivity to a well-defined exposure event, we developed an instrument with self-rating scales to assess Symptom Severity, Chemical (Inhalant) Intolerances, Other Intolerances (e.g., foods, medications, alcohol), Life Impact, and Masking (a measure of ongoing chemical exposures). When administered to four patient groups and controls, the scales showed good reliability and validity overall (n=421) and in each group. Used together, the scales provided sensitivity of 92% and specificity of 95% in differentiating chemically sensitive persons from controls. Our results support use of these scales individually or collectively for a variety of applications including the selection of chemically sensitive subjects and controls for research, assessment of chemical sensitivity in various study populations, cross-comparison of groups studied by different investigators, pre- and post-assessment of therapeutic interventions, clinical evaluation of complex patients who report intolerances, and teaching medical residents and students how to evaluate patients for chemical sensitivity and MCS.
In science, anomalies expose the limitations of existing paradigms and drive the search for new ones. In the late 1800s, physicians observed that certain illnesses spread from sick, feverish individuals to those contacting them, paving the way for the germ theory of disease. The germ theory served as a crude, but elegant formulation that explained dozens of seemingly unrelated illnesses affecting literally every organ system. Today, we are witnessing another medical anomaly—a unique pattern of illness involving chemically exposed groups in more than a dozen countries, who subsequently report multisystem symptoms and new-onset chemical, food, and drug intolerances. These intolerances may be the hallmark for a new disease process or paradigm, just as fever is a hallmark for infection. The fact that diverse demographic groups, sharing little in common except some initial chemical exposure event, develop these intolerances is a compelling anomaly pointing to a possible new theory of disease, one that has been referred to as "Toxicant-Induced Loss of Tolerance" ("TILT"). TILT has the potential to explain certain cases of asthma, migraine headaches, and depression, as well as chronic fatigue, fibromyalgia, and "Gulf War syndrome". It appears to evolve in two stages: (1) initiation, characterized by a profound breakdown in prior, natural tolerance resulting from either acute or chronic exposure to chemicals (pesticides, solvents, indoor air contaminants, etc.), followed by (2) triggering of symptoms by small quantities of previously tolerated chemicals (traffic exhaust, fragrances, gasoline), foods, drugs, and food/drug combinations (alcohol, caffeine). While the underlying dynamic remains an enigma, observations indicating that affected individuals respond to structurally unrelated drugs and experience cravings and withdrawal-like symptoms, paralleling drug addiction, suggest that multiple neurotransmitter pathways may be involved.


Using the Environmental Exposure and Sensitivity Inventory (EESI), a standardized instrument for measuring chemical sensitivity, we obtained and compared ratings of symptoms, chemical (inhalant) intolerances, other intolerances (e.g., drugs, caffeine, alcohol, skin contactants), lifeimpact, and masking (ongoing exposures) in five populations: multiple chemical sensitivity (MCS) patients who did (n=96) or did not (n=90) attribute onset of their illness to a specific exposure event, patients with implanted devices (n=87), Gulf War veterans (n=72), and controls (n=76). For each patient group, mean scores on the first four scales were significantly greater than for controls. MCS patients reported avoiding more chemical exposures (were less masked) than the other groups. Across groups, for a given level of symptoms, as masking increased, mean scores on the Chemical Intolerance Scale decreased. In contrast, mean scores on the Other Intolerance Scale appeared to be less affected by masking. These findings suggest that some patients with antecedent chemical exposures, whether exogenous (chemical spill, pesticide application, indoor air contaminants) or endogenous (implant), develop new chemical, food, and drug intolerances. Reports of new caffeine, alcohol, medication, food, or other intolerances by patients may signal exposure-related illness. Masking may reduce individuals' awareness of chemical intolerances, and, to a lesser degree, other intolerances.

`Toxicant-induced loss of tolerance' (or TILT) describes a two-step disease process in which (1) certain chemical exposures, e.g., indoor air contaminants, chemical spills, or pesticide applications, cause certain susceptible persons to lose their prior natural tolerance for common chemicals, foods, and drugs (initiation); (2) subsequently, previously tolerated exposures trigger symptoms. Responses may manifest as addictive or abdictive (avoidant) behaviors. In some affected individuals, overlapping responses to common chemical, food, and drug exposures, as well as habituation to recurrent exposures, may hide (mask) responses to particular triggers. Accumulating evidence suggests that this disease process might underlie a broad array of medical illnesses including chronic fatigue, fibromyalgia, migraine headaches, depression, asthma, the unexplained illnesses of Gulf War veterans, multiple chemical sensitivity, and attention deficit disorder.


Conceivably, chemicals contacting olfactory nerve projections in the nose could either be transported into or relay electrical signals to the limbic region, leading to a vast array of symptoms. Likewise, thought processes and mood states may trigger or interrupt pre-existing limbic activity. At present, however, no evidence suggests that limbic activity triggered by environmental exposures can be entirely overcome by psychologic interventions. One important ramification of a limbic hypothesis, if true, is that no convenient biologic marker for multiple chemical sensitivity may exist at the present time. Ten years from now, we may finally confirm the existence of multiple chemical sensitivities (by careful, blinded challenges) but still have no single mechanism to explain it; that is, after all avenues of biochemical and immunologic inquiry have been exhausted, no single cause or marker for this disorder may be apparent. The theory that adaptation plays a role in MCS is based on the observed responses of patients in a deadapted state who have been housed in an environmental unit. Although adaptation is only an observation at this time, not a mechanism, biologic limits might regulate how much an organism can adapt. Such limits could be highly individual and vary by orders of magnitude. Certainly adaptation occurs at all levels of biologic systems, from enzyme systems to cells, tissues, organs, and even behavior (Fregly, 1969). Theoretically, a major insult or the accumulation of lower-level injuries within these systems could lead to a kind of "overload" or "saturation" effect with respect to adaptive capacity. This might cause an individual to have environmental responses, which, instead of being flexible and fluid, would become fragile and overly responsive. Many MCS patients report that years, and in some cases decades, after the onset of their problems, they have recovered only a portion of their former energies and tolerance for their environment. Their descriptions seem to suggest the loss of an intangible capacity to adapt, parts of which may be temporary and recoverable and other parts of which may not. Perhaps our patients have been telling us the diagnosis.

Several different meanings have been attached to the term “chemical sensitivity” by those who use it. Feeling ill from odors is a *symptom* reported by approximately one-third of the population. The *syndrome* of chemical sensitivity, frequently called “Multiple Chemical Sensitivity” or “MCS” has been the subject of three federally sponsored workshops; at least five different case definitions for research on MCS have been proposed. In contrast, the hypothesis that chemical sensitivity may be a *mechanism for disease* posits that a broad spectrum of “recognized” chronic illnesses, ranging from asthma and migraine to depression and chronic fatigue, may be the consequence of environmental chemical exposures. According to this theory, a two-step process occurs: (1) an initial salient exposure event(s) (for example, a one-time, intermittent, or continuous exposure to pesticides, solvents, or air contaminants in a sick building) interacts with a susceptible individual, causing loss of tolerance for everyday, low level chemical inhalants (car exhaust, fragrances, cleaning agents), as well as for foods, drugs, alcohol, and caffeine; (2) thereafter, such common, formerly well-tolerated substances trigger symptoms, thus perpetuating illness. “Masking” (acclimatization, apposition, and addiction) may hide these exposure-symptom relationships, thus obfuscating the environmental etiology of the illness. Accumulating clinical observations lend credence to a view of chemical sensitivity as an emerging theory of disease causation and underscore the need for its testing in a rational, scientific manner. While chemical sensitivity may be the consequence of chemical exposure, the term “toxicant-induced loss of tolerance” more fully describes the two-step process under scrutiny.


This paper attempts to clarify the nature of chemical sensitivity by proposing a theory of disease that unites the disparate clinical observations associated with the condition. Sensitivity to chemicals appears to be the consequence of a two-step process: loss of tolerance in susceptible persons following exposure to various toxicants, and subsequent triggering of symptoms by extremely small quantities of previously tolerated chemicals, drugs, foods, and food and drug combinations including caffeine and alcohol. Although chemical sensitivity may be the consequence of this process, a term that may more clearly describe the observed process is toxicant-induced loss of tolerance. Features of this yet-to-be-proven mechanism or theory of disease that affect the design of human exposure studies include the stimulatory and withdrawal-like nature (resembling addiction) of symptoms reported by patients and masking. Masking, which may blunt or eliminate responses to chemical challenges, appears to have several components: apposition, which is the overlapping of the effects of closely timed exposures, acclimatization or habituation, and addiction. A number of human challenge studies in this area have concluded that there is no physiological basis for chemical sensitivity. However, these studies have failed to address the role of masking. To ensure reliable and reproducible responses to challenges, future studies in which subjects are evaluated in an environmental medical unit, a hospital-based facility in which background chemical exposures are reduced to the lowest levels practicable, may be necessary. A set of postulates is offered to determine whether there is a causal relationship between low-level chemical exposures and symptoms using an environmental medical unit.
Drug addiction and multiple chemical intolerance (abdiction) appear to be polar opposites - the former characterized by craving and dependency, the latter by aversion. However, when the two are viewed in juxtaposition similarities emerge, revealing a common underlying dynamic, one which appears to be a new paradigm of disease. TILT, or toxicant-induced loss of tolerance, bridges the gap between addiction and abdiction and has the potential to explain a variety of illnesses, including certain cases of asthma, migraine headaches and depression, as well as chronic fatigue syndrome, fibromyalgia and "Gulf War syndrome". This paper argues that both addiction and chemical intolerance involve a fundamental breakdown in innate tolerance, resulting in an amplification of various biological effects, particularly withdrawal symptoms. While addicts seek further exposures so as to avoid unpleasant withdrawal symptoms, chemically intolerant individuals shun their problem exposures, but for the same reason - to avoid unpleasant withdrawal symptoms. These observations raise critical questions: do addictive drugs and environmental pollutants initiate an identical disease process? Once this process begins, can both addictants and pollutants trigger symptoms and cravings? TILT opens a new window between the fields of addiction and environmental medicine, one that has the potential to transform neighboring realms of medicine, psychology, psychiatry and toxicology.


In earlier studies, we have shown that patients with a history of sensory hyperreactivity develop asthma-like symptoms when exposed to strong scents, even if they cannot smell any scent. METHODS: For study of possible pathophysiologic mechanisms behind sensory hyperreactivity, the patients' airways and eyes were separately exposed to a common inducing factor, perfume. Eleven patients with a history of hyperreactivity to chemical trigger factors, such as perfume, were provoked single-blindly in a placebo-controlled, randomized study. During airway exposure, the eyes were covered and, during the eye exposure, the patients inhaled fresh air. A special face mask or a nose clip was used to avoid any smell. RESULTS: During the 30-min exposure to perfume, there was a gradual increase in three main symptoms; i.e., eye irritation, cough, and dyspnea, after both the airway and eye exposures. The increases were significant compared with placebo. CONCLUSIONS: Asthma-like and other symptoms, such as irritation of the eyes, may be induced by exposure of both the airways and the eyes in patients with sensory hyperreactivity. This points to the importance of studying the sensory nervous system, not only in the airways, but also in other organs.


Patients complaining of upper and lower airway symptoms caused by scents and chemicals have previously been shown to have increased cough sensitivity to inhaled capsaicin, but the precise mechanisms behind this reaction are unknown. Hypothesizing that a neurochemical alteration related to sensory hyperreactivity (SHR) of the airway mucosa occurs, we measured levels of nerve growth factor (NGF) in nasal lavage fluid (NAL) before and after capsaicin inhalation provocations and related the capsaicin cough sensitivity to the NGF levels. Thirteen patients with
SHR and 14 control subjects were provoked with capsaicin inhalation at three different doses. We measured NGF in NAL before and after provocation and recorded cough and capsaicin-induced symptoms. All subjects demonstrated a dose-dependent cough response to capsaicin inhalation, with a more pronounced effect in patients than in controls. Basal levels of NGF were significantly lower in the patient group than in the control subjects ($p < 0.01$). After capsaicin provocation, the patients showed a significant increase in NGF ($p < 0.01$), which was related to capsaicin cough sensitivity. The findings demonstrate that, in patients with airway symptoms induced by scents and chemicals, SHR is real and measurable, demonstrating a pathophysiology in the airways of these patients compared to healthy subjects.


**Objectives** This study explored the subjective reactions and psychological test performance of smell-intolerant subjects during consecutive challenges to chemicals with contrasting neurotoxic properties.

**Methods:** Women with symptoms compatible with multiple chemical sensitivity (N=10) and healthy referents (N=20) were individually challenged in an exposure chamber. All the subjects attended two separate 2-hour sessions of exposure to n-butyl acetate and toluene, in counterbalanced sequence. After an initial phase without exposure, air concentrations were increased in steps ranging from 3.6 to 57 mg/m$^3$ for n-butyl acetate and from 11 to 180 mg/m$^3$ for toluene. The response measures comprised ratings of annoyance and smell intensity and also neurobehavioral test performance.

**Results:** Both groups showed an increase in annoyance ratings and a decrease in test performance in the initial unexposed chamber phase and also in the first phase of the chemical exposure, these results indicating slight immediate expectancy or "suggestion" effects. During the six chamber phases, the ratings of mucous membrane irritation and fatigue showed a steeper increase in the group with multiple chemical sensitivity than among the referents, while the ratings of smell intensity and smell annoyance were similar in the two groups. A reduction in test performance was observed during the chamber phases, particularly in the group with multiple chemical sensitivity. No relation was found between the ratings or performance and chemical substance.

**Conclusions:** Stronger immediate expectancy or "suggestion" reactions than normal did not characterize the group with multiple chemical sensitivity. This group showed a stronger than normal gradual build-up of fatigue, mucous membrane irritation, and reduced performance during chemical exposure. The results offer the most support to an irritative basis for multiple chemical sensitivity.


The fact that only some individuals exposed to environmental chemicals develop chemical intolerance raises the possibility that genetic factors could be contributing factors. The present communication summarizes evidence from a genetic animal model of cholinergic supersensitivity that suggests that an abnormal cholinergic system could be one predisposing genetic factor. The Flinders Sensitive Line (FSL) rats were established by selective breeding for
increased responses to an organophosphate. It was subsequently found that these FSL rats were also more sensitive to direct-acting muscarinic agonists and had elevated muscarinic receptors compared to the selectively bred parallel group, the Flinders Resistant Line (FRL) rats, or randomly bred control rats. Increased sensitivity to cholinergic agents has also been observed in several human populations, including individuals suffering from chemical intolerance. Indeed, the FSL rats exhibit certain behavioral characteristics such as abnormal sleep, activity, and appetite that are similar to those reported in these human populations. In addition, the FSL rats have been reported to exhibit increased sensitivity to a variety of other chemical agents. Peripheral tissues, such as intestinal and airway smooth muscle, appear to be more sensitive to both cholinergic agonists and an antigen, ovalbumin. Hypothermia, a centrally mediated response, is more pronounced in the FSL rats after nicotine and alcohol, as well as agents that are selective for the dopaminergic and serotonergic systems. In some cases, the increased sensitivity has been detected in the absence of any changes in the receptors with which the drugs interact (dopamine receptors), while receptor changes have been seen in other cases (nicotine receptors). Therefore, there may be multiple mechanisms underlying the multiple chemical sensitivity-chemical intolerance of the FSL rats. An elucidation of these mechanisms may provide useful clues to those involved in chemical intolerance in humans.


Multiple chemical sensitivity (MCS) is a condition where previous exposure to hydrophobic organic solvents or pesticides appears to render people hypersensitive to a wide range of chemicals, including organic solvents. The hypersensitivity is often exquisite, with MCS individuals showing sensitivity that appears to be at least two orders of magnitude greater than that of normal individuals. This paper presents a plausible set of interacting mechanisms to explain such heightened sensitivity. It is based on two earlier theories of MCS: the elevated nitric oxide/peroxynitrite theory and the neural sensitization theory. It is also based on evidence implicating excessive NMDA activity in MCS. Four sensitization mechanisms are proposed to act synergistically, each based on known physiological mechanisms: Nitric oxide-mediated stimulation of neurotransmitter (glutamate) release; peroxynitrite-mediated ATP depletion and consequent hypersensitivity of NMDA receptors; peroxynitrite-mediated increased permeability of the blood–brain barrier, producing increased accessibility of organic chemicals to the central nervous system; and nitric oxide inhibition of cytochrome P450 metabolism. Evidence for each of these mechanisms, which may also be involved in Parkinson’s disease, is reviewed. These interacting mechanisms provide explanations for diverse aspects of MCS and a framework for hypothesis-driven MCS research.—Pall, M. L. NMDA sensitization and stimulation by peroxynitrite, nitric oxide, and organic solvents as the mechanism of chemical sensitivity in multiple chemical sensitivity.


The elevated nitric oxide/peroxynitrite and the neural sensitization theories of multiple chemical sensitivity (MCS) are extended here to propose a central mechanism for the exquisite sensitivity...
to organic solvents apparently induced by previous chemical exposure in MCS. This mechanism is centered on the activation of N-methyl-d-aspartate (NMDA) receptors by organic solvents producing elevated nitric oxide and peroxynitrite, leading in turn to increased stimulating of and hypersensitivity of NMDA receptors. In this way, organic solvent exposure may produce progressive sensitivity to organic solvents. Pesticides such as organophosphates and carbamates may act via muscarinic stimulation to produce a similar biochemical and sensitivity response. Accessory mechanisms of sensitivity may involve both increased blood-brain barrier permeability, induced by peroxynitrite, and cytochrome P450 inhibition by nitric oxide. The NMDA hyperactivity/hypersensitivity and excessive nitric oxide/peroxynitrite view of MCS provides answers to many of the most puzzling aspects of MCS while building on previous studies and views of this condition.


The article analyzes the role of the vanilloid receptor in Multiple Chemical Sensitivity (MCS). The vanilloid receptor, which appears to play a central role in the irritant response, is the putative major target for organic solvents and certain other compounds in MCS. Its widespread distribution in both the central and peripheral nervous systems, as well as in certain other tissues, suggests a possible important role for this receptor as the main target of diverse chemicals in both central and peripheral chemical sensitivity mechanisms. The vanilloid receptor is reportedly hyperresponsive in MCS and can increase nitric oxide levels and stimulate N-methyl-D-aspartate. Vanilloid receptor activity is markedly altered by multiple mechanisms, possibly providing an explanation for the increased activity in MCS and symptom masking by previous chemical exposure. Activation of this receptor by certain mycotoxins may account for some cases of sick building syndrome, a frequent precursor of MCS. Twelve types of evidence implicate the vanilloid receptor as the major target of chemicals, including volatile organic solvents in MCS.


Short-term stressors, capable of increasing nitric oxide levels, act to initiate cases of illnesses including chronic fatigue syndrome, multiple chemical sensitivity, fibromyalgia and posttraumatic stress disorder. These stressors, acting primarily through the nitric oxide product, peroxynitrite, are thought to initiate a complex vicious cycle mechanism, known as the NO/ONOO— cycle that is responsible for chronic illness. The complexity of the NO/ONOO— cycle raises the question as to whether the mechanism that switches on this cycle is this complex cycle itself or whether a simpler mechanism is the primary switch. It is proposed here that the switch involves a combination of two variable switches, the increase of nitric oxide synthase (NOS) activity and the partial uncoupling of the NOS activity, with uncoupling caused by a tetrahydrobiopterin (BH4) deficiency. NOS uncoupling causes the NOS enzymes to produce superoxide, the other precursor of peroxynitrite, in place of nitric oxide. Thus partial uncoupling will cause NOS proteins to act like peroxynitrite synthases, leading, in turn to increased NF-κB activity. Peroxynitrite is known to oxidize BH4, and consequently partial uncoupling may initiate a vicious cycle, propagating the partial uncoupling over time. The combination of high NOS activity and BH4 depletion will lead to a potential vicious cycle that may be expected to switch
on the larger NO/ONOO– cycle, thus producing the symptoms and signs of chronic illness. The role of peroxynitrite in the NO/ONOO– cycle also implies that such uncoupling is part of the chronic phase cycle mechanism such that agents that lower uncoupling will be useful in treatment.


Three types of overlap occur among the disease states chronic fatigue syndrome (CFS), fibromyalgia (FM), multiple chemical sensitivity (MCS) and posttraumatic stress disorder (PTSD). They share common symptoms. Many patients meet the criteria for diagnosis for two or more of these disorders and each disorder appears to be often induced by a relatively short-term stress which is followed by a chronic pathology, suggesting that the stress may act by inducing a self-perpetuating vicious cycle. Such a vicious cycle mechanism has been proposed to explain the etiology of CFS and MCS, based on elevated levels of nitric oxide and its potent oxidant product, peroxynitrite. Six positive feedback loops were proposed to act such that when peroxynitrite levels are elevated, they may remain elevated. The biochemistry involved is not highly tissue-specific, so that variation in symptoms may be explained by a variation in nitric oxide/peroxynitrite tissue distribution. The evidence for the same biochemical mechanism in the etiology of PTSD and FM is discussed here, and while less extensive than in the case of CFS and MCS, it is nevertheless suggestive. Evidence supporting the role of elevated nitric oxide/peroxynitrite in these four disease states is summarized, including induction of nitric oxide by common apparent inducers of these disease states, markers of elevated nitric oxide/peroxynitrite in patients and evidence for an inductive role of elevated nitric oxide in animal models. This theory appears to be the first to provide a mechanistic explanation for the multiple overlaps of these disease states and it also explains the origin of many of their common symptoms and similarity to both Gulf War syndrome and chronic sequelae of carbon monoxide toxicity. This theory suggests multiple studies that should be performed to further test this proposed mechanism. If this mechanism proves central to the etiology of these four conditions, it may also be involved in other conditions of currently obscure etiology and criteria are suggested for identifying such conditions.


Chronic fatigue syndrome (CFS), multiple chemical sensitivity (MCS), post-traumatic stress disorder (PTSD), and fibromyalgia (FM) show three distinct types of overlap: each is typically induced by a short-term stress leading to a chronic pathology; all four show a set of substantial overlapping symptoms; and many patients have been diagnosed as having several of these disorders. These and other similarities have led to the suggestion that all four of these may be essentially identical, sharing a common, yet previously undefined etiology. For example, Buchwald and Garrity concluded a study of CFS, MCS, and FM patients by suggesting that, "Despite their different diagnostic labels, existing data, though limited, suggest that these illnesses may be similar if not identical conditions...." Miller suggested that CFS, MCS, PTSD,
FM, and several other disorders may share a common, if undefined etiology, asking whether these constitute "an emerging theory of disease". One of us (M. L. Pall) has proposed a novel theory for the cause of CFS, based on elevated levels of peroxynitrite and its precursors, nitric oxide and superoxide. Central to this theory are six positive feedback loops, which act such that elevated peroxynitrite increases the levels of both nitric oxide and superoxide, reacting to form more peroxynitrite. By this vicious cycle mechanism (Fig. 1A), once the cycle is established, elevated levels of peroxynitrite and other components of this mechanism, notably nitric oxide, superoxide, and inflammatory cytokines, may produce the symptoms of CFS. Because the biochemical mechanisms involved here are not highly tissue-specific, some variation in tissue distribution of elevated peroxynitrite may produce the differences in symptoms often seen between, for example, classic cases of CFS and MCS. In this paper, we focus on MCS, asking whether the proposed elevated nitric oxide/peroxynitrite mechanism may be central to the etiology of MCS. The evidence examined here includes each of the following: evidence that incitants of MCS act to induce increased levels of nitric oxide; evidence for induction of the inducible nitric oxide synthase in MCS; evidence for elevated levels of oxidative stress, as might be produced by peroxynitrite; evidence that incitants can induce inflammatory cytokines; and multiple types of evidence from animal models of MCS showing that increased nitric oxide has an essential role in producing the responses in these models. We also suggest that peroxynitrite may play an additional role in MCS by inducing breakdown of the blood-brain barrier.


The relationship of solvent exposure to self-reported neurologic and somatic symptoms as well as neuropsychological performance was examined in a sample of 567 female blue collar workers who were members of the International Brotherhood of Electrical Workers (IBEW). Structured interviews were conducted at IBEW offices. Five solvent exposure categories were derived—never exposed, exposed prior to but not during the past year, exposed during the past year but not currently, currently exposed less than 50% of the time, and currently exposed more than 50% of the time. No differences among the groups on neuropsychological performance were found. On the other hand, heightened exposure was significantly related to depression, severe headaches, light-headedness, room spinning, appetite difficulties, funny taste in mouth, weakness/fatigue, rashes, and abdominal pain after controlling for the effects of seven risk factors (age, smoking, moderate-heavy alcohol consumption, severe obesity, history of physician-diagnosed chronic illness, working in a clean room, and exposure to other chemicals). These findings are consistent with Scandinavian studies of solvent-exposed male workers and point to the need for careful prospective research.


As surgeons, otolaryngologists tend to most be interested in operative procedures and leave the hospital environment to the care of administrators and the nursing staff. Given the dangers that are present, it would seem prudent to spend some time considering the agents that are used in patient care and in operating suites, to minimize the risk to patients and co-workers.

Susceptibility to environmental incitants such as air, food and water components is becoming an increasingly recognized health problem. These sensitivities and reactions can induce a spectrum of symptoms affecting smooth muscle, mucous membranes and collagen in the respiratory, gastrointestinal, genitourinary and vascular systems. These reactions may be mistaken for hypochondriasis, but actually are due to reactions to foods and chemicals found in the patient's home and work environments. Careful clinical histories should alert the nurse and physician, who can confirm suspicions by eliminating and challenging the patient with potentially offending agents under controlled circumstances.


In this study, different modes of therapy for the removal of toxic chemicals from the human body have been assessed and compared. This consisted of: 1) thirteen inpatients in an environmentally controlled area in a hospital, 2) forty-one outpatients with home environmental control and work area change, and 3) fifteen outpatients in a physical therapy/sauna program with a good environmental control. Attention to manipulation of food, food contaminants, water and air pollution as well as nutritional therapy was important in all groups. Each modality seemed efficacious in its own right; 100% inpatients, 80% sauna/physical therapy patients, and 70% outpatients improved their signs and symptoms. Inpatient therapy in a finally controlled environment was far superior to the other two modalities in clearing of symptoms, as well as in clearing of organic chemicals. Outpatient and sauna/physical therapy are efficacious for less ill patients.


Fifty chemically sensitive patients with vascular, asthmatic and arthritic signs, ranging in age from 21 to 61, were exposed to double-blind challenges of ambient doses of inhaled toxic chemicals in a specially designed booth in an Environmental Control Unit (ECU). Primary signs and symptoms were recorded before and after challenge with five chemicals and three placebos. Inhaled challenges included phenol (less than .0025 ppm), petroleum-derived ethyl alcohol (less than .5 ppm), formaldehyde (less than .2 ppm), chlorine (less than .3 ppm), and pesticide (2, 3-D at less than .0034 ppm). Placebos were water or saline. A set on testing criteria were evaluated for maximizing the likelihood of well-defined, reproducible information from these ambient-dose double-blind challenges. For best results, these testing criteria include: Before testing, the patient must be housed in a chemically less polluted environment. The individual must have been de-adapted to food, air, and water pollutants by means of a water fat for three to four days. At the time of the challenge, the patient must be on food and water previously determined to be safe. An enclosed non-polluted challenge booth must be used for these chemical exposures. Sign and symptom scores appropriate for that patient must be recorded, before and after challenge. Appropriate doses of the chemical in question (determined by air concentration and length of
exposure) are necessary to investigate a particular problem. The conclusion of the study is that in these patients, chemical sensitivity clearly does exist (pulse rate differences between positive responses and placebo - p .001). (ABSTRACT TRUNCATED AT 250 WORDS).


Some individuals report that, following either a single high-level or repeated lower-level exposures to chemicals (initiation), subsequent exposure to very low concentrations of chemicals (triggering) produces a variety of adverse effects, including disruption of cognitive processes. Our objective was to model this two-step process in a laboratory animal. Two groups of 16 rats, eight male and eight female, received whole-body inhalation exposure to toluene, either at 80 ppm for 6 h/day for 4 weeks (Repeat group) or to 1600 ppm for 6 h/day on one day only (Acute group). Two other groups (Trigger group and Clean group) of 16 were sham-exposed. After 17 days without toluene exposure, the Acute, Repeat and Trigger groups began a series of daily toluene 'trigger' exposures (10 ppm for 1 h) followed immediately by testing on an operant repeated-acquisitions task requiring learning within and across sessions. The Clean group was sham-exposed prior to operant testing. Trigger or sham exposures and operant testing continued 5 days/week for 17 sessions. Analysis of variance revealed a variety of statistically significant ($P<0.05$) differences between treatment groups. Furthermore, the patterns of differences between groups differed ($P<0.05$) for female and male rats. For example, male rats of the Trigger group made the most responses, and female rats of the Repeat group responded most slowly. The observation of important changes in the operant behavior of female and male rats previously exposed to toluene, at relatively low concentrations (80 or 1600 ppm) and then later re-exposed at very low concentrations (10 ppm), is consistent with the experiences of humans reporting cognitive difficulties following acute or chronic exposures to chemicals.


The subset of patients reporting chemical sensitivity with neurocognitive complaints usually exhibits specific abnormalities of brain metabolism consistent with neurotoxicity, on imaging with single photon emission computed tomography (SPECT). These recurrent neurotoxic patterns are characterized by a mismatch in tracer uptake between early- and late-phase imaging, multiple hot and cold foci throughout the cortex, temporal asymmetry and increased tracer uptake into the soft tissues and, sometimes, the basal ganglia. Previous studies confirm these neurotoxic findings in patients with neurotoxic chemical exposures and breast implants. Affective processes such as depression do not, alone, show this pattern. These abnormalities in SPECT images correlate with documented neurocognitive impairment. Controlled challenges to ambient chemicals can induce profound neurotoxic changes seen on SPECT imaging in chemically sensitive patients. Detoxification treatment techniques frequently produce significant improvement on brain SPECT brain imaging in these patients. Neurotoxicity appears to be characteristic in many cases of chemical sensitivity.

A case history of the induction of asthma and chemical sensitivity in a 42-year-old registered nurse illustrates several of the characteristic features of multiple chemical sensitivity (MCS). This patient's problems started shortly after moving into a new home under construction, with associated chemical exposures. Other MCS patients report the onset of the condition with other chemical exposures such as those encountered at their places of work or use of pesticides at their residences. Patients often describe a spreading phenomenon of increasing intolerance to commonly encountered chemicals at concentrations well tolerated by other people. Symptoms usually wax and wane with exposures, and are more likely to occur in patients or families with preexisting histories of migraine or with classical allergies. Idiosyncratic medication reactions (especially to preservative chemicals) are common in MCS patients, as are dysautonomia symptoms (such as vascular instability) and poor temperature regulation. Myalgia and joint pains and food intolerance are common features as well. Contamination with xenobiotic chemicals is frequently found in these patients when they are tested. Reactive airways dysfunction syndrome is a recently identified condition that exhibits features of both asthma and chemical sensitivity. MCS patients frequently have patterns of neurotoxic brain metabolism that can be confirmed on single photo emission computed tomography imaging.


It has been suggested that the neurobehavioral dysfunction observed in persons presenting with symptoms of Multiple Chemical Sensitivity (MCS) syndrome involves sensitization of neural circuits. Two hypotheses for the route of exposure in induction of neural sensitization in MCS are: (a) direct chemical stimulation of olfactory processes, or (b) general systemic response to inhaled chemicals. In either case, the mechanism of action may involve chemical kindling or kindling-related phenomena. A neural sensitization mechanism based on kindling or kindling-related phenomena is attractive and has been previously demonstrated in both in vitro and in vivo animal models. Without a testable animal model for chemically mediated induction of MCS, however, any argument that MCS is mediated by kindling or kindling-related phenomena is reduced to the circular argument "the mechanism of sensitization is sensitization." The present survey provides an overview of the experimental paradigms that result in sensitization, differentiated on the basis of probable neurophysiological and neurochemical mechanisms. Neurophysiological potentiation, electrical kindling, chemical kindling and behavioral sensitization are evaluated and discussed in relationship to MCS.


The central nervous, immune, and endocrine systems communicate through multiple common messengers. Over evolutionary time, what may be termed integrated defense system(s) (IDS) have developed to coordinate these communications for specific contexts; these include the stress response, acute-phase response, nonspecific immune response, immune response to antigen, kindling, tolerance, time-dependent sensitization, neurogenic switching, and traumatic dissociation (TD). These IDSs are described and their overlap is examined. Three models of
disease production are generated: damage, in which IDSs function incorrectly; inadequate/inappropriate, in which IDS response is outstripped by a changing context; and evolving/learning, in which the IDS learned response to a context is deemed pathologic. Mechanisms of multiple chemical sensitivity (MCS) are developed from several IDS disease models. Model 1A is pesticide damage to the central nervous system, overlapping with body chemical burdens, TD, and chronic zinc deficiency; model 1B is benzene disruption of interleukin-1, overlapping with childhood developmental windows and hapten-antigenic spreading; and model 1C is autoimmunity to immunoglobulin-G (IgG), overlapping with spreading to other IgG-inducers, sudden spreading of inciters, and food-contaminating chemicals. Model 2A is chemical and stress overload, including comparison with the susceptibility/sensitization/trigging/spreading model; model 2B is genetic mercury allergy, overlapping with: heavy metals/zinc displacement and childhood/gestational mercury exposures; and model 3 is MCS as evolution and learning. Remarks are offered on current MCS research. Problems with clinical measurement are suggested on the basis of IDS models. Large-sample patient self-report epidemiology is described as an alternative or addition to clinical biomarker and animal testing.


**BACKGROUND:** N-acetyltransferases (NAT) and glutathione S-transferases (GST) are involved in the metabolism of several ubiquitous chemical substances leading to the activation and detoxification of carcinogenic heterocyclic and aromatic amines. Since polymorphisms within these genes are described to influence the metabolism of ubiquitous chemicals, we conducted the present study to determine if individuals with self-reported chemical-related sensitivity differed from controls without self-reported chemical-related sensitivity with regard to the distribution of genotype frequencies of NAT2, GSTM1, GSTT1, and GSTP1 polymorphisms.

**METHODS:** Out of 800 subjects who answered a questionnaire of ten items with regard to their severity of chemical sensitivity 521 unrelated individuals agreed to participate in the study. Subsequently, genetic variants of the NAT2, GSTM1, GSTT1, and GSTP1 genes were analyzed.

**RESULTS:** The results show significant differences between individuals with and without self-reported chemical-related sensitivity with regard to the distribution of NAT2, GSTM1, and GSTT1 gene variants. Cases with self-reported chemical-related sensitivity were significantly more frequently NAT2 slow acetylators (controlled OR = 1.81, 95% CI = 1.27-2.59, P = 0.001). GSTM1 and GSTT1 genes were significantly more often homozygously deleted in those individuals reporting sensitivity to chemicals compared to controls (GSTM1: controlled OR 2.08, 95% CI = 1.46-2.96, P = 0.0001; GSTT1: controlled OR = 2.80, 95% CI = 1.65-4.75, P = 0.0001). Effects for GSTP1 gene variants were observed in conjunction with GSTM1, GSTT1 and NAT2 gene. **CONCLUSION:** The results from our study population show that individuals being slow acetylators and/or harbouring a homozygous GSTM1 and/or GSTT1 deletion reported chemical-related hypersensitivity more frequently.

Objective: To examine analytically the question of whether the characterization of somatoform disorders (SFDs) in Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) provides adequate grounds for classifying them as mental disorders rather than as physical disorders.

Methods: Analytical examination.

Results: There are prima facie grounds for classifying SFDs as physical disorders since they are characterized by physical symptoms. The characterization of SFDs in DSM-IV does not provide adequate grounds for classifying them as mental disorders.

Conclusion: The spectrum of SFDs is drawn too widely in DSM-IV. At least some of the conditions now listed as SFDs in DSM-IV should be either given a dual diagnosis or classified simply as physical disorders.


Multiple chemical sensitivity (MCS) is characterized by chemically induced symptoms from multiple organ systems. No consistent physical findings or laboratory abnormalities have been determined for the associated symptoms. Twelve patients with chemically induced airway symptoms, who satisfied Cullen’s criteria for MCS, were provoked double-blind, randomized with saline and three increments of inhaled capsaicin. The recordings were compared with those of a control group of healthy individuals. The results found that the patients coughed more than the control subjects at each dose of capsaicin (P < 0.05 for 0.4 _mol/L capsaicin and P < 0.005 for 2 _mol/L and 10 _mol/L). The capsaicin provocation also induced significantly more symptoms in patients with MCS. We conclude that airway sensory reactivity is increased in patients with MCS, a finding which suggests that neurogenic factors may be of importance in this condition.


Four groups of patients with long-term inhalation exposure to formaldehyde (HCHO) were compared with controls who had short-term periodic exposure to HCHO. The following were determined for all groups: total white cell, lymphocyte, and T cell counts; T helper/suppressor ratios; total Ta1+, IL2+, and B cell counts; antibodies to formaldehyde-human serum albumin (HCHO-HSA) conjugate and autoantibodies. When compared with the controls, the patients had significantly higher antibody titers to HCHO-HSA. In addition, significant increases in Ta1+, IL2+, and B cells and autoantibodies were observed. Immune activation, autoantibodies, and anti-HCHO-HSA antibodies are associated with long-term formaldehyde inhalation.

The health effects of low-dose occupational exposure to organic solvents remains unclear. A cross-sectional survey was conducted among 762 male printing workers to assess the impacts of exposure to mixtures of n-hexane, toluene, isopropyl alcohol, and benzene on neurological and other symptoms. After controlling for age, smoking, alcohol drinking, past exposure history, working hours and shift work, current exposure to solvent mixtures was significantly associated with the total number of neurological symptoms and with the prevalence of specific symptoms of the nervous system and mucous membrane irritation. The adjusted odds ratio of neurovegetative lability (1.7–5.9), abnormal or reduced smell (1.6–4.1), memory loss (1.8), and mucous membrane irritation symptoms (1.5–4.6) significantly increased in the exposed group, especially when the summation index of exposure exceeded one.


BACKGROUND: Published epidemiological information relating the effects of occupational exposure to organic solvents (OS) to olfaction is limited. AIMS: The objectives of this pilot study were to measure the chemosensory abilities of medical laboratory employees occupationally exposed to OS mixtures, to compare these with control workers employed within the same occupational setting and to correlate chemosensory performance with OS exposure history and with employees' hedonic (pleasantness) perceptions about workplace OS odors. METHODS: Twenty-four medical laboratory employees (OS-exposed technicians plus control workers minimally exposed to OS) completed a health-related questionnaire, a test of pyridine odor detection threshold, along with a gustatory detection threshold test involving aqueous quinine solutions. Estimates of cumulative hours of OS exposure (CSI) were calculated from self-reports. RESULTS: OS-exposed laboratory technicians detected weaker concentrations of pyridine odor. Positive correlations were detected between CSI estimates to both pyridine detection and the degree that participants reported that OS odors were present in the workplace. However, no association was detected between pyridine detection and how unpleasant workplace OS odors were perceived. The OS-exposed participants were able to detect weaker concentrations of quinine. Compared to controls, OS-exposed workers complained more of experiencing several symptoms while working, including headaches, nasal irritation and mild cognitive impairment. CONCLUSIONS: The results of this cross-sectional pilot study indicated that, compared to controls, medical laboratory technicians exposed to low-level OS mixtures displayed evidence of elevated olfactory sensitivity (hyperosmia) to pyridine odor. The relation of this study's results to chemical intolerance warrants further investigation.


Exposures which can induce multiple chemical sensitivity (MCS) involve symptomatic, usually repeated, exposures to pesticides, solvents, combustion products, remodeling, sick buildings, carbonless copy paper (occupational heavy use) and other irritants and petrochemicals.
Accompanying toxic injury often involves the immune, endocrine and nervous systems as well as impairments in detoxification, energy and neurotransmitter metabolism, protein, mineral, and other nutrient deficiencies and gastrointestinal changes such as candida, parasites, reduced chymotrypsin (marker enzyme for reduced pancreatic enzyme function), gluten intolerance, and reduced Secretory IgA. Chronic cortisol elevation leading to adrenal insufficiency if not corrected is common. Such elevation can lead to protein and mineral deficiencies with increased osteoporosis and reduced steroid precursors for normal estrogen and testosterone production. Detoxification changes often involve reduction in one or more Phase II pathways which causes excess free radical production. Impaired digestive enzymes can reduce breakdown of foods, with larger more antigenic molecules being absorbed and consequent food intolerances. Many of these conditions are treatable. There is extensive overlap of MCS with Chronic Fatigue Syndrome and Fibromyalgia which may be one condition in many cases. Current occupational exposure limits are not health based and thus may not prevent MCS and are totally inadequate to accommodate sensitive persons. Warning symptoms indicating increased risk for MCS onset include repeated headache, eye and respiratory irritation and fatigue. Eliminating exposures which cause repeated symptoms is a critical strategy for preventing sensitization and MCS. It also significantly reduces the degree of disability in persons with MCS, the single most important factor from the literature. Affected persons with disability can utilize the Americans With Disability Act to request reasonable accommodations for work, home (condo, apartment), and school.


Patients reporting sensitivity to multiple chemicals at levels usually tolerated by the healthy population were administered standardized questionnaires to evaluate their symptoms and the exposures that aggravated these symptoms. Many patients were referred for medical tests. It is thought that patients with chemical sensitivity have organ abnormalities involving the liver, nervous system (brain, including limbic, peripheral, autonomic), immune system, and porphyrin metabolism, probably reflecting chemical injury to these systems. Laboratory results are not consistent with a psychologic origin of chemical sensitivity. Substantial overlap between chemical sensitivity, fibromyalgia, and chronic fatigue syndrome exists: the latter two conditions often involve chemical sensitivity and may even be the same disorder. Other disorders commonly seen in chemical sensitivity patients include headache (often migraine), chronic fatigue, musculoskeletal aching, chronic respiratory inflammation (rhinitis, sinusitis, laryngitis, asthma), attention deficit, and hyperactivity (affected younger children). Less common disorders include tremor, seizures, and mitral valve prolapse. Patients with these overlapping disorders should be evaluated for chemical sensitivity and excluded from control groups in future research. Agents whose exposures are associated with symptoms and suspected of causing onset of chemical sensitivity with chronic illness include gasoline, kerosene, natural gas, pesticides (especially chlordane and chlorpyrifos), solvents, new carpet and other renovation materials, adhesives/glues, fiberglass, carbonless copy paper, fabric softener, formaldehyde and glutaraldehyde, carpet shampoos (lauryl sulfate) and other cleaning agents, isocyanates, combustion products (poorly vented gas heaters, overheated batteries), and medications (dinitrochlorobenzene for warts, intranasally packed neosynephrine, prolonged antibiotics, and general anesthesia with petrochemicals). Multiple mechanisms of chemical injury that magnify
response to exposures in chemically sensitive patients can include neurogenic inflammation (respiratory, gastrointestinal, genitourinary), kindling and time-dependent sensitization (neurologic), impaired porphyrin metabolism (multiple organs), and immune activation.
Appendix: Related Articles


To evaluate whether emissions of a commercial air freshener produced acute toxic effects in a mammalian species, the authors allowed male Swiss-Webster mice to breathe the emissions of one commercial-brand solid air freshener for 1 h. Sensory irritation and pulmonary irritation were evaluated with the ASTM-E-981 test. A computerized version of this test measured the duration of the break at the end of inspiration and the duration of the pause at the end of expiration--two parameters subject to alteration via respiratory effects of airborne toxins. Measurements of expiratory flow velocity indicated changes in airflow limitation. The authors then subjected mice to a functional observational battery, the purpose of which was to probe for changes in nervous system function. Emissions of this air freshener at several concentrations (including concentrations to which many individuals are actually exposed) caused increases in sensory and pulmonary irritation, decreases in airflow velocity, and abnormalities of behavior measured by the functional observational battery score. The test atmosphere was subjected to gas chromatography/mass spectroscopy, and the authors noted the presence of chemicals with known irritant and neurotoxic properties. The Material Safety Data Sheet for the air freshener indicated that there was a potential for toxic effects in humans. The air freshener used in the study did not diminish the effect of other pollutants tested in combination. The results demonstrated that the air freshener may have actually exacerbated indoor air pollution via addition of toxic chemicals to the atmosphere.


To evaluate whether fragrance products can produce acute toxic effects in mammals, we allowed groups of male Swiss-Webster mice to breathe the emissions of five commercial colognes or toilet water for 1 h. We used the ASTM-E-981 test method to evaluate sensory irritation and pulmonary irritation. We used a computerized version of this test to measure the duration of the break at the end of inspiration and the duration of the pause at the end of expiration. Decreases in expiratory flow velocity indicated airflow limitation. We subjected the mice to a functional observational battery to probe for changes in nervous system function. The emissions of these fragrance products caused various combinations of sensory irritation, pulmonary irritation, decreases in expiratory airflow velocity, as well as alterations of the functional observational battery indicative of neurotoxicity. Neurotoxicity was more severe after mice were repeatedly exposed to the fragrance products. Evaluation of one of the test atmospheres with gas chromatography/mass spectrometry revealed the presence of chemicals for which irritant and neurotoxic properties had been documented previously. In summary, some fragrance products emitted chemicals that caused a variety of acute toxicities in mice.

To determine whether there is any biological basis for complaints that fabric softener emissions can cause acute adverse effects in certain individuals, screening tests were performed in which groups of mice were exposed to the emissions of 5 commercial fabric softener products (antistatic pads used in laundry dryers) for 90 min. Pneumotachographs and a computerized version of ASTM test method E-981 were used to measure acute changes in several respiratory cycle parameters, especially the pause after inspiration, the pause after expiration, and the midexpiratory airflow velocity. From these changes, sensory irritation (SI), pulmonary irritation (PI), and airflow limitation (AFL) of differing intensities were measured with each of the five brands tested. At the peak effect, SI ranged from 21 to 58% of the breaths, PI ranged from 4 to 23% of the breaths, and AFL ranged from 6 to 32% of the breaths. After three exposures, histopathology revealed mild inflammation of interalveolar septae of the lungs. Gas chromatography/mass spectroscopy (GC/MS) analysis of the emissions of one pad identified several known irritants (isopropylbenzene, styrene, trimethylbenzene, phenol, and thymol). Laundry that had been dried with one the fabric softener pads emitted sufficient chemicals to elicit SI in 49% of breaths at the peak effect. Placing one fabric softener pad in a small room overnight resulted in an atmosphere that caused marked SI (61% of breaths). These results demonstrate that some commercial fabric softeners emit mixtures of chemicals that can cause SI, PI, and reduce midexpiratory airflow velocity in normal mice. The results provide a toxicological basis to explain some of the human complaints of adverse reactions to fabric softener emissions.


Mice were monitored with pneumotachographs while they breathed emissions of three brands of disposable diapers (described herein as brands A, B, and C) and one brand of cloth diapers for 1 hr. The authors used a computerized version of the ASTM-E-981 test method to measure changes in the pattern and frequency of respiration. In response to two brands of disposable diapers, many mice exhibited reduced mid-expiratory airflow velocity, sensory irritation, and pulmonary irritation. During the peak effects, brand A caused sensory irritation in 47% of the breaths and reduced mid-expiratory airflow velocity in 17% of the breaths (n = 39 mice), whereas the respective percentages noted for brand B were 20% and 15% of the breaths (n = 28 mice). The effects were generally larger during repeat exposures to these emissions, with up to 89% of breaths showing sensory irritation in response to brand A and up to 35% of breaths showing reduced mid-expiratory airflow velocity with brand B. A third brand of disposable diapers caused increases in respiratory rate, tidal volume, and mid-expiratory airflow velocity. The emissions of cloth diapers produced only slight SI and slight PI. Chemical analysis of the emissions revealed several chemicals with documented respiratory toxicity. The results demonstrate that some types of disposable diapers emit mixtures of chemicals that are toxic to the respiratory tract. Disposable diapers should be considered as one of the factors that might cause or exacerbate asthmatic conditions.
To evaluate complaints of adverse reactions to marking pen emissions, groups of mice were exposed for 1 h to the emissions of 8 brands of felt-tip markers or white-board cleaner. Pneumotachographs and a computerized version of ASTM E-981 test method were used to measure changes in respiration. Sensory irritation (SI), pulmonary irritation (PI), and/or air flow limitation (AFL) of differing intensities were documented with each of the eight brands tested. At the peak of the effects, the largest SI was observed with pen F (72% of the breaths); the largest PI occurred with pen D (13% of the breaths), and the largest AFL was seen with pen F (25% of the breaths). Pens G and H produced minimal SI, PI, or AFL. A functional observational battery was used to screen for signs of neurotoxicity. Emissions from all eight of the pens produced behavioral abnormalities such as altered posture and gait, tremors, falling, and hyperactivity. The exposure concentrations were similar to the total volatile organic compounds (TVOC) values near marking pens in actual use. Gas chromatography identified mixtures of alcohols, acetates, and/or ketones. Exposures to white-board cleaner solution resulted in similar toxicity (SI, PI, AFL, and neurotoxicity). These results document that some marking pens and white-board cleaner emit mixtures of chemicals that can produce acute respiratory toxicity and acute behavioral abnormalities in normal mice. These results provide a toxicological explanation for some of the human complaints concerning respiratory and neurological reactions to marking pen emissions.


Groups of male Swiss-Webster mice breathed emissions of several brands of crib mattresses for two 1-hr periods. The authors used a computerized version of ASTM-E-981 test method to monitor respiratory frequency, pattern, and airflow velocity and to diagnose abnormalities when statistically significant changes appeared. The emissions of four mattresses caused various combinations of upper-airways irritation (i.e., sensory irritation), lower-airways irritation (pulmonary irritation), and decreases in mid-expiratory airflow velocity. At the peak effect, a traditional mattress (wire springs with fiber padding) caused sensory irritation in 57% of breaths, pulmonary irritation in 23% of breaths, and airflow decrease in 11% of breaths. All mattresses caused pulmonary irritation, as shown by 17-23% of breaths at peak. The largest airflow decrease (i.e., affecting 26% of the breaths) occurred with a polyurethane foam pad covered with vinyl. Sham exposures produced less than 6% sensory irritation, pulmonary irritation, or airflow limitation. Organic cotton padding caused very different effects, evidenced by increases in both respiratory rate and tidal volume. The authors used gas chromatography/mass spectrometry to identify respiratory irritants (e.g., styrene, isopropylbenzene, limonene) in the emissions of one of the polyurethane foam mattresses. Some mattresses emitted mixtures of volatile chemicals that had the potential to cause respiratory-tract irritation and decrease airflow velocity in mice.
To evaluate factors that might contribute to the rise in prevalence of childhood asthma, we allowed groups of male Swiss-Webster mice to breathe the emissions of six brands of waterproof crib mattress covers for 1 h. We used a computerized version of ASTM-E-981 test method to monitor respiratory frequency, pattern, and airflow velocity. Single exposure to the emissions of these mattress covers caused various combinations of sensory irritation, pulmonary irritation, and decreases in mid-expiratory airflow velocity. At the peak effects of these emissions, sensory irritation ranged from 9% to 51% of the breaths, pulmonary irritation ranged from 4% to 16% of the breaths, and airflow limitation ranged from 9% to 38% of the breaths. Three brands caused airflow limitation that persisted for at least 24 h after a single 1-h exposure of naive mice to these emissions. Repeat exposures to the emissions of four brands caused more marked effects (i.e., up to 96% of the breaths showing sensory irritation, up to 44% of the breaths showing pulmonary irritation, and up to 75% of the breaths showing airflow limitation). Histological evaluation of the lungs revealed a mild inflammatory response, with focal collections of polymorphonuclear leukocytes and edema, but there were no eosinophils and no bronchial mucosa changes. We used gas chromatography/mass spectrometry to evaluate one of the test atmospheres, and there was evidence of chemicals for which toxic properties have been documented previously. The results of our study demonstrated that some mattress covers emit mixtures of chemicals that can cause a variety of acute toxic effects in mice, including asthma-like reactions.


Products containing scent are a part of daily life. The majority of cosmetics, toiletries, household and laundry products contain fragrance. In addition, there is exposure to fragrance from products that are used to scent the air, such as air fresheners and fragranced candles. In spite of this widespread use and exposure, there is little information available on the materials used in fragrance. Fragrance formulas are considered trade secrets and components that make up the fragrance portion of the product are not revealed on labels. Fragrance is increasingly cited as a trigger in health conditions such as asthma, allergies and migraine headaches. In addition, some fragrance materials have been found to accumulate in adipose tissue and are present in breast milk. Other materials are suspected of being hormone disruptors. The implications are not fully known, as there has been little evaluation of systemic effects. There are environmental concerns as well, as fragrances are volatile compounds, which add to both indoor and outdoor air pollution. Synthetic musk compounds are persistent in the environment and contaminate waterways and aquatic wildlife. At present there is little governmental regulation of fragrance. The fragrance industry has in place a system of self-regulation. However, the present system has failed to address many of the emerging concerns. Industry needs to responsibly address concerns and ensure that scented products are safe for users, those inadvertently exposed and the environment. It is essential that an industry that is, and wishes to continue to be, self-regulated should identify and address concerns in a forthright and responsible manner.

Institutions are increasingly being asked to accommodate individuals with multiple chemical sensitivity (MCS). Most establishments have chosen to provide such accommodations on a case-by-case basis only. This paper investigates feasible actions that may be taken by institutions to reduce exposure of MCS individuals as well as the general institutional population to pesticides and other substances. Emphasis is placed on procedures that can be instituted on a regular basis and may be combined with case-by-case management for better resolution of problems.


Exposure to volatile organic compounds (VOCs) in the indoor environment has received substantial research attention in the past several years, with the goal of better understanding the impact of such exposures on human health and well-being. Many VOCs can arise from consumer products used within the indoor environment. The VOCs emitted from five representative consumer products were collected onto Tenax-GC and subjected to thermal desorption and analysis by gas chromatography, in combination with low-resolution mass spectrometry (MS), high-resolution MS, and matrix-isolation Fourier transform infrared spectroscopy for structural characterization. An emphasis was placed on the polar organic compounds often used to provide fragrance in these products. The structures of a number of these compounds were confirmed, and an electronic literature search was carried out on them to determine any known toxic properties. The search revealed that many of the VOCs possess toxic properties when studied at acute, relatively high-level exposures. In addition, toxic effects were reported for a few of the chemicals, such as benzaldehyde, alpha-terpineol, benzyl acetate, and ethanol, at relatively low dose levels of 9-14 mg/kg. In general, the data were unclear as to the effect of chronic, low-level exposures. The widespread use of such chemicals suggests that the health effects of chronic exposures need to be determined. Validated analytical methods for the quantitative characterization of polar organic compounds at low concentrations will be required to make such work possible.


Ozone-driven chemistry is a source of indoor secondary pollutants of potential health concern. This study investigates secondary air pollutants formed from reactions between constituents of household products and ozone. Gas-phase product emissions were introduced along with ozone at constant rates into a 198-L Teflon-lined reaction chamber. Gas-phase concentrations of reactive terpenoids and oxidation products were measured. Formaldehyde was a predominant oxidation byproduct for the three studied products, with yields for most conditions of 20-30% with respect to ozone consumed. Acetaldehyde, acetone, glycolaldehyde, formic acid, and acetic acid were each also detected for two or three of the products. Immediately upon mixing of
reactants, a scanning mobility particle sizer detected particle nucleation events that were followed by a significant degree of secondary particle growth. The production of secondary gaseous pollutants and particles depended primarily on the ozone level and was influenced by other parameters such as the air-exchange rate. Hydroxyl radical concentrations in the range 0.04-200 x 10^5 molecules cm(-3) were determined by an indirect method. OH concentrations were observed to vary strongly with residual ozone level in the chamber, which was in the range 1-25 ppb, as is consistent with expectations from a simplified kinetic model. In a separate chamber study, we exposed the dry residue of two products to ozone and observed the formation of gas-phase and particle-phase secondary oxidation products.


Phthalates are multifunctional chemicals used in a variety of applications, including personal care products. The present study explored the relationship between patterns of personal care product use and urinary levels of several phthalate metabolites. Subjects include 406 men who participated in an ongoing semen quality study at the Massachusetts General Hospital Andrology Laboratory between January 2000 and February 2003. A nurse-administered questionnaire was used to determine use of personal care products, including cologne, aftershave, lotions, hair products, and deodorants. Phthalate monoester concentrations were measured in a single spot urine sample by isotope dilution-high-performance liquid chromatography coupled to tandem mass spectrometry. Men who used cologne or aftershave within 48 hr before urine collection had higher median levels of monoethyl phthalate (MEP) (265 and 266 ng/mL, respectively) than those who did not use cologne or aftershave (108 and 133 ng/mL, respectively). For each additional type of product used, MEP increased 33% (95% confidence interval, 14-53%). The use of lotion was associated with lower urinary levels of monobutyl phthalate (MBP) (14.9 ng/mL), monobenzyl phthalate (MBzP) (6.1 ng/mL), and mono(2-ethylhexyl) phthalate (MEHP) (4.4 ng/mL) compared with men who did not use lotion (MBP, 16.8 ng/mL; MBzP, 8.6 ng/mL; MEHP, 7.2 ng/mL). The identification of personal care products as contributors to phthalate body burden is an important step in exposure characterization. Further work in this area is needed to identify other predictors of phthalate exposure.


Four outcomes that evidence suggests are candidates for "environmental causation" were chosen for analysis: diabetes, Parkinson's disease (PD), neurodevelopmental effects and hypothyroidism, and deficits in intelligence quotient (IQ). These are an enormous burden in the United States, Canada, and other industrial countries. We review findings on actual social and economic costs, construct estimates of some of the costs from pertinent sources, and provide several hypothetical examples consistent with published evidence. Many detailed costs are estimated, but these are fragmented and missing in coverage and jurisdiction. Nonetheless, the cumulative costs identified are very large, totaling $568 billion to $793 billion per year for Canada and the United States combined. Partial Canadian costs alone are $46 billion to $52 billion per year. Specifics
include diabetes (United States and Canada), $128 billion per year; PD in the United States, $13 billion to $28.5 billion per year; neurodevelopmental deficits and hypothyroidism are endemic and, including estimates of costs of childhood disorders that evidence suggests are linked, amount to $81.5 billion to $167 billion per year for the United States and $2 billion per year in Ontario; loss of 5 IQ points cost $30 billion per year in Canada and $275 billion to $326 billion per year in the United States; and hypothetical dynamic economic impacts cost another $19 billion to $92 billion per year for the United States and Canada combined. Reasoned arguments based on the weight of evidence can support the hypothesis that at least 10%, up to 50% of these costs are environmentally induced--between $57 billion and $397 billion per year.


Fragranced consumer products—such as air fresheners, laundry supplies, personal care products, and cleaners—are widely used in homes, businesses, institutions, and public places. While prevalent, these products can contain chemicals that are not disclosed to the public through product labels or material safety data sheets (MSDSs). What are some of these chemicals and what limits their disclosure? This article investigates these questions, and brings new pieces of evidence to the science, health, and policy puzzle. Results from a regulatory analysis, coupled with a chemical analysis of six best-selling products (three air fresheners and three laundry supplies), provide several findings. First, no law in the U.S. requires disclosure of all chemical ingredients in consumer products or in fragrances. Second, in these six products, nearly 100 volatile organic compounds (VOCs) were identified, but none of the VOCs were listed on any product label, and one was listed on one MSDS. Third, of these identified VOCs, ten are regulated as toxic or hazardous under federal laws, with three (acetaldehyde, chloromethane, and 1,4-dioxane) classified as Hazardous Air Pollutants (HAPs). Results point to a need for improved understanding of product constituents and mechanisms between exposures and effects.


United States environmental regulations, intended to protect human health, generally fail to address major sources of pollutants that endanger human health. These sources are surprisingly close to us and within our control, such as consumer products and building materials that we use within our homes, workplaces, schools, and other indoor environments. Even though these indoor sources account for nearly 90% of our pollutant exposure, they are virtually unregulated by existing laws. Even pollutant levels found in typical homes, if found outdoors, would often violate federal environmental standards. This article examines the importance of human exposure as a way to understand and reduce effects of pollutants on human health. Results from exposure studies challenge traditional thinking about pollutant hazards, and reveal deficiencies in our patchwork of laws. And results from epidemiological studies, showing increases in exposure-related diseases, underscore the need for new protections. Because we cannot rely solely on regulations to protect us, and because health effects from exposures can develop insidiously, greater efforts are needed to reduce and prevent significant exposures before they occur. Recommendations include the development and use of safer alternatives to common products,
public education on ways to reduce exposure, systematic monitoring of human exposure to pollutants, and a precautionary approach in decision-making.


Over the past half-century there have been major changes in building materials and consumer products used indoors. Composite-wood, synthetic carpets, polymeric flooring, foam cushioning, plastic items and scented cleaning agents have become ubiquitous. The same is true for mechanical and electrical appliances such as washer/dryers, TVs and computers. These materials and products emit an array of chemicals including solvents, unreacted monomers, and additives. The consequent changes in emission profiles for indoor pollutants have been accompanied by modifications in building operations. Residences and non-residences are less ventilated than they were decades ago. Air-conditioned buildings are more numerous, especially in certain parts of the world. Most of these recirculate a high fraction of their air. The personal habits of building occupants, including the fraction who smoke indoors, have also changed. Taken together, these changes have altered the kind and concentrations of chemicals that occupants are exposed to in their homes, workplaces and schools. Since the 1950s, levels of certain indoor pollutants (e.g., formaldehyde, aromatic and chlorinated solvents, chlorinated pesticides, PCBs) have increased and then decreased. Levels of other indoor pollutants have increased and remain high (e.g., phthalate esters, brominated flame-retardants, nonionic surfactants and their degradation products). Many of the chemicals presently found in indoor environments, as well as in the blood and urine of occupants, were not present 50 years ago. Given the public’s exposure to such species, there would be exceptional value in monitoring networks that provided cross-sectional and longitudinal information regarding pollutants found in representative buildings.
