SYMPTOMATIC RESPONSES TO LOW-LEVEL OCCUPATIONAL AND ENVIRONMENTAL EXPOSURES

BRIAN LINDE, MD, MPH AND CARRIE A. REDLICH, MD, MPH

1 INTRODUCTION

There are individuals who experience symptom responses at low levels of exposure (i.e. exposures at levels below those generally considered toxic). Though enigmatic and at times controversial, there is a basis of plausibility for these reactions. For any given exposure, interindividual variability in responsiveness exists, such that there is a proportion of individuals who demonstrate heightened responses compared to others. In addition, there is an increasing awareness that mixed exposures can produce different dose–response curves than of the isolated single exposures that have historically been the focus of laboratory investigation and regulatory efforts. Despite the centrality of the dose–response relationship to the fields of toxicology, industrial hygiene, and occupational health, certain human responses and diseases are not easily explained by traditional dose–response relationships.

Workers with symptomatic responses or sensitivity to low-level exposures are particularly challenging for occupational health and safety professionals as such exposures are difficult to avoid and well below regulatory limits such as threshold limit values (TLVs) or lowest observed effect levels (LOELs). Nonetheless, a better understanding of low-level exposures is of great importance given that the symptoms experienced, whether they reflect a well-identified pathology or not, can impact health and lead to substantial disability.

This chapter provides an overview of the clinical presentation of symptomatic responses to low-level exposures, the epidemiology, disease mechanisms, clinical evaluation, and treatment options. Not included in the discussion are the better characterized immunological conditions caused by low-dose exposures such as acute allergic reactions, occupational asthma, chronic beryllium disease, hypersensitivity pneumonitis, and allergic contact dermatitis. Also not included are approaches to assessing indoor air quality in nonindustrial settings, which is covered in **Indoor Air Quality in Nonindustrial Occupational Environments**.

2 DEFINITION(S)

Recurrent symptomatic responses to low-level work and environmental exposures are common and can generate substantial concern. Such symptomatic responses encompass a broad spectrum of clinical presentations and severity, from mild to disabling. A variety of diagnostic terms have been used to describe these conditions as shown in Table 1. The terms multiple chemical sensitivity (MCS) or idiopathic environmental intolerance have tended to be used for more severe forms of the condition (1–3). Other terms, such as chemical intolerance, environmental sensitivity, or environmental illness, typically are more inclusive of the full range of response severities that have been observed and

Patty's Industrial Hygiene, Seventh Edition. Edited by Barbara Cohrssen.

are encountered in more recent literature (4). One group has employed the term environmental intolerance to encompass chemical sensitivity, building intolerance, electromagnetic hypersensitivity, and sound intolerance (5).

The origins of "chemical intolerance" trace back to the clinical ecology movement of the 1960s (6). Theron Randolph, a Chicago-based physician, described a treatment population with symptoms that included fatigue, confusion, weakness, headache, depression, and anxiety, which he attributed to "food allergies" and everyday exposures to common chemicals (7). Despite controversies surrounding this approach, as increasing numbers of patients with symptoms triggered by low-level environmental exposures continued to be seen in occupational and environmental medicine clinics into the 1980s, there was a need to better define and understand the condition.

In 1987, Cullen defined MCS as "an acquired disorder characterized by recurrent symptoms, referable to multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects. No single widely accepted test of physiologic function can be shown to correlate with symptoms." Cullen identified the following major components:

1. MCS is *acquired* in relation to some documentable environmental exposure(s) that may have initially produced a demonstrable toxic effect. This excludes patients with long-standing health problems who later attribute certain symptoms to chemical exposure.
2. Symptoms involve more than one organ system. This excludes patients with specific more localized symptoms, such as environmentally triggered cough or headache.
3. Symptoms occur in response to predictable, demonstrable environmental stimuli, and improve away from the exposure. The triggers involve multiple exposures, frequently structurally unrelated, and mixed exposures such as cleaning products, gasoline, or new carpeting. The stimuli occur at very low levels, well below the levels known to cause well-defined toxic, or irritant health effects in humans.
4. No widely available diagnostic testing of organ system function, such as pulmonary function testing or standard blood tests, can explain symptoms (8). This definition excludes patients with specific conditions such as asthma or migraines whose symptoms are triggered by environmental exposures.

A variety of additional definitions and diagnostic terms have been put forward in the intervening years to describe patients who respond to low-level work or environmental triggers and lack a clearly defined clinical diagnosis that explains their symptoms (Table 1). The common elements in the majority of existing definitions are (i) patient report of multiple symptoms that are (ii) attributed to low-dose exposures to commonly encountered substances (9). Some definitions also stipulate a minimum duration of symptoms, or chronicity, such as more than six months, and the presence of significantly associated lifestyle or functional impairment (10). The nomenclature "MCS" has been criticized given that the term "sensitivity" implies to many clinicians an allergic immune-mediated process, for which there is no clear evidence, and also because symptoms can be provoked by a variety of exposures in addition to chemicals, such as particulates, fumes, and physical factors such as electromagnetic fields or noise.

TABLE 1 Terms describing symptomatic responses associated with low-level work and environmental exposures.

Chemical hypersensitivity syndrome
Chemical intolerance
Environmental sensitivity
Environmental illness
Environmental irritant syndrome
Idiopathic environmental intolerance
Multiple chemical sensitivity
Nonspecific building-related illness
Sick building syndrome

In 1996, the term idiopathic environmental illness (IEI) was proposed to replace MCS but has not been universally embraced (11). MCS and IEI are often used interchangeably, typically referring to patients with more severe symptoms and associated lifestyle or functional impairment who come to medical attention. In epidemiology research settings, the entity "chemical intolerance" is often assessed with questions such as, "Do chemical odors make you sick?" or "Compared to other people, do you consider yourself allergic or unusually sensitive to everyday chemicals like those in household cleaning products, paints, perfumes, detergents, insect spray and things like that?" (4, 12).

The term building-related illness has been used to indicate disorders related to a specific building, such as an office building or school. These include defined illnesses such as asthma or hypersensitivity pneumonitis, in addition to nonspecific symptoms related to the building, but not linked to a specific disease (13). Nonspecific building-related symptoms have generally replaced the older term "sick building syndrome," as the people in the building have symptoms rather than the building being sick (13). These terms have tended to be used when multiple inhabitants in a single building report symptoms related to a specific building.

TABLE 2 Common symptoms reported in association with low-level work and environmental exposures.

Category	Symptoms triggered by exposure
Cognitive and neurologic symptoms	Headache
	Difficulty with concentration and/or memory
	Lack of coordination or balance
Systemic symptoms	Fatigue
	Tiredness
	Lethargy
Eyes, ears, nose symptoms	Eye irritation: redness, tearing
	Pain in eyes
	Blocked ears
	Stuffy nose
	Sinus and nasal stuffiness, pain, infections
Respiratory symptoms	Cough
	Wheezing
	Shortness of breath
Gastrointestinal symptoms	Nausea
	Bloating
	Reflux
	Abdominal pain
Musculoskeletal symptoms	Joint and muscle pain
	Weakness
Dermatological symptoms	Flushing
	Rashes
	Itching

Similar symptoms occur in all of these environmentally triggered entities, as shown in Table 2. These are primarily cognitive-neurological (e.g. headache and concentration difficulties), mucosal, and airway-related (e.g. eye irritation, cough, nasal congestion, throat irritation) and neuromuscular (e.g. weakness, clumsiness, numbness) (7, 8, 10, 14). Additional symptoms include nausea, fatigue, malaise, and digestive complaints (Table 2). Symptom severity can range from mild in chemical or environmental intolerance to debilitating in severe MCS.

Chemical intolerance and MCS share similarities with other conditions that involve nonspecific symptoms that cannot be explained in terms of traditional medical diagnoses, also termed "medically unexplained symptoms" or "functional somatic syndromes." These syndromes include chronic fatigue syndrome, fibromyalgia, chronic Lyme disease, and gulf war-related illnesses (15, 16). A fundamental difference with these conditions is that with chemical intolerance, MCS and IEI the symptoms are triggered by low-level exposures, rather than being present irrespective of environmental triggers.

A large number of diverse substances and exposure settings are reported to trigger symptoms; most are usually airborne and frequently associated with an odor (Table 3). Major categories include: industrial and household chemicals (including solvents), pesticides, motor vehicle exhaust, wood smoke, cigarette smoke, cleaning products, freshly printed papers or magazines, perfumes, and fragrances (17–19). Noise and electromagnetic fields have also been reported (20). These exposures can occur in a range of settings, from industrial workplaces to office and home environments (18). Triggering exposures can shift over time with changing technologies and lifestyles. A recent study from Japan found that compared to the period 1999–2003, from 2012 to 2015 the proportion of patients affected by insecticides and second-hand smoke decreased, while the proportion of patients affected by electromagnetic fields and perfumes and scented products increased (21).

TABLE 3 Common work and environmental triggers.

Diesel or gasoline exhaust
Tar, asphalt
Insecticides and pesticides
Paint, paint thinner, solvents
Cleaning products
Fragrances, air fresheners
Tobacco smoke
Salon products, nail polish, hairspray
Construction, renovation, and repair work
Adhesive, glue, coatings
New furnishings, carpeting

Commonly patients will attribute the onset of their symptoms to a specific atypical higher exposure event, such as an acute accidental spill or a specific construction or remodeling event. After such an event they develop recurrent symptoms to lower-level exposures (22). Symptomatic responses may initially occur to a small number of triggering exposures and over time "spread" to an increasing number of, often unrelated substances, such as perfumes and cigarette smoke (23).

In this chapter, the terms MCS, IEI, and chemical intolerance will be used somewhat interchangeably, as they all describe the spectrum of individuals with symptomatic responses to low-level exposures, and the literature has not consistently differentiated these different terms. MCS and IEI will generally be used when referring to patients with more severe symptoms and chemical intolerance will be used as a broader term that also includes those with milder symptoms.

Two case examples will serve to illustrate the spectrum of clinical presentations of chemical intolerance.

3 CASE EXAMPLES

3.1 Case 1

A 37-year-old female English professor experienced an accidental chlorine exposure when a cleaning product spill occurred at work. In the immediate period, she reported facial and eye irritation, and cough. Over the ensuing months, her symptoms progressively worsened to include general weakness, headache, and difficulty concentrating, and she developed these symptoms after exposures such as perfume, gasoline, household cleaning products, and cigarette smoke. Extensive medical evaluation was unrevealing. The patient ultimately lost her job as she was no longer able to regularly go to class or grade exams. She avoided triggering exposures and began working with a cognitive-behavioral therapist. These measures increased her functionality to the point where she could teach part-time. Ten years later, she continues to teach part-time at a well-maintained school that follows "green cleaning" practices. She continues to avoid triggers such as car fumes or perfumed products and has gradually been able to resume other activities, such as grocery shopping and socializing more.

3.2 Case 2

A 51-year-old female nurse at a local hospital was in excellent health on the day she began to notice an unusual odor coming through the ventilation system at her desk. She traced the source of these odors to the installation of new carpeting in a nearby unit. She reported symptoms of redness in her eyes and nose, headaches, vertigo, nausea, and burning sensation in her lungs, which improved away from exposure. Medical evaluation, including spirometry testing and physical examination, was unremarkable. Other employees experienced similar types of symptoms immediately after the new carpeting, which resolved after a few days. However, the nurse developed recurrent symptoms each time she returned to her office. She was relocated to a new work area and was able to continue to perform the duties of her job effectively for the next several years until another major renovation was performed at the hospital. Her work-related symptoms, such as headache, eye irritation, dizziness, and fatigue returned. Her employer tried to make accommodations, but her symptoms became more debilitating and were triggered by an ever-increasing number of previously tolerated exposures, including routine dusts, perfumes, and cleaning products. Although the renovation project was completed, she was unable to return to work due to her recurrent symptoms. She is trying to find work she can do in her home. She now avoids travel and public places in order to reduce triggering exposures, ordering all needed groceries and supplies to be delivered to her home. As a result, her financial, personal, and family relationships have deteriorated.

4 EPIDEMIOLOGY

Over the past 30 years, clinical and epidemiology studies have better defined the spectrum and prevalence of chemical sensitivity. These studies have generally made a distinction between chemical sensitivity, an umbrella term describing the subjective experience of symptoms in response to low levels of exposure, and MCS, a more severe and at times debilitating manifestation of chemical intolerance for which typically the person has sought medical evaluation. Initial research on the prevalence of MCS primarily included self-selected subjects, such as those drawn from a medical clinic population (18, 19, 24), before randomly selected, population-based studies were initiated (25).

Population-based studies in the United States have generally shown variable prevalence of chemical sensitivity with lower prevalence for physician-diagnosed MCS compared to more general chemical sensitivity. For example, one of the earliest population studies done in the United States was a telephone survey of 1446 households in a rural population of eastern North Carolina in 1993 (26). Respondents were asked about becoming sick after exposure to natural things (e.g. pollen, dust, grass, trees, cats, dogs, mold, feathers, food), defined as allergy, as well as chemical odors (e.g. perfume, pesticides, fresh paint, cigarette smoke, new carpets, car exhaust), defined as chemical sensitivity. Allergies were reported by 35% of respondents, chemical sensitivity was reported by 33% of respondents and both allergy and chemical sensitivity was reported by 16.9% (26).

In 1995, questions about chemical sensitivity were added to the California Behavioral Risk Factor Survey (BRFS) (27). In this telephone survey of 4046 subjects, 6.3% of respondents reported a doctor's diagnosis of "environmental illness" or "MCS" and 15.9% reported being "allergic or unusually sensitive to everyday chemicals." This was one of the first estimates of doctor-diagnosed environmental illness/MCS in a population-based survey. Another study of 1582 randomly selected residents of the Atlanta, Georgia metropolitan area between 1999 and 2000, using the same questions as the California Department of Health Services Study, found that 12.6% of respondents reported that, compared with others, they had unusual sensitivity to common chemical products similar to the estimate of 15.9% in California (28). Of note, 13.5% of respondents who reported unusual sensitivity to chemicals reported losing their jobs as a result. A more recent population-based online survey of 1137 individuals selected to be representative of the broader US population found that 12.8% of respondents reported medically diagnosed "multiple chemical sensitivities" and 25.9% reported chemical sensitivity (12),

possibly suggesting an increase in the prevalence of these conditions.

While the studies cited above focused on the United States, multiple large population-based epidemiological studies conducted in Europe, Asia, and Australia have similarly found the prevalence of chemical intolerances to be estimated between 8% and 33% (5, 12, 17, 29–31) depending on the population and definition used. Thus, there is a reliable body of epidemiologic evidence indicating that chemical sensitivities are common, with more severe chemical sensitivities, such as MCS, having a lower prevalence than less severe forms.

5 RISK FACTORS AND COMORBIDITIES

The epidemiologic and clinical literature points to several consistent demographic features of chemical intolerance. There is general agreement that chemical intolerance is more prevalent among women than men (27, 28, 30). In the above household study in North Carolina, 39% of women and 24% of men reported chemical sensitivity (26). In another widely cited study, Bell et al. estimated that women outnumber men in reported environmental illness by a ratio of 2 : 1 (32). MCS is most common between ages 30–50 and less common in persons above 60 years of age (17, 26, 33). Though rare, childhood cases have been reported (34).

Psychiatric comorbidity appears to be another frequent feature of chemical intolerance, with major depression, somatoform disorders, anxiety, and panic disorder being among the most common associated diagnoses (35–40). A review of 12 studies found the prevalence of psychiatric disorders in those diagnosed with IEI ranged from 42% to 100% (35). It is less clear whether psychotic disorders and substance use disorders are linked with chemical intolerance. An important limitation of these estimates is that they likely combine pre-existing psychiatric conditions with psychiatric illnesses that may have developed secondary to the condition (41, 42). Nevertheless, the evidence suggests, even if estimates are overstated, that psychiatric diagnoses are a common comorbidity of chemical intolerances.

There is also a high degree of comorbidity between asthma/allergy and chemical intolerance. A large population-based survey conducted in Sweden found that 38.2% of participants with self-reported chemical intolerance and 63.4% of participants with physician-diagnosed chemical tolerance also had physician-diagnosed asthma and/or allergy (43). Other studies have similarly found a high prevalence of asthma and/or allergy in those with chemical intolerance (14, 44, 45). The implication is that, while it is important to distinguish between the two conditions, it is also important to be aware that they can co-occur. Chamber studies of volatile organic compounds have shown that individuals with atopy respond with more symptoms at lower levels of exposure (46).

6 NATURAL HISTORY

There has been relatively little information published on the natural history of chemical intolerances. Lax and Henneberger's 1995 report on 35 patients meeting the criteria for MCS at the Central New York Occupational Health Clinical Center is one of the earliest publications with data on natural history (19). After a mean follow-up period of 1.4 years (range: 0.4–2.4 years), almost half of the subjects (16 of 35) reported that their MCS improved, even though they also reported an average of 7.4 more symptoms at follow-up than on the initial visit. One of the longest follow-up studies, the Iowa Follow-Up Study of Chemically Sensitive Persons, 1988–1997, reevaluated 18 of the 26 original subjects with MCS/IEI at nine years (47, 48). Global assessment showed that almost all of those reevaluated (16 out of 18) were improved, with five subjects (28%) feeling fully better and only two subjects (11%) still impaired socially and psychiatrically. However, the study was small and almost one-third of the original patients were lost to follow-up.

More recently, Azuma and colleagues conducted a five-year follow-up study of individuals with chemical intolerance in Japan, 2012–2017 (49). Of the 269 subjects with chemical intolerance at baseline, 182 (68%) reported improvement at follow-up. One limitation of the study was a response rate at follow-up of only 37%. Nevertheless, this and other studies indicate that chemical intolerance, although frequently characterized as chronic or even progressing to more debilitating symptoms, particularly in the short term, can in fact improve substantially overtime (49–51). Greater symptom severity as well as time elapsed prior to first clinic appointment may predict likelihood of persistence (19).

7 PATHOGENESIS

Given the large number of environmental stimuli and variability in response symptoms in patients with chemical sensitivities, these conditions likely result from multiple pathways rather than having a single unifying mechanism. Nevertheless, attaining greater understanding of the pathogenesis of symptomatic responses to low-level exposures has practical importance in that this knowledge can inform disease classification as well as prevention and treatment approaches. Not surprisingly there is support for a number of different etiologic mechanisms involving both physiological and psychological pathways.

The following is intended to be an overview, rather than a complete review, of the mechanisms that may underlie

symptomatic responses to low-level exposures. It should be noted that the published literature on this topic has largely focused on MCS and IEI, presumably because milder forms of chemical intolerance are less likely to rise to clinical attention. Nevertheless, the majority of these mechanisms likely are also applicable to chemical intolerance.

7.1 Olfactory Physiology

Given the prominent role of inhalational exposures in chemical intolerance, the olfactory pathway has been a focal point of many of the pathophysiologic theories of chemical intolerance. From an evolutionary standpoint, the olfactory system is considered a phylogenetically older portion of the brain with highly conserved structural and functional features (52). The olfactory system consists of the olfactory epithelium, the main olfactory bulb, and higher brain centers including central nervous system (CNS) limbic circuits (53). Olfactory receptor cells within the olfactory epithelium are specialized neurons with direct connections to the CNS; olfactory nerve fibers connect the olfactory receptor cells to neurons in the olfactory bulb (54). These neurons then converge into olfactory tracts, which connect to higher cortical regions of the brain as well as the limbic system, which supports a variety of functions including emotion and memory. In this way, a simple odor can have far-reaching effects within the CNS.

This direct contact with the external environment is unique within the CNS; in contrast, other CNS neurons are located more centrally. As a result, it is possible for substances to bypass the blood–brain barrier via the olfactory route. This creates the potential for direct action of exogenous chemicals on the CNS. This is limited to some degree by what has been called the "nose–brain barrier," which refers to the inefficiency of transmucosal absorption through the olfactory epithelium (7).

Two other features of the olfactory system are notable. Olfactory neurons are replaced continuously throughout the life span through neurogenesis, presumably owing to their increased susceptibility to injury (7). In addition, the olfactory system displays a high degree of plasticity to enable odor processing and storage of information (learning). These features are important in considering how diverse responses to low levels of inhalational exposures may occur, as well as the inter-individual variability in these responses (55, 56).

The research to date does not support the hypothesis that individuals with chemical intolerance have a heightened sense of smell or lower threshold at which they detect odors or pungency (57–59). Rather, it appears that it is the response to inhaled stimuli that can be highly variable and subject to change. Theories of neural sensitization and neurogenic inflammation have been posited to model this response pathway. It is important to highlight that the term sensitization here is not used in the sense of allergic sensitization, but rather in the general sense of defining a progressive increase in neural response to a stimulus (60).

7.2 Neural Sensitization and Neurogenic Inflammation

The neural sensitization process is described in two phases (61). In the initiation phase, several strong exposures (or repeated low or medium-level exposures) result in a persistent alteration in function (hyper-responsiveness). In the elicitation phase, even weak exposures are capable of provoking a response. Commentators have pointed out parallels with central sensitization theories of pain, such as in fibromyalgia, which are considered functional disorders (62). Spreading can be described as the phenomenon by which exposures unrelated to the initial triggering stimulus begin to elicit a response (63).

One of the main theoretical models for how sensitization occurs in MCS is limbic kindling (64, 65). Kindling has been described in animal models: repeated low-level electrical stimulation applied to specific brain regions results in permanent increases in seizure susceptibility (66). Kindling can also be induced by chemical stimuli: in animal experiments, repeated exposure to certain pesticides has induced behavioral seizures and signs of hyperexcitability in the amygdala.

The hypothesis as applied to MCS states that chemical kindling in the olfactory bulb (at levels below the seizure threshold) leads to alterations in the limbic system that amplify reactivity to low-level chemical exposure. The main strength of this theory is that it provides a model whereby progressive low-level exposures lead to persistent alterations in affective and cognitive behavior (diverse functions mediated by the limbic system). However, limitations are that kindling is a model for epilepsy, and also that it does not explain the multiple symptoms patients typically experience (66).

The understanding of neuro-immune interactions in asthma and other diseases is rapidly expanding (67). Many inhalational exposures directly trigger peripheral nerve receptors in the airways (53, 68). Neuroinflammatory pathways depend on the transient receptor potential (TRP) superfamily of cation channels, including TRP receptors TRPV1 and TRPA1. These receptors are activated by a wide range of chemicals and also physical stimuli, including chemicals at very low concentrations, such as capsaicin, which induces coughing (69). TRPV1 and TRPA1, originally recognized on sensory neurons, are also present in other cell types, such as dendritic cells, endothelial cells, and mast cells (70).

Activation of TRPV1 and TRPA1 also modulates pain, anxiety, and panic responses, in addition to inflammation

(71, 72). These receptors provide a plausible mechanism by which chemical stimuli could trigger diverse symptomatic responses related to multiple sites, such as headaches, airway symptoms, abdominal pain, or anxiety (73–75). Ongoing research is exploring the role of these receptors in chemical intolerance, including capsaicin inhalation challenge testing in MCS patients and controls (76). Polymorphisms in TRPV1 or other receptors may explain individual differences in susceptibility to chemical exposures, such as has been shown with cough sensitivity to capsaicin (77).

There are several general hypotheses for how chemically induced neurogenic airway inflammation could impact other organs. One possibility is that inflammatory signals are sent from the brain to other sites through the sympathetic and parasympathetic nervous system (4). Another hypothesis, termed neurogenic switching, is that a sensory impulse from a site of activation can be rerouted via the CNS to a distant location (78). Finally, it is likely that the underlying inflammation generated by such a process would contribute to increased responsiveness to successive stimuli. That is to say, neurogenic inflammation and neural sensitization may be related processes (4). There is a rapidly expanding understanding of the importance of sensory neuron – immune signaling pathways, including TRP cation channels, and how neuro-immune interactions can mediate immune and inflammatory responses in multiple organs (79).

7.3 Behavioral – Conditioning

The idea of sensitization is distinct from classical conditioning, which has been posited as a behavioral model of chemical intolerance. The conditioning hypothesis states that the symptoms of chemical intolerance reflect conditioned behavior and physiological responses to chemical stimuli (80–82). In this model, a previous pairing of a particular stimulus with a response to a known aversive stimulus (for example, a noxious odor) subsequently results in an aversive response when this particular stimulus is encountered independently in the future. This hypothesis explains responses that are considered atypical, given that the response in question would in fact be typical for the paired stimulus (though it is now absent). Notably, the evidence for this theory comes largely from animal models. An extension of classical conditioning is contextual conditioning in which the location and/or circumstances of the original offending stimulus can, in the future, elicit a response in the absence of the chemical (80).

7.4 Psychological

Several hypotheses lie more firmly in the psychological realm. Some investigators have noted the influence of belief systems in chemical intolerance (83). This can take two forms: (i) belief that an exposure is harmful can alter the individual's response to that exposure (emotional bias), and (ii) heightened concern about the health effects of man-made chemicals and other pollutants can lead to attribution of symptoms to these exposures (attributional bias) and/or heightened focus on one's symptoms (attentional bias) (14, 37, 84–86). Inherent in each of these models is the idea that beliefs shape experience.

Observed similarities between MCS and conditions such as fibromyalgia and chronic fatigue syndrome have led some commentators to suspect a role for somatization in chemical sensitivity (42). Another psychological theory of MCS is that symptoms represent the effects of panic and/or hyperventilation. This theory originates in case reports associating organic solvents with panic attacks (40, 56, 87). Finally, some have considered an atypical variant of posttraumatic stress disorder wherein somatic symptoms follow an acute, traumatic exposure to toxic substances (88).

7.5 Immunological

Finally, there are immunological theories of MCS. Immune mechanisms have been sought in part because they fit with the large degree of interindividual variability in responses to low-level exposures. Some studies have shown altered T-cell subset ratios and immunological regulation in humans following prolonged low-dose exposures to chemicals such as formaldehydes, hydrocarbons, and organochlorines (89, 90). However, attempts to characterize immunological profiles that distinguish MCS patients from controls have been inconsistent and inconclusive (91–93). Similarly, the reproducibility, significance, and specificity of the immunological deviations that have been detected is unclear. As such, the role of the immune system in the pathophysiology of chemical intolerance remains undetermined. Based on the evidence to date, chemical intolerance is not likely to be caused by traditional IgE or cell-mediated allergic mechanisms (94, 95). Given the immune system's role in defending the body from exogenous influences, it is anticipated that research in this area will continue.

It is important to bear in mind that the preceding section describes a number of potential mechanisms that can explain the pathogenesis of chemical intolerance/MCS. Given the wide range of exposures and varied clinical presentations, it can be expected that no single mechanism will fully explain the phenomenon. Rather, it is more plausible that in any given case a combination of interconnected factors results in heightened sensitivity to low-level chemical or environmental exposures and the associated symptoms. Importantly, it is important to recognize that there are many medical

conditions that are recognized and accepted despite uncertainty regarding pathogenesis.

8 CLINICAL EVALUATION

A detailed history, including environmental and work exposures, and medical history, combined with a clinical evaluation to rule out other medical diagnoses, is the cornerstone of the diagnostic approach in suspected chemical intolerance (96–98). Often, but not always, there is an initial, memorable exposure event (99). This should be described in detail, including estimates of the magnitude and duration of exposure. The clinician should identify triggering exposures and settings, associated symptoms, and temporal relationships between exposures and symptoms. It is important not to overlook the possibility of traditional occupational conditions, such as irritant-induced asthma or solvent encephalopathy, as well as exacerbations of underlying disorders, such as environmentally triggered asthma. Such conditions should be ruled out prior to arriving at a diagnosis of chemical intolerance or MCS.

The past medical history should document the patient's health status prior to the onset of chemical intolerance. This includes querying for history of asthma and allergy, as well as any prior reactions or exposure-related health concerns. A thorough occupational history with special attention to past exposures and work-related symptoms and medical absences from prior jobs is also recommended. Abnormal findings on the physical examination suggest other medical conditions.

9 DIAGNOSTIC TESTING

There is no accepted diagnostic test for chemical sensitivity (100). As such, diagnostic testing is primarily performed to rule out known conditions such as asthma, allergy, and established toxicities of the specific exposure in question. Excessive diagnostic testing can reinforce maladaptive illness beliefs (101). It is not uncommon for patients to present to clinic with blood, urine, or hair biomonitoring test results for a wide range of chemical and metal exposures. These results should be put in context and the provider should educate the patient on how to correctly interpret the results.

With regard to more specialized testing, no form of immunological testing has been shown to effectively diagnose MCS or specific chemical exposures (102). Similarly, advanced CNS imaging techniques such as MRI or PET scans have been used in research to evaluate neurologic responses to exposures in subjects and controls. Such CNS testing has had inconsistent findings and is not currently indicated for clinical evaluation (43, 103, 104). In summary, diagnostic testing is done foremost to rule in or out other medical conditions.

10 EXPOSURE ASSESSMENT

If the symptoms are triggered by work exposures, a walk-through assessment of the workplace, with attention to sources of exposure such as irritants and known sensitizers, work processes, recent construction or renovation, odors, and use of cleaning products, is recommended. Temperature, humidity, water problems, the ventilation system, and fresh air intake should also be evaluated. The degree of control the individual has over his/her environment should be noted. Assessing whether other workers are symptomatic is also helpful. Quantifying low-level exposures for the purposes of identifying the causative agent or documenting that the environment is safe is generally not recommended. Care should be taken to transmit exposure information in a nonjudgmental manner and to protect employee privacy regarding any medical information.

11 CLINICAL MANAGEMENT

There are currently no evidence-based medical guidelines regarding management of these conditions. Given the lack of a consensus definition for symptomatic responses to low-level exposures and the heterogeneous nature of chemical intolerances, this is not surprising. However, substantial clinical experience supports that workplace and individual interventions can improve symptoms and enable patients to continue to work. The most common approaches focus on reducing triggering exposures, addressing psychosocial components of illness, and patient education.

11.1 Reducing Exposures

Prudent avoidance of exposures plays an important role. A short period of removal from the environment can help clarify the diagnosis as well as identify triggering exposures and settings. Symptom diaries can be helpful to better understand relevant exposures but can also heighten the individual's attention to symptoms. In general, radical avoidance measures are to be avoided as they are frequently detrimental to quality of life and can even worsen sensitivity in some individuals (105). There is no role for chelation, detoxification regimens, or specific dietary interventions.

The goal is to reduce offending exposures without socially isolating the individual. Efforts to avoid triggers often result in loss of work and isolation from family and friends (85, 93, 106, 107). Modification of the environment, work accommodations, and a strategy of prudent avoidance on the patient's part can be helpful in preserving social and occupational functioning. Balancing the benefits of avoidance with the risk of restriction and isolation is one of the greatest challenges in coping with chemical intolerances (108).

In the workplace, a number of beneficial practices can be implemented to improve indoor air quality and reduce triggering exposures. It is important to ensure ventilation systems are appropriate and well maintained, have adequate fresh air intake, and are not distributing pollutants from other sources inside or outside the building. Use of HEPA filters in the ventilation system can also be helpful. The use of windows and/or exhaust systems, particularly in areas where there is potential for generation of noxious or irritating exposures, is recommended. Institution of fragrance-free and smoke-free workplace policies as well as reduction of cleaning agents, fragranced products, and pesticides are often effective strategies.

With respect to construction and cleaning, providing pre-notification when these activities are scheduled to occur is often a helpful strategy. In these scenarios, administrative controls such as scheduling required work or cleaning at times when the building is not occupied, as well as temporary relocation/accommodation of the employee during planned work can be highly effective. Care should be taken into consideration of the building materials, furnishings, and supplies that will be used. Many nontoxic or less-toxic alternatives are available. The same also applies to the choice of solvents, primers, paints, and stains. The Job Accommodation Network (109) has freely available materials to assist with this process. Strategically timed work breaks and increased work flexibility can be effective strategies as well.

11.2 The Biopsychosocial Approach

When caring for patients, it is important that providers do not let the uncertainties in the precise mechanism and classification of chemical intolerances lead them to doubt the patient's experience of illness as any less real (110, 111). Rather, a nonjudgmental and supportive relationship as part of a biopsychosocial approach to illness is considered to be central to the approach to patients with chemical intolerance (112).

As with many conditions, there are likely multiple pathways contributing to the experience of illness. Spurgeon has proposed two pathways leading from hazard to symptom: a physical pathway consisting of the exposure and underlying biologic vulnerabilities and a psychosocial pathway consisting of contextual factors such as stress, personality, and attitudes (16). A successful approach considers not only the exposures but also these contextual factors.

It is important that the occupational health practitioner establishes goals of therapy and a supportive and trusting rapport. In general, the goal of treatment in symptomatic responses to low-level exposures is control of symptoms rather than cure. Scheduling regular visits can be helpful in building a therapeutic alliance and reinforcing goals of therapy (97). Arguing with patients about their illness beliefs, a practice referred to as contested causation, is counterproductive to partnering with the patient and achieving treatment progress (113).

From a therapeutic standpoint, the psychosocial approach to symptomatic responses to low-level exposures consists of behavioral modification and coping techniques (114). While medical treatment of mental health comorbidities, such as depression or anxiety, is appropriate, there are no pharmacotherapies specifically indicated for chemical intolerance itself (115). There are case reports of efficacious treatment of chemical intolerance; however, many individuals with clinically apparent chemical intolerances are sensitive to medications and averse to medication trials (116).

There are a variety of low-cost techniques that have been used successfully in chemical intolerances. Biofeedback and relaxation methods can be used to address anxiety about exposure and symptoms (96, 117). Additional strategies include joining a support group, prayer and meditation, mind-body therapies such as breathing exercises, and regular exercise (49). These modalities can play an important role in modifying exposure response. In implementing these practices, care should be taken to make one change at a time.

Mindfulness and cognitive-behavioral therapy have been shown to be effective in reducing functional disability in trials of MCS patients and more generally in patients with medically unexplained symptoms (118). Behavioral desensitization involves graduated exposure to odors and other triggers and is often incorporated with cognitive behavior therapy (117, 119). Where possible, increasing an individual's sense of control over their work environment and work organization to reduce stress is encouraged.

Newer treatments, such as pulsed electromagnetic fields, are the subject of ongoing research (120).

11.2.1 Patient Education

Patients with chemical intolerances have frequently sought treatment with environmental and other alternative medicine providers. It is important to review the testing and treatment offered by these providers for unnecessary and/or potentially harmful interventions. This includes expansive biomonitoring panels (for heavy metals, chemicals, metabolites) that are not hypothesis-driven and which often do not have accepted normative values, chelation therapies outside of accepted indications, detoxification and other supplements, and restrictive diets that may pose harm to the individual. Educating patients on how to critically interpret information they are finding online or from other sources and explaining all findings and medical rationale clearly are both beneficial practices in achieving treatment goals.

12 CONCLUSION

Chemical intolerance and chemical sensitivity remain challenging conditions for the patient and provider. Decades of clinical experience with patients that experience symptomatic responses to low-level exposures indicate that, despite uncertainties regarding pathogenic mechanisms, the condition is real and can result in substantial disability. As such, symptoms triggered by low exposures should be taken seriously by treating providers and industrial hygienists, even though such exposures are generally well below regulatory guidelines, if they exist, and will seem nonexistent to others. Work controls and/or accommodations to reduce such triggering exposures can be effective in improving symptoms and reducing lost work time and disability. Personal behavioral and coping strategies can also help patients manage their symptoms. It is important for providers to recognize how isolating the condition can be and to advocate encouraging measures that will keep the individual as integrated into society and their regular daily activities as much as possible. Despite uncertainties and differences in opinion regarding the genesis of chemical intolerance, there is nevertheless much we can still do.

Bibliography

1. Watanabe, M., Tonori, H., and Aizawa, Y. (2003). Multiple chemical sensitivity and idiopathic environmental intolerance (part one). *Environ Health Prev Med* **7** (6): 264–272. doi: 10.1007/BF02908885.
2. Watanabe, M., Tonori, H., and Aizawa, Y. (2003). Multiple chemical sensitivity and idiopathic environmental intolerance (part two). *Environ Health Prev Med* **7** (6): 273–282. doi: 10.1007/BF02908886.
3. Rossi, S. and Pitidis, A. (2018). Multiple chemical sensitivity: review of the state of the art in epidemiology, diagnosis, and future perspectives. *J Occup Environ Med* **60** (2): 138–146. doi: 10.1097/JOM.0000000000001215.
4. Dantoft, T.M., Andersson, L., Nordin, S., and Skovbjerg, S. (2015). Chemical intolerance. *Curr Rheumatol Rev* **11** (2): 167–184.
5. Karvala, K., Sainio, M., Palmquist, E. et al. (2018). Prevalence of various environmental intolerances in a Swedish and Finnish general population. *Environ Res* **161**: 220–228. doi: 10.1016/j.envres.2017.11.014.
6. Shorter, E. (1997). Multiple chemical sensitivity: pseudodisease in historical perspective. *Scand J Work Environ Health* **23** (Suppl 3): 35–42.
7. Ross, P.M., Whysner, J., Covello, V.T. et al. (1999). Olfaction and symptoms in the multiple chemical sensitivities syndrome. *Prev Med* **28** (5): 467–480.
8. Cullen, M.R. (1987). The worker with multiple chemical sensitivities: an overview. *Occup Med* **2** (4): 655–661.
9. Sparks, P.J. (2000). Idiopathic environmental intolerances: overview. *Occup Med* **15** (3): 497–510.
10. Lacour, M., Zunder, T., Schmidtke, K. et al. (2005). Multiple chemical sensitivity syndrome (MCS) – suggestions for an extension of the U.S. MCS-case definition. *Int J Hyg Environ Health* **208** (3): 141–151. doi: 10.1016/j.ijheh.2005.01.017.
11. (1996). Annals of multiple chemical sensitivities: state-of-the-science symposium. Proceedings. Baltimore, Maryland, October 30-November 1, 1995. *Regul Toxicol Pharmacol* **24** (1 Pt 2): S1–S189.
12. Steinemann, A. (2018). National prevalence and effects of multiple chemical sensitivities. *J Occup Environ Med* **60** (3): e152–e156. doi: 10.1097/JOM.0000000000001272.
13. Ahasic, A.M., Redlich, C.A., and Linde, B. (2019). In: *Building-Related Illness and Building-Related Symptoms* (ed. T.W. Post). Waltham, MA: UpToDate.
14. Andersson, M.J., Andersson, L., Bende, M. et al. (2009). The idiopathic environmental intolerance symptom inventory: development, evaluation, and application. *J Occup Environ Med* **51** (7): 838–847. doi: 10.1097/JOM.0b013e3181a7f021.
15. Kipen, H.M. and Fiedler, N. (2002). The role of environmental factors in medically unexplained symptoms and related syndromes: conference summary and recommendations. *Environ Health Perspect* **110** (Suppl 4): 591–595. doi: 10.1289/ehp.02110s4591.
16. Kipen, H.M. and Fiedler, N. (2002). Environmental factors in medically unexplained symptoms and related syndromes: the evidence and the challenge. *Environ Health Perspect* **110** (Suppl 4): 597–599. doi: 10.1289/ehp.02110s4597.
17. Berg, N.D., Linneberg, A., Dirksen, A., and Elberling, J. (2008). Prevalence of self-reported symptoms and consequences related to inhalation of airborne chemicals in a Danish general population. *Int Arch Occup Environ Health* **81** (7): 881–887. doi: 10.1007/s00420-007-0282-0.
18. Cullen, M.R., Pace, P.E., and Redlich, C.A. (1992). The experience of the Yale Occupational and Environmental Medicine Clinics with multiple chemical sensitivities, 1986-1991. *Toxicol Ind Health* **8** (4): 15–19.
19. Lax, M.B. and Henneberger, P.K. (1995). Patients with multiple chemical sensitivities in an occupational health clinic: presentation and follow-up. *Arch Environ Health* **50** (6): 425–431. doi: 10.1080/00039896.1995.9935978.
20. Bell, I.R., Hardin, E.E., Baldwin, C.M., and Schwartz, G.E. (1995). Increased limbic system symptomatology and sensitizability of young adults with chemical and noise sensitivities. *Environ Res* **70** (2): 84–97. doi: 10.1006/enrs.1995.1052.
21. Hojo, S., Mizukoshi, A., Azuma, K. et al. (2018). Survey on changes in subjective symptoms, onset/trigger factors, allergic diseases, and chemical exposures in the past decade of Japanese patients with multiple chemical sensitivity. *Int J Hyg Environ Health* **221** (8): 1085–1096. doi: 10.1016/j.ijheh.2018.08.001.
22. Bell, I.R., Rossi, J. 3rd, Gilbert, M.E. et al. (1997). Testing the neural sensitization and kindling hypothesis for illness from low levels of environmental chemicals. *Environ Health Perspect* **105** (Suppl 2): 539–547. doi: 10.1289/ehp.97105s2539.
23. Winder, C. (2002). Mechanisms of multiple chemical sensitivity. *Toxicol Lett* **128** (1-3): 85–97.

24. Skovbjerg, S., Johansen, J.D., Rasmussen, A. et al. (2009). General practitioners' experiences with provision of healthcare to patients with self-reported multiple chemical sensitivity. *Scand J Prim Health Care* **27** (3): 148–152. doi: 10.1080/02813430902888355.
25. Caress, S.M. and Steinemann, A.C. (2003). A review of a two-phase population study of multiple chemical sensitivities. *Environ Health Perspect* **111** (12): 1490–1497. doi: 10.1289/ehp.5940.
26. Meggs, W.J., Dunn, K.A., Bloch, R.M. et al. (1996). Prevalence and nature of allergy and chemical sensitivity in a general population. *Arch Environ Health* **51** (4): 275–282. doi: 10.1080/00039896.1996.9936026.
27. Kreutzer, R., Neutra, R.R., and Lashuay, N. (1999). Prevalence of people reporting sensitivities to chemicals in a population-based survey. *Am J Epidemiol* **150** (1): 1–12.
28. Caress, S.M. and Steinemann, A.C. (2004). Prevalence of multiple chemical sensitivities: a population-based study in the southeastern United States. *Am J Public Health* **94** (5): 746–747.
29. Azuma, K., Ohyama, M., Azuma, E., and Nakajima, T. (2018). Background factors of chemical intolerance and parent-child relationships. *Environ Health Prev Med* **23** (1): 52. doi: 10.1186/s12199-018-0743-y.
30. Hausteiner, C., Bornschein, S., Hansen, J. et al. (2005). Self-reported chemical sensitivity in Germany: a population-based survey. *Int J Hyg Environ Health* **208** (4): 271–278. doi: 10.1016/j.ijheh.2005.03.006.
31. Jeong, I., Kim, I., Park, H.J. et al. (2014). Allergic diseases and multiple chemical sensitivity in korean adults. *Allergy Asthma Immunol Res* **6** (5): 409–414. doi: 10.4168/aair.2014.6.5.409.
32. Bell, I.R., Schwartz, G.E., Peterson, J.M., and Amend, D. (1993). Self-reported illness from chemical odors in young adults without clinical syndromes or occupational exposures. *Arch Environ Health* **48** (1): 6–13. doi: 10.1080/00039896.1993.9938387.
33. Andersson, L., Johansson, A., Millqvist, E. et al. (2008). Prevalence and risk factors for chemical sensitivity and sensory hyperreactivity in teenagers. *Int J Hyg Environ Health* **211** (5-6): 690–697. doi: 10.1016/j.ijheh.2008.02.002.
34. Woolf, A. (2000). A 4-year-old girl with manifestations of multiple chemical sensitivities. *Environ Health Perspect* **108** (12): 1219–1223. doi: 10.1289/ehp.001081219.
35. Black, D.W. (2000). The relationship of mental disorders and idiopathic environmental intolerance. *Occup Med* **15** (3): 557–570.
36. Bornschein, S., Forstl, H., and Zilker, T. (2001). Idiopathic environmental intolerances (formerly multiple chemical sensitivity) psychiatric perspectives. *J Intern Med* **250** (4): 309–321.
37. Hausteiner, C., Bornschein, S., Zilker, T. et al. (2007). Dysfunctional cognitions in idiopathic environmental intolerances (IEI) – an integrative psychiatric perspective. *Toxicol Lett* **171** (1-2): 1–9. doi: 10.1016/j.toxlet.2007.04.010.
38. Hausteiner, C., Mergeay, A., Bornschein, S. et al. (2006). New aspects of psychiatric morbidity in idiopathic environmental intolerances. *J Occup Environ Med* **48** (1): 76–82. doi: 10.1097/01.jom.0000182207.68987.d7.
39. Johnson, D. and Colman, I. (2017). The association between multiple chemical sensitivity and mental illness: evidence from a nationally representative sample of Canadians. *J Psychosom Res* **99**: 40–44. doi: 10.1016/j.jpsychores.2017.06.002.
40. Tarlo, S.M., Poonai, N., Binkley, K. et al. (2002). Responses to panic induction procedures in subjects with multiple chemical sensitivity/idiopathic environmental intolerance: understanding the relationship with panic disorder. *Environ Health Perspect* **110** (Suppl 4): 669–671. doi: 10.1289/ehp.02110s4669.
41. Davidoff, A.L., Fogarty, L., and Keyl, P.M. (2000). Psychiatric inferences from data on psychologic/psychiatric symptoms in multiple chemical sensitivities syndrome. *Arch Environ Health* **55** (3): 165–175. doi: 10.1080/00039890009603402.
42. Skovbjerg, S., Rasmussen, A., Zachariae, R. et al. (2012). The association between idiopathic environmental intolerance and psychological distress, and the influence of social support and recent major life events. *Environ Health Prev Med* **17** (1): 2–9. doi: 10.1007/s12199-011-0210-5.
43. Lind, N., Soderholm, A., Palmquist, E. et al. (2017). Comorbidity and multimorbidity of asthma and allergy and intolerance to chemicals and certain buildings. *J Occup Environ Med* **59** (1): 80–84. doi: 10.1097/JOM.0000000000000930.
44. Levy, F. (1997). Clinical features of multiple chemical sensitivity. *Scand J Work Environ Health* **23** (Suppl 3): 69–73.
45. Katerndahl, D.A., Bell, I.R., Palmer, R.F., and Miller, C.S. (2012). Chemical intolerance in primary care settings: prevalence, comorbidity, and outcomes. *Ann Fam Med* **10** (4): 357–365. doi: 10.1370/afm.1346.
46. Hodgson, M. (2002). Indoor environmental exposures and symptoms. *Environ Health Perspect* **110** (Suppl 4): 663–667. doi: 10.1289/ehp.02110s4663.
47. Black, D.W., Okiishi, C., and Schlosser, S. (2000). A nine-year follow-up of people diagnosed with multiple chemical sensitivities. *Psychosomatics* **41** (3): 253–261. doi: 10.1176/appi.psy.41.3.253.
48. Black, D.W., Okiishi, C., and Schlosser, S. (2001). The Iowa follow-up of chemically sensitive persons. *Ann N Y Acad Sci* **933**: 48–56. doi; 10.1111/j.1749-6632.2001.tb05813.x.
49. Azuma, K., Uchiyama, I., and Kunugita, N. (2019). Factors affecting self-reported chemical intolerance: A five-year follow-up study in Japan. *J Psychosom Res* **118**: 1–8. doi: 10.1016/j.jpsychores.2019.01.001.
50. Eek, F., Karlson, B., Osterberg, K., and Ostergren, P.O. (2010). Factors associated with prospective development of environmental annoyance. *J Psychosom Res* **69** (1): 9–15. doi: 10.1016/j.jpsychores.2009.12.001.
51. Azuma, K., Uchiyama, I., Katoh, T. et al. (2015). Prevalence and characteristics of chemical intolerance: a Japanese population-based study. *Arch Environ Occup Health* **70** (6): 341–353. doi: 10.1080/19338244.2014.926855.
52. Bell, I.R., Schwartz, G.E., Baldwin, C.M. et al. (1997). Individual differences in neural sensitization and the role of context in illness from low-level environmental chemical exposures. *Environ Health Perspect* **105** (Suppl 2): 457–466. doi: 10.1289/ehp.97105s2457.

53. Win-Shwe, T.T., Fujimaki, H., Arashidani, K., and Kunugita, N. (2013). Indoor volatile organic compounds and chemical sensitivity reactions. *Clin Dev Immunol* **2013**: 623812. doi: 10.1155/2013/623812.
54. Dalton, P. (2001). Psychophysical methods in the study of olfaction and respiratory tract irritation. *AIHAJ* **62** (6): 705–710. doi: 10.1080/15298660108984678.
55. Shusterman, D. (1992). Critical review: the health significance of environmental odor pollution. *Arch Environ Health* **47** (1): 76–87. doi: 10.1080/00039896.1992.9935948.
56. Shusterman, D. (2002). Review of the upper airway, including olfaction, as mediator of symptoms. *Environ Health Perspect* **110** (Suppl 4): 649–653. doi: 10.1289/ehp.02110s4649.
57. Caccappolo-van Vliet, E., Kelly-McNeil, K., Natelson, B. et al. (2002). Anxiety sensitivity and depression in multiple chemical sensitivities and asthma. *J Occup Environ Med* **44** (10): 890–901. doi: 10.1097/00043764-200210000-00006.
58. Karnekull, S.C., Jonsson, F.U., Larsson, M., and Olofsson, J.K. (2011). Affected by smells? Environmental chemical responsivity predicts odor perception. *Chem Senses* **36** (7): 641–648. doi: 10.1093/chemse/bjr028.
59. Nordin, S., Martinkauppi, M., Olofsson, J. et al. (2005). Chemosensory perception and event-related potentials in self-reported chemical hypersensitivity. *Int J Psychophysiol* **55** (2): 243–255. doi: 10.1016/j.ijpsycho.2004.08.003.
60. Rainville, P., Bushnell, M.C., and Duncan, G.H. (2001). Representation of acute and persistent pain in the human CNS: potential implications for chemical intolerance. *Ann N Y Acad Sci* **933**: 130–141. doi: 10.1111/j.1749-6632.2001.tb05820.x.
61. Bell, I.R., Baldwin, C.M., Fernandez, M., and Schwartz, G.E. (1999). Neural sensitization model for multiple chemical sensitivity: overview of theory and empirical evidence. *Toxicol Ind Health* **15** (3-4): 295–304. doi: 10.1177/074823379901500303.
62. Yunus, M.B. (2008). Central sensitivity syndromes: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. *Semin Arthritis Rheum* **37** (6): 339–352. doi: 10.1016/j.semarthrit.2007.09.003.
63. Sorg, B.A. (1999). Multiple chemical sensitivity: potential role for neural sensitization. *Crit Rev Neurobiol* **13** (3): 283–316. doi: 10.1615/critrevneurobiol.v13.i3.30.
64. Bell, I.R., Miller, C.S., and Schwartz, G.E. (1992). An olfactory-limbic model of multiple chemical sensitivity syndrome: possible relationships to kindling and affective spectrum disorders. *Biol Psychiatry* **32** (3): 218–242. doi: 10.1016/0006-3223(92)90105-9.
65. Sorg, B.A. and Prasad, B.M. (1997). Potential role of stress and sensitization in the development and expression of multiple chemical sensitivity. *Environ Health Perspect* **105** (Suppl 2): 467–471. doi: 10.1289/ehp.97105s2467.
66. Gilbert, M.E. (2001). Does the kindling model of epilepsy contribute to our understanding of multiple chemical sensitivity? *Ann N Y Acad Sci* **933**: 68–91. doi: 10.1111/j.1749-6632.2001.tb05815.x.
67. Nassenstein, C., Krasteva-Christ, G., and Renz, H. (2018). New aspects of neuroinflammation and neuroimmune crosstalk in the airways. *J Allergy Clin Immunol* **142** (5): 1415–1422. doi: 10.1016/j.jaci.2018.09.011.
68. Kimata, H. (2004). Effect of exposure to volatile organic compounds on plasma levels of neuropeptides, nerve growth factor and histamine in patients with self-reported multiple chemical sensitivity. *Int J Hyg Environ Health* **207** (2): 159–163. doi: 10.1078/1438-4639-00262.
69. Claeson, A.S. and Andersson, L. (2017). Symptoms from masked acrolein exposure suggest altered trigeminal reactivity in chemical intolerance. *Neurotoxicology* **60**: 92–98. doi: 10.1016/j.neuro.2017.03.007.
70. Gouin, O., L'Herondelle, K., Lebonvallet, N. et al. (2017). TRPV1 and TRPA1 in cutaneous neurogenic and chronic inflammation: pro-inflammatory response induced by their activation and their sensitization. *Protein Cell* **8** (9): 644–661. doi: 10.1007/s13238-017-0395-5.
71. Aguiar, D.C., Moreira, F.A., Terzian, A.L. et al. (2014). Modulation of defensive behavior by transient receptor potential vanilloid type-1 (TRPV1) channels. *Neurosci Biobehav Rev* **46** (Pt 3): 418–428. doi: 10.1016/j.neubiorev.2014.03.026.
72. Jardin, I., Lopez, J.J., Diez, R. et al. (2017). TRPs in pain sensation. *Front Physiol* **8**: 392. doi: 10.3389/fphys.2017.00392.
73. Straub, R.H. (2014). TRPV1, TRPA1, and TRPM8 channels in inflammation, energy redirection, and water retention: role in chronic inflammatory diseases with an evolutionary perspective. *J Mol Med* **92** (9): 925–937. doi: 10.1007/s00109-014-1175-9.
74. Zielinska, M., Jarmuz, A., Wasilewski, A. et al. (2015). Role of transient receptor potential channels in intestinal inflammation and visceral pain: novel targets in inflammatory bowel diseases. *Inflamm Bowel Dis* **21** (2): 419–427. doi: 10.1097/MIB.0000000000000234.
75. Millqvist, E. (2015). TRP channels and temperature in airway disease-clinical significance. *Temperature* **2** (2): 172–177. doi: 10.1080/23328940.2015.1012979.
76. Ternesten-Hasseus, E. (2016). Long-term follow-up in patients with airway chemical intolerance. *J Occup Environ Med* **58** (4): 421–426. doi: 10.1097/JOM.0000000000000695.
77. Liviero, F., Campisi, M., Scarpa, M.C. et al. (2020). Multiple single nucleotide polymorphisms of the transient receptor potential vanilloid 1 (TRPV1) genes associate with cough sensitivity to capsaicin in healthy subjects. *Pulm Pharmacol Ther* **61**: 101889. doi: 10.1016/j.pupt.2020.101889.
78. Meggs, W.J. (1995). Neurogenic switching: a hypothesis for a mechanism for shifting the site of inflammation in allergy and chemical sensitivity. *Environ Health Perspect* **103** (1): 54–56. doi: 10.1289/ehp.9510354.
79. Voisin, T., Bouvier, A., and Chiu, I.M. (2017). Neuro-immune interactions in allergic diseases: novel targets for therapeutics. *Int Immunol* **29** (6): 247–261. doi: 10.1093/intimm/dxx040.
80. Otto, T. and Giardino, N.D. (2001). Pavlovian conditioning of emotional responses to olfactory and contextual stimuli: a potential model for the development and expression of chemical intolerance. *Ann N Y Acad Sci* **933**: 291–309.
81. Siegel, S. and Kreutzer, R. (1997). Pavlovian conditioning and multiple chemical sensitivity. *Environ Health Perspect* **105** (Suppl 2): 521–526. doi: 10.1289/ehp.97105s2521.

82. Van den Bergh, O., Devriese, S., Winters, W. et al. (2001). Acquiring symptoms in response to odors: a learning perspective on multiple chemical sensitivity. *Ann N Y Acad Sci* **933**: 278–290.
83. Sparks, P.J., Daniell, W., Black, D.W. et al. (1994). Multiple chemical sensitivity syndrome: a clinical perspective. I. Case definition, theories of pathogenesis, and research needs. *J Occup Med* **36** (7): 718–730.
84. Andersson, L., Claeson, A.S., Ledin, L. et al. (2013). The influence of health-risk perception and distress on reactions to low-level chemical exposure. *Front Psychol* **4**: 816. doi: 10.3389/fpsyg.2013.00816.
85. Bailer, J., Witthoft, M., and Rist, F. (2008). Psychological predictors of short- and medium term outcome in individuals with idiopathic environmental intolerance (IEI) and individuals with somatoform disorders. *J Toxicol Environ Health A* **71** (11-12): 766–775. doi: 10.1080/15287390801985562.
86. Skovbjerg, S., Zachariae, R., Rasmussen, A. et al. (2010). Attention to bodily sensations and symptom perception in individuals with idiopathic environmental intolerance. *Environ Health Prev Med* **15** (3): 141–150. doi: 10.1007/s12199-009-0120-y.
87. Leznoff, A. and Binkley, K.E. (2000). Idiopathic environmental intolerances: results of challenge studies. *Occup Med* **15** (3): 529–537.
88. Schottenfeld, R.S. and Cullen, M.R. (1985). Occupation-induced posttraumatic stress disorders. *Am J Psychiatry* **142** (2): 198–202. doi: 10.1176/ajp.142.2.198.
89. Hoover, D.R., Donnay, A., Mitchell, C.S. et al. (2003). Reproducibility of immunological tests used to assess multiple chemical sensitivity syndrome. *Clin Diagn Lab Immunol* **10** (6): 1029–1036. doi: 10.1128/cdli.10.6.1029-1036.2003.
90. Vojdani, A., Ghoneum, M., and Brautbar, N. (1992). Immune alteration associated with exposure to toxic chemicals. *Toxicol Ind Health* **8** (5): 239–254.
91. Kipen, H., Fiedler, N., Maccia, C. et al. (1992). Immunologic evaluation of chemically sensitive patients. *Toxicol Ind Health* **8** (4): 125–135.
92. Mitchell, C.S., Donnay, A., Hoover, D.R., and Margolick, J.B. (2000). Immunologic parameters of multiple chemical sensitivity. *Occup Med* **15** (3): 647–665.
93. Simon, G.E., Daniell, W., Stockbridge, H. et al. (1993). Immunologic, psychological, and neuropsychological factors in multiple chemical sensitivity. A controlled study. *Ann Intern Med* **119** (2): 97–103. doi: 10.7326/0003-4819-119-2-199307150-00001.
94. Labarge, X.S. and McCaffrey, R.J. (2000). Multiple chemical sensitivity: a review of the theoretical and research literature. *Neuropsychol Rev* **10** (4): 183–211. doi: 10.1023/a:1026460726965.
95. Gibson, P.R. and Lindberg, A. (2011). Physicians' perceptions and practices regarding patient reports of multiple chemical sensitivity. *ISRN Nurs* **2011**: 838930. doi: 10.5402/2011/838930.
96. Kipen, H.M. and Fiedler, N. (2000). A 37-year-old mechanic with multiple chemical sensitivities. *Environ Health Perspect* **108** (4): 377–381. doi: 10.1289/ehp.00108377.
97. Sparks, P.J. (2000). Diagnostic evaluation and treatment of the patient presenting with idiopathic environmental intolerance. *Occup Med* **15** (3): 601–609.
98. Sparks, P.J., Daniell, W., Black, D.W. et al. (1994). Multiple chemical sensitivity syndrome: a clinical perspective. II. Evaluation, diagnostic testing, treatment, and social considerations. *J Occup Med* **36** (7): 731–737.
99. Fiedler, N. and Kipen, H. (1997). Chemical sensitivity: the scientific literature. *Environ Health Perspect* **105** (Suppl 2): 409–415. doi: 10.1289/ehp.97105s2409.
100. Kreutzer, R. (2000). Idiopathic environmental intolerance: case definition issues. *Occup Med* **15** (3): 511–517.
101. Barsky, A.J. and Borus, J.F. (1999). Functional somatic syndromes. *Ann Intern Med* **130** (11): 910–921. doi: 10.7326/0003-4819-130-11-199906010-00016.
102. Salvaggio, J.E. (1996). Understanding clinical immunological testing in alleged chemically induced environmental illnesses. *Regul Toxicol Pharmacol* **24** (1 Pt 2): S16–S27. doi: 10.1006/rtph.1996.0072.
103. Andersson, L., Claeson, A.S., Nyberg, L. et al. (2014). Brain responses to olfactory and trigeminal exposure in idiopathic environmental illness (IEI) attributed to smells – an fMRI study. *J Psychosom Res* **77** (5): 401–408. doi: 10.1016/j.jpsychores.2014.09.014.
104. Azuma, K., Uchiyama, I., Tanigawa, M. et al. (2019). Chemical intolerance: involvement of brain function and networks after exposure to extrinsic stimuli perceived as hazardous. *Environ Health Prev Med* **24**, **61** (1): doi: 10.1186/s12199-019-0816-6.
105. Terr, A.I. (1986). Environmental illness. A clinical review of 50 cases. *Arch Intern Med* **146** (1): 145–149. doi: 10.1001/archinte.146.1.145.
106. Lipson, J.G. (2004). Multiple chemical sensitivities: stigma and social experiences. *Med Anthropol Q* **18** (2): 200–213. doi: 10.1525/maq.2004.18.2.200.
107. Lipson, J.G. and Doiron, N. (2006). Environmental issues and work: women with multiple chemical sensitivities. *Health Care Women Int* **27** (7): 571–584. doi: 10.1080/07399330600803709.
108. Gibson, P.R., Sledd, L.G., McEnroe, W.H., and Vos, A.P. (2011). Isolation and lack of access in multiple chemical sensitivity: a qualitative study. *Nurs Health Sci* **13** (3): 232–237. doi: 10.1111/j.1442-2018.2011.00606.x.
109. Job Accommodation Network (2019). Accommodation network. https://askjan.org/ (accessed 11 January 2019).
110. Gibson, P.R., Kovach, S., and Lupfer, A. (2015). Unmet health care needs for persons with environmental sensitivity. *J Multidiscip Healthc* **8**: 59–66. doi: 10.2147/JMDH.S61723.
111. Gibson, P.R., Lockaby, S.D., and Bryant, J.M. (2016). Experiences of persons with multiple chemical sensitivity with mental health providers. *J Multidiscip Healthc* **9**: 163–172. doi: 10.2147/JMDH.S100688.
112. Spurgeon, A. (2002). Models of unexplained symptoms associated with occupational and environmental exposures. *Environ Health Perspect* **110** (Suppl 4): 601–605. doi: 10.1289/ehp.02110s4601.
113. Engel, C.C. Jr., Adkins, J.A., and Cowan, D.N. (2002). Caring for medically unexplained physical symptoms after

toxic environmental exposures: effects of contested causation. *Environ Health Perspect* **110** (Suppl 4): 641–647. doi: 10.1289/ehp.02110s4641.

114. Nordin, M., Andersson, L., and Nordin, S. (2010). Coping strategies, social support and responsibility in chemical intolerance. *J Clin Nurs* **19** (15-16): 2162–2173. doi: 10.1111/j.1365-2702.2010.03264.x.
115. Das-Munshi, J., Rubin, G.J., and Wessely, S. (2007). Multiple chemical sensitivities: review. *Curr Opin Otolaryngol Head Neck Surg* **15** (4): 274–280. doi: 10.1097/MOO.0b013e328259c360.
116. Del Casale, A., Rapinesi, C., Kotzalidis, G.D. et al. (2017). Stable remission of multiple chemical sensitivity syndrome and major depression with citalopram and 1-month deep transcranial magnetic stimulation: a case report. *J ECT* **33** (3): e27–e29. doi: 10.1097/YCT.0000000000000420.
117. Guglielmi, R.S., Cox, D.J., and Spyker, D.A. (1994). Behavioral treatment of phobic avoidance in multiple chemical sensitivity. *J Behav Ther Exp Psychiatry* **25** (3): 197–209. doi: 10.1016/0005-7916(94)90020-5.
118. Hauge, C.R., Rasmussen, A., Piet, J. et al. (2015). Mindfulness-based cognitive therapy (MBCT) for multiple chemical sensitivity (MCS): results from a randomized controlled trial with 1 year follow-up. *J Psychosom Res* **79** (6): 628–634. doi: 10.1016/j.jpsychores.2015.06.010.
119. Staudenmayer, H. (2000). Psychological treatment of psychogenic idiopathic environmental intolerance. *Occup Med* **15** (3): 627–646.
120. Tran, M.T.D., Skovbjerg, S., Arendt-Nielsen, L. et al. (2017). A randomised, placebo-controlled trial of transcranial pulsed electromagnetic fields in patients with multiple chemical sensitivity. *Acta Neuropsychiatr* **29** (5): 267–277. doi: 10.1017/neu.2016.51.

PATTY'S INDUSTRIAL HYGIENE

Seventh Edition

Volume 1

Hazard Recognition

Edited by

BARBARA COHRSSEN MS, CIH, FAIHA, MLS
San Francisco, CA, USA

WILEY

This edition first published 2021

Edition History
John Wiley & Sons, Inc. (6e, 2011)

Registered Office
John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA

Editorial Office
111 River Street, Hoboken, NJ 07030, USA

For details of our global editorial offices, customer services, and more information about Wiley products visit us at www.wiley.com.

Wiley also publishes its books in a variety of electronic formats and by print-on-demand. Some content that appears in standard print versions of this book may not be available in other formats.

Library of Congress Cataloging-in-Publication Data has been applied for.

978-1-119-79151-5 (Volume 1, cloth)
978-1-119-43802-1 (4-volume Set, cloth)

Cover Image: Factory © Rashad Ashur / Shutterstock, Factory © Arcady / Shutterstock, Rod of Asclepius © Christos Georghiou / Shutterstock, Laboratory glass © Kristyna Henkeova / Shutterstock
Cover Design: Wiley

Set in 10/12pt Times LTStd by SPi Global, Chennai, India
Printed and bound by CPI Group (UK) Ltd, Croydon, CR0 4YY

C115560_050321

CONTENTS