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Invited Testimony by

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There's an old parable: For want of a nail, the horseshoe was lost; for want of a shoe, the horse was lost; then the rider was lost; then the battle; the war; and finally the kingdom—all for want of a nail.

This is precisely the situation we find ourselves in today. For want of a paradigm, our veterans are—lost in a sea of inconclusive reports, redundant studies, expanding budgets, programs and committees, and cries of conspiracy—all for want of a paradigm, something to explain the relationship between the exposures they experienced during the Gulf War and the multi-system symptoms that now plague them.

Different specialists apply different monikers to their symptoms.

—The rheumatologist observing diffuse muscle pain diagnoses myalgias.

—The neurologist hearing head pain and nausea diagnoses migraine headaches.

—The pulmonologist finding airway reactivity diagnoses asthma.

—The psychiatrist seeing chronic malaise diagnoses depression.

—The gastroenterologist noting GI complaints diagnoses irritable bowel syndrome.

Most ill veterans have symptoms involving several organ systems simultaneously. For them there is no unifying diagnosis, no known etiology, and no identified disease process.

This is not the first time doctors have found themselves baffled by wartime disease. One hundred and thirty years ago, during the Civil War, doctors were faced with a similarly mysterious “syndrome” characterized by fever. Hundreds of thousands of soldiers died. The doctors did what good epidemiologists do today. They classified the cases. Since the hallmark symptom was fever, they classified the cases by fever type—remittent, intermittent, or relapsing. In doing so, they unknowingly lumped together dozens of

unrelated illnesses—everything from typhus and typhoid to malaria and tuberculosis (Sartin, 1993). Who would have dreamed it—this germ theory of disease? This war going on between invisible invaders and the body's immune defenses, with the only outward sign being—literally—the heat of battle.

Today we face this same situation with Gulf War veterans, only this time the hallmark symptom is not as simple as fever. It's the newly acquired intolerances these veterans have been experiencing since the War. Like the mechanic who before the war used to "bathe" in solvents and now becomes ill after one whiff of gasoline. Or the young woman soldier who recalls how she used to be able to drink any man in her company under the table, but since the war she can't take even one drink without becoming violently ill. The vast majority of sick veterans report these newly acquired intolerances which date from their experiences in the Persian Gulf.

During the past seven years I have served as the environmental medical consultant to the Houston VA's regional referral center. Approximately 90% of veterans interviewed described new-onset intolerances to everyday chemical exposures which set off their symptoms: 78 percent were intolerant of fragrances, tobacco smoke, gasoline vapors, etc.; 78 percent described food intolerances; 66 percent reported alcohol intolerance; 25 percent were intolerant of caffeine; and nearly 40 percent reported adverse reactions to medications—all since the Gulf War. These intolerances, resulting in flare-ups of symptoms, including fatigue, headaches, gastrointestinal problems, mood changes, cognitive impairment and diffuse musculoskeletal pain, are like the fevers experienced by the Civil War soldiers—they are the outward manifestation of the underlying disease process.

This is not the first time this illness pattern has appeared on the medical landscape. Researchers have described these same new-onset intolerances and multi-system symptoms in demographically diverse groups in more than a dozen countries—sheep dippers exposed to organophosphate pesticides in the United Kingdom; radiography workers exposed to Xray developers containing glutaraldehyde, etc. in New Zealand; U.S. aerospace workers on the West Coast exposed to solvents and plasticizers; and environmental scientists exposed to indoor air contaminants at the EPA's own headquarters in Washington, D.C., to name a few (Ashford and Miller, 1998).

What ties all these groups together is the common experience of an initiating toxic exposure followed by newly acquired intolerances and multi-system symptoms. These observations provide compelling scientific evidence for a shared underlying disease mechanism—one involving a *fundamental breakdown in natural tolerance*. This two-step process—an initiating toxic exposure followed by newly acquired intolerances that trigger multi-system symptoms—has been referred to with the acronym "TILT," or Toxicant-induced Loss of Tolerance (Golomb, 1999; Newlin, 1997; Miller, 1999, 1997; Miller et al, 1997).

This two-step process is the key to understanding Gulf War illness. It doesn't matter so much which exposure caused the breakdown in tolerance—be it pesticides, smoke from

the oil fires or pyridostigmine bromide pills; those things have long since left these veterans' bodies. It's the aftermath of these exposures—the new-onset intolerances to low-level chemical exposures—which appear to be perpetuating their symptoms. In some cases, it may be difficult to sort out individual intolerances, or "triggers," because of a phenomenon called "masking." This occurs when individuals are reacting to so many exposures that they become a confusion of overlapping symptoms.

But the confusion clears for both the patient and the physician when the underlying paradigm is understood. And questions that could not be answered, are answered.

Like why some veterans became ill and others didn't—because individuals react differently to toxic exposures; some have no response at all.

Or why researchers have been unable to isolate a single culprit exposure—because the answer to the question "What caused Gulf War illness?" is more likely to be "all of the above."

It explains why veterans remain sick almost a decade after the War, long after their initiating exposures.

It explains why symptoms wax and wane unpredictably—as daily exposures wax and wane.

What can be done to diagnose and treat the chemically intolerant? There is evidence that removing them from the exposures that are affecting them by putting them in an environmental medical unit (EMU), will cause their symptoms to subside. The EMU is an environmentally controlled in-patient hospital unit designed to help patients avoid common, low-level exposures. Previous experience shows that within days of entering the EMU, patients will arrive at a "clean baseline," and their exposure-related symptoms will disappear. During the next two weeks, each patient is exposed to potential triggers—such as caffeine, gasoline, perfume, various foods, medications, and tobacco smoke—one at a time, to determine what is setting them off.

Epidemiological data and literature reviews can only go so far in determining the nature of a new disease process. New paradigms require new approaches, and new tools. EMU studies will enable doctors to witness this disease mechanism firsthand and understand Gulf War illness for what it is, while providing a built-in treatment component—one that enables veterans to understand their disease and emerge less confused, less hopeless, and more in control of their lives.

A validated questionnaire (attached) is available in the medical literature which VA and military doctors could use as a first step toward introducing physicians and patients to this paradigm so they can begin to see it for themselves.

If we are going to help these veterans, what is needed is not more epidemiologic studies or literature reviews, but, rather, a Manhattan Project-style approach consisting of EMU studies and other patient-oriented diagnostic and treatment studies.

References

Ashford NA, Miller CS, 1998. Chemical Exposures: Low Levels and High Stakes. New York: John Wiley and Sons, New York. 440 pp.

Golomb, BA. 1999. Pyridostigmine bromide. A review of the scientific literature as it pertains to Gulf War illnesses. Vol.2. RAND, Santa Monica, CA.

Miller CS. 1999. Are we on the threshold of a new theory of disease? Toxicant-induced loss of tolerance and its relationship to addiction and abdiction. Toxicology and Industrial Health 15:284-294.

Miller CS. 1997. Toxicant-induced loss of tolerance: An emerging theory of disease? Environmental Health Perspectives 105(Suppl 2):445-453.

Miller C, Ashford N, Doty R, Lamielle M, Otto D, Rahill A, Wallace L. 1997. Empirical approaches for the investigation of toxicant-induced loss of tolerance. Environmental Health Perspectives 105(Suppl. 2):515-519.

Newlin, D. 1997. A behavior-genetic approach to multiple chemical sensitivity. Environmental Health Perspectives 105(Suppl. 2): 505-508.

Sartin, JS. 1993. Infectious diseases during the Gulf War: the triumph of the “Third Army.” Clinical and Infectious Diseases 16:580-584.

Figure 1. Exposures that may initiate TILT or trigger symptoms

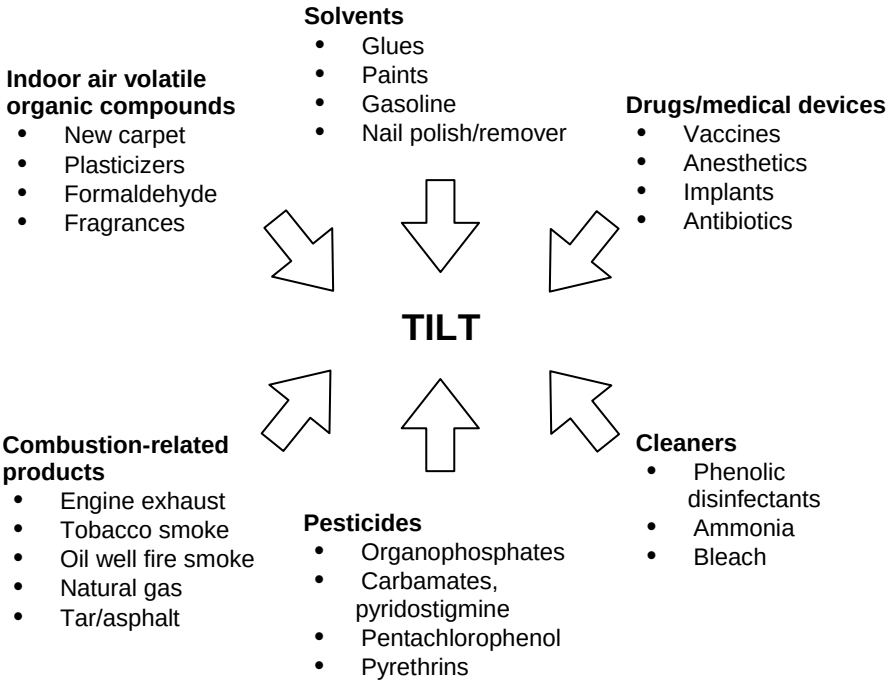
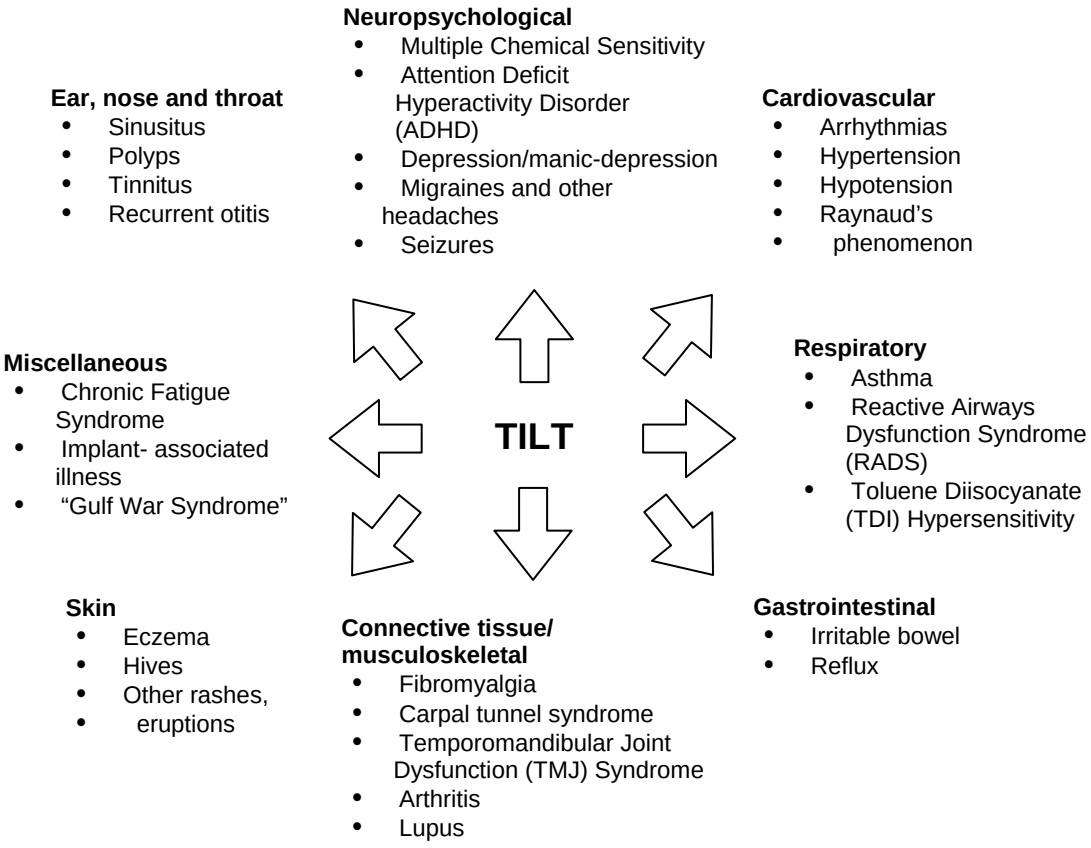


Figure 2. Conditions that may have their origins in TILT



The QEESI©

The Quick Environmental Exposure and Sensitivity Inventory (QEESI©) was developed as a screening questionnaire for multiple chemical intolerances (MCI). The instrument has four scales: Symptom Severity, Chemical Intolerances, Other Intolerances, and Life Impact. Each scale contains 10 items which are scored from 0 = "not a problem" to 10 = "severe or disabling problem." A 10-item Masking Index gauges ongoing exposures that may affect individuals' awareness of their intolerances as well as the intensity of their responses to environmental exposures. The QEESI© can be used for:

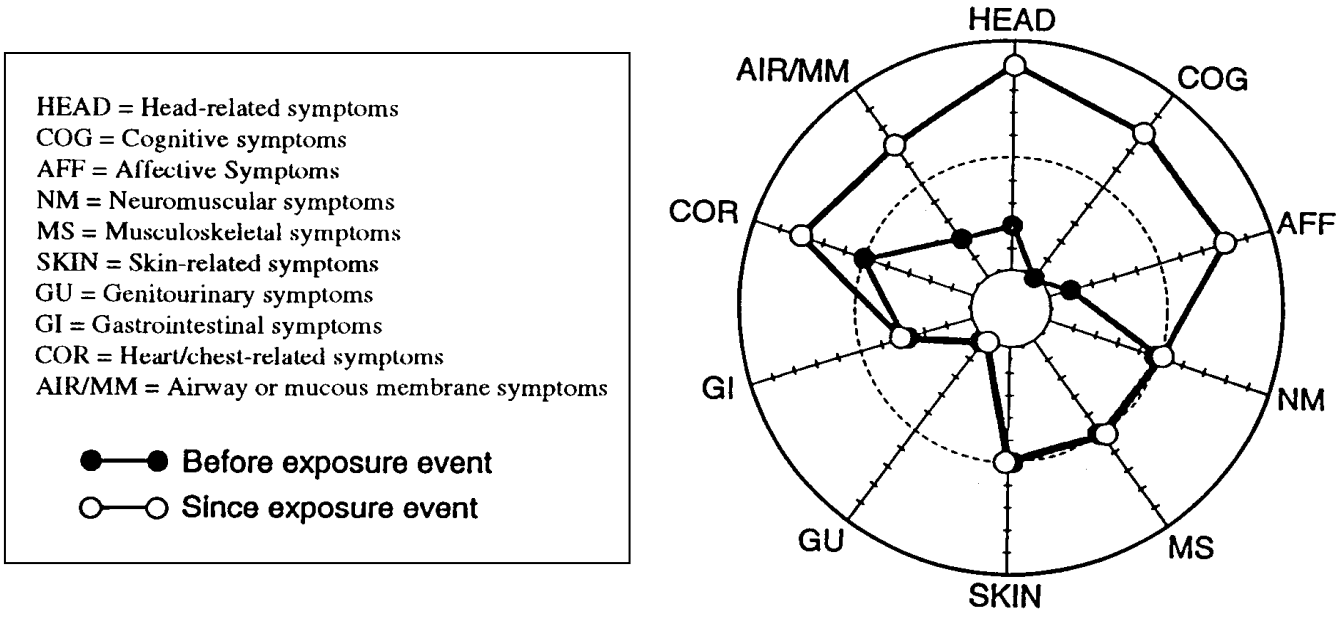
(1) Research, to characterize and compare study populations and to select subjects and controls.

(2) Clinical evaluations, to obtain a profile of patients' self-reported symptoms and intolerances. Patients can be asked to complete a QEESI© at intervals in order to follow the course of their illness over time or in response to treatment or exposure avoidance.

(3) Workplace or community investigations, to identify and provide self-assessment information to individuals who may be more susceptible or who report new intolerances. Affected employees should have the option to discuss the results with investigators or their personal physicians.

Individuals whose health problems began or became worse following a particular exposure event can fill out the QEESI© using one color of ink to illustrate how they were before the event, and a second color to illustrate how they have been since the event. On the cover of the QEESI© is a "Symptom Star" (Figure 1) which provides a graphical representation of patients' responses on the Symptom Severity Scale.

Figure 1. QEESI Symptom Star illustrating symptom severity in an individual before and after an exposure event (e.g., pesticide application, indoor air contaminants, chemical spill)



For additional copies of the QEESI©, contact Claudia S. Miller, M.D., M.S., University of Texas Health Science Center at San Antonio, Department of Family Practice BCT 150, 7703 Floyd Curl Drive, San Antonio, Texas 78229-3900. Phone: (210) 567-7760; fax: (210) 567-7764; email: millercs@uthscsa.edu. For further information see Chemical Exposures: Low Levels and High Stakes by Nicholas A. Ashford and Claudia S. Miller, John Wiley & Sons, 1998 (1-800-225-5945).

Interpreting the QEESI©

In a study of 421 individuals, including four exposure groups and a control group, the QEESI© provided sensitivity of 92% and specificity of 95% in differentiating between chemically intolerant persons with multiple chemical intolerances (MCI) and the general population (Miller and Prihoda 1999).

Cronbach's alpha reliability coefficients for the QEESI©s four scales—Symptom Severity, Chemical Intolerances, Other Intolerances and Life Impact—were high (0.76-0.97) for each of the groups, as well as over all subjects, indicating that the questions on the QEESI© form scales showing good internal consistency. Pearson correlations for each of the four scales with validity items of interest, i.e., life quality, health status, energy level, body pain, ability to work and employment status, were all significant and in the expected direction, thus supporting good construct validity.

Information on the development of this instrument, its interpretation, and results for several populations have been published (Miller and Prihoda 1999a,b). Proposed ranges for the QEESI©'s scales and guidelines for their interpretation appear in Tables 1 and 2 below:

Table 1. Criteria for low, medium, and high scale scores

Scale/Index	Score: Low	Medium	High
Symptom Severity	0-19	20-39	40-100
Chemical Intolerance	0-19	20-39	40-100
Other Intolerance	0-11	12-24	25-100
Life Impact	0-11	12-23	24-100
Masking Index	0-3	4-5	6-10

Table 2. Distribution of subjects by group using "high" cutoff points for symptom severity (≥ 40) and chemical intolerances (≥ 40), with masking low or not low (< 4 or ≥ 4)

Risk Criteria[1]				Percentage of Each Group Meeting Risk Criteria				
Degree to Which MCI is Suggested[2]	Symptom Severity Score	Chemical Intolerance Score	Masking Score	Controls n=76	MCS - No Event n=90	MCS – Event n=96	Implant n=87	Gulf War Veterans n=72
Very suggestive	≥ 40	≥ 40	≥ 4	7	16	23	39	45
Very suggestive	≥ 40	≥ 40	< 4	0	65	66	36	4
Somewhat suggestive	≥ 40	< 40	≥ 4	3	1	2	16	26
Not suggestive	≥ 40	< 40	< 4	0	0	2	3	6
Problematic	< 40	≥ 40	≥ 4	7	3	1	1	0
Problematic	< 40	≥ 40	< 4	3	13	4	2	0
Not suggestive	< 40	< 40	≥ 4	68	1	0	2	18
Not Suggestive	< 40	< 40	< 4	12	1	2	1	1
				100	100	100	100	100

[1] Subjects must meet all three criteria, i.e., Symptom Severity, Chemical Intolerance, and Masking scores, as indicated in each row of this table.

[2] "Very suggestive" = high symptom and chemical intolerance scores.
"Somewhat suggestive" = high symptom score but possibly masked chemical intolerance
"Not suggestive" = either (1) high symptom score but low chemical intolerance score with low masking, or (2) low symptom and chemical intolerance scores.
"Problematic" = low symptom score but high chemical intolerance score. Persons in this category with low masking (<4) may be sensitive individuals who have been avoiding chemical exposures for an extended period (months or years).

References:

Miller CS, Prihoda TJ: The Environmental Exposure and Sensitivity Inventory (EESI): a standardized approach for measuring chemical intolerances for research and clinical applications. *Toxicology and Industrial Health* 15:370-385, 1999a.

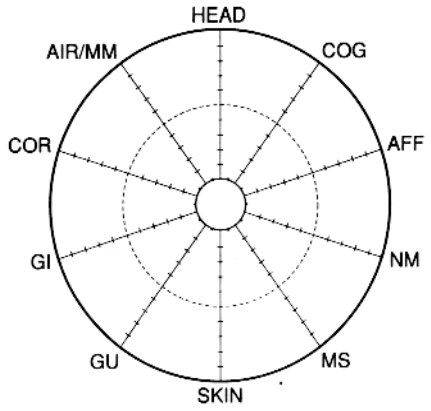
Miller CS, Prihoda TJ: A controlled comparison of symptoms and chemical intolerances reported by Gulf War veterans, implant recipients and persons with multiple chemical sensitivity. *Toxicology and Industrial Health* 15:386-397, 1999b.

Quick Environmental Exposure and Sensitivity Inventory V-1

(QEESI)©

The purpose of this questionnaire is to help identify health problems you may be having and to understand your responses to various exposures. If your health problems began suddenly or became much worse after a particular exposure event, such as a pesticide exposure or moving to a new home or office building, complete pages 1-3 describing how you are now, then go back through these same questions a second time, and identify how you were before the exposure event. After you have completed all of the items on pages 1-5, fill in the "target" diagram below.

Symptom Star



Instructions: After completing pages 1 through 5, unfold page 3 so that it lies just to the right of this page. Place a small dot on the corresponding spoke for each symptom item on page 3. Connect these points, For "before and after " scores (described above), use two different colors.

CHEMICAL EXPOSURES

The following items ask about your responses to various odors or chemical exposures. Please indicate whether or not these odors or exposures would make you feel sick, for example, you would get a headache, have difficulty thinking, feel weak, have trouble breathing, get an upset stomach, feel dizzy, or something like that. For any exposure that makes you feel sick, on a 0-10 scale rate the severity of your symptoms with that exposure. For exposures that do not bother you, answer "0." Do not leave any items blank.

0 = not at all a problem
5 = moderate symptoms
10 = disabling symptoms

For each item, circle one number only:

1.	Diesel or gas engine exhaust	0 1 2 3 4 5 6 7 8 9 10
2.	Tobacco smoke	0 1 2 3 4 5 6 7 8 9 10
3.	Insecticide	0 1 2 3 4 5 6 7 8 9 10
4.	Gasoline, for example at a service station while filling the gas tank	0 1 2 3 4 5 6 7 8 9 10
5.	Paint or paint thinner	0 1 2 3 4 5 6 7 8 9 10
6.	Cleaning products such as disinfectants, bleach, bathroom cleansers or floor cleaners	0 1 2 3 4 5 6 7 8 9 10
7.	Certain perfumes, air fresheners or other fragrances	0 1 2 3 4 5 6 7 8 9 10
8.	Fresh tar or asphalt	0 1 2 3 4 5 6 7 8 9 10
9.	Nailpolish, nailpolish remover, or hairspray	0 1 2 3 4 5 6 7 8 9 10
10.	New furnishings such as new carpeting, a new soft plastic shower curtain or the interior of a new car	0 1 2 3 4 5 6 7 8 9 10

Total Chemical Intolerance Score (0-100): ____

Name any additional chemical exposures that make you feel ill and score them from 0 to 10:_____

_____

_____

_____

_____

OTHER EXPOSURES

The following items ask about your responses to a variety of other exposures. As before, please indicate whether these exposures would make you feel sick. Rate the severity of your symptoms on a 0-10 scale. Do not leave any items blank.

0 = not at all a problem
5 = moderate symptoms
10 = disabling symptoms

For each item, circle one number only:

1.	Chlorinated tap water	0 1 2 3 4 5 6 7 8 9 10
2.	Particular foods, such as candy, pizza, milk, fatty foods, meats, barbecue, onions, garlic, spicy foods, or food additives such as MSG	0 1 2 3 4 5 6 7 8 9 10
3.	Unusual cravings, or eating any foods as though you were addicted to them; or feeling ill if you miss a meal	0 1 2 3 4 5 6 7 8 9 10
4.	Feeling ill after meals	0 1 2 3 4 5 6 7 8 9 10
5.	Caffeine, such as coffee, tea, Snapple, cola drinks, Big Red, Dr. Pepper or Mountain Dew, or chocolate	0 1 2 3 4 5 6 7 8 9 10
6.	Feeling ill if you drink or eat less than your usual amount of coffee, tea, caffeinated soda or chocolate, or miss it altogether	0 1 2 3 4 5 6 7 8 9 10
7.	Alcoholic beverages in small amounts such as one beer or a glass of wine	0 1 2 3 4 5 6 7 8 9 10
8.	Fabrics, metal jewelry, creams, cosmetics, or other items that touch your skin	0 1 2 3 4 5 6 7 8 9 10
9.	Being unable to tolerate or having adverse or allergic reactions to any drugs or medications (such as antibiotics, anesthetics, pain relievers, x-ray contrast dye, vaccines or birth control pills), or to an implant, prosthesis, contraceptive chemical or device, or other medical, surgical or dental material or procedure	0 1 2 3 4 5 6 7 8 9 10
10.	Problems with any classical allergic reactions (asthma, nasal symptoms, hives, anaphylaxis or eczema) when exposed to allergens such as: tree, grass or weed pollen, dust, mold, animal dander, insect stings or particular foods	0 1 2 3 4 5 6 7 8 9 10

Total Other Intolerance Score (0-100): ____

SYMPTOMS

The following questions ask about symptoms you may have experienced commonly. Rate the severity of your symptoms on a 0-10 scale. Do not leave any items blank.

0 = not at all a problem
5 = moderate symptoms
10 = disabling symptoms

For each item, circle one number only:

1	Problems with your muscles or joints, such as pain, aching, cramping, stiffness or weakness?	MS 0 1 2 3 4 5 6 7 8 9 10
2	Problems with burning or irritation of your eyes, or problems with your airway or breathing, such as feeling short of breath, coughing, or having a lot of mucus, post-nasal drainage, or respiratory infections?	AIR/MM 0 1 2 3 4 5 6 7 8 9 10
3	Problems with your heart or chest, such as a fast or irregular heart rate, skipped beats, your heart pounding, or chest discomfort?	COR 0 1 2 3 4 5 6 7 8 9 10
4	Problems with your stomach or digestive tract, such as abdominal pain or cramping, abdominal swelling or bloating, nausea, diarrhea, or constipation?	GI 0 1 2 3 4 5 6 7 8 9 10
5	Problems with your ability to think, such as difficulty concentrating or remembering things, feeling spacey, or having trouble making decisions?	COG 0 1 2 3 4 5 6 7 8 9 10
6.	Problems with your mood, such as feeling tense or nervous, irritable, depressed, having spells of crying or rage, or loss of motivation to do things that used to interest you?	AFF 0 1 2 3 4 5 6 7 8 9 10
7.	Problems with balance or coordination, with numbness or tingling in your extremities, or with focusing your eyes?	NM 0 1 2 3 4 5 6 7 8 9 10
8.	Problems with your head, such as headaches or a feeling of pressure or fullness in your face or head?	HEAD 0 1 2 3 4 5 6 7 8 9 10
9.	Problems with your skin, such as a rash, hives or dry skin?	SKIN 0 1 2 3 4 5 6 7 8 9 10
10.	Problems with your urinary tract or genitals, such as pelvic pain or frequent or urgent urination? (For women: or discomfort or other problems with your menstrual period?)	GU 0 1 2 3 4 5 6 7 8 9 10

Total Symptom Score (0-100): ☐

MASKING INDEX

The following items refer to ongoing exposures you may be having. Circle "0" if the answer is NO, or if you don't know whether you have the exposure. Circle "1" if the answer is YES, you do have the exposure. Do not leave any items blank.

Circle "0" or "1" only:

1.	Do you smoke or dip tobacco once a week or more often?	NO=0 YES=1
2.	Do you drink any alcoholic beverages, beer, or wine once a week or more often?	NO=0 YES=1
3.	Do you consume any caffeinated beverages once a week or more often?	NO=0 YES=1
4.	Do you routinely (once a week or more) use perfume, hairspray, or other scented personal care products?	NO=0 YES=1
5.	Has either your home or your workplace been sprayed for insects or fumigated in the past year?	NO=0 YES=1
6.	In your current job or hobby, are you routinely (once a week or more) exposed to any chemicals, smoke or fumes?	NO=0 YES=1
7.	Other than yourself, does anyone routinely smoke inside your home?	NO=0 YES=1
8.	Is either a gas or propane stove used for cooking in your home?	NO=0 YES=1
9.	Is a scented fabric softener (liquid or dryer sheet) routinely used in laundering your clothes or bedding?	NO=0 YES=1
10.	Do you routinely (once a week or more) take any of the following: steroid pills, such as prednisone; pain medications requiring a prescription; medications for depression, anxiety, or mood disorders; medications for sleep; or recreational or street drugs?	NO=0 YES=1

Masking Index (0-10):
(Total number of YES answers) ☐

IMPACT OF SENSITIVITIES

If you are sensitive to certain chemicals or foods, on a scale of 0-10 rate the degree to which your sensitivities have affected various aspects of your life. If you are not sensitive or if your sensitivities do not affect these aspects of your life, answer "0." Do not leave any items blank.

0 = not at all
5 = moderately
How much have your sensitivities affected: **10 = severely**

1.	Your diet	0 1 2 3 4 5 6 7 8 9 10
2.	Your ability to work or go to school	0 1 2 3 4 5 6 7 8 9 10
3.	How you furnish your home	0 1 2 3 4 5 6 7 8 9 10
4.	Your choice of clothing	0 1 2 3 4 5 6 7 8 9 10
5.	Your ability to travel to other cities or drive a car	0 1 2 3 4 5 6 7 8 9 10
6.	Your choice of personal care products, such as deodorants or makeup	0 1 2 3 4 5 6 7 8 9 10
7.	Your ability to be around others and enjoy social activities, for example, going to meetings, church, restaurants, etc.	0 1 2 3 4 5 6 7 8 9 10
8.	Your choice of hobbies or recreation	0 1 2 3 4 5 6 7 8 9 10
9.	Your relationship with your spouse or family	0 1 2 3 4 5 6 7 8 9 10
10.	Your ability to clean your home, iron, mow the lawn, or perform other routine chores	0 1 2 3 4 5 6 7 8 9 10

Total Life Impact Score (0-100): ☐

For additional copies of the **QEESI**, call 210-567-7760. For more information about this questionnaire, refer to Chemical Exposures: Low Levels and High Stakes (2nd Edition) by Nicholas A. Ashford and Claudia S. Miller, John Wiley & Sons, Inc., 1998. To order, call toll-free 1-800-225-5945.

Biosketch

Claudia S. Miller, M.D., M.S., is an Associate Professor in Environmental and Occupational Medicine in the Department of Family Practice of the University of Texas Health Science Center at San Antonio. She is board-certified in Allergy/Immunology and Internal Medicine, and has a Master's degree in Public Health/Environmental Health. Her research interests include the health effects of low level chemical exposures, pesticides, indoor air pollution, and Gulf War veterans' illnesses. Dr. Miller has held appointments to several federal advisory committees, including the National Advisory Committee on Occupational Safety and Health, the National Toxicology Program Board of Scientific Counselors, and the Department of Veterans Affairs Persian Gulf Expert Scientific Advisory Committee. She is co-author of the WHO-award-winning *New Jersey Report on Chemical Sensitivity* and a professionally acclaimed book, *Chemical Exposures: Low Levels and High Stakes* (Ashford, NA and Miller, CS, John Wiley and Sons, Inc. 1998, New York).