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Taylor & Francis Group

Archives of Environmental Health: An International Journal

ISSN: 0003-9896 (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/vzeh20

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To cite this article: James R. Nethercott M.D. , Linda Lee Davidoff , Barbara Curbow & Helen Abbey (1993) Multiple Chemical Sensitivities Syndrome: Toward a Working Case Definition, Archives of Environmental Health: An International Journal, 48:1, 19-26, DOI: 10.1080/00039896.1993.9938389

To link to this article: https://doi.org/10.1080/00039896.1993.9938389

Multiple Chemical Sensitivities Syndrome: Toward a Working Case Definition

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ABSTRACT. A study was conducted to identify clinical diagnostic criteria that experts regarded as *major* for categorizing patients as having multiple chemical sensitivities (MCS) syndrome. A cross-sectional survey of 148 medical practitioners with an interest in, or familiarity with, the condition was performed scoreable questionnaires were returned by 60.1% of those surveyed. The following five criteria, all based on self-reports, were selected as major for diagnosing the syndrome by more than 50% of the respondents: (1) symptoms are reproducible with exposure; (2) condition is chronic; (3) low levels of exposure result in manifestations of the syndrome; (4) symptoms resolve with removal of incitants; and (5) responses occur to multiple, chemically unrelated substances. It is proposed that the major criteria accepted by the majority of survey respondents be used provisionally as the basis for categorizing cases in investigations of MCS syndrome.

THE MULTIPLE CHEMICAL SENSITIVITIES (MCS) syndrome, also known by numerous other names (e.g., chemical sensitivity, environmental or ecologic illness, environmental hypersensitivity or hypersusceptibility, chemical hypersensitivity syndrome, and total allergy syndrome) has been described as "the most puzzling clinical entity in the 1980s."[1] No basis for categorizing patients into this syndrome has been generally accepted, although several definitions have been proposed.[2,3]

Descriptions of MCS syndrome have concurred on several points.[2-6] Although the symptoms of affected individuals vary, they are typically related to more than one organ system, and symptoms referable to the central nervous system are usually apparent. Nonspecific symptoms, such as chronic overwhelming fatigue and headache, and complaints attributable to the upper- and lower-respiratory systems, muscular-skeletal system, and gastrointestinal system are also commonly reported. The symptoms are chronic or recurrent and appear after exposure to chemically unrelated substances that may include synthetic chemicals, foods, alcohol, medications, and allergens. Affected individuals tend to describe an alteration in their responses such that progressively smaller amounts of a widening array of incitants provoke symptoms. Sometimes the condition has been attributed to a particular exposure, most frequently to a "sick building"

or to a petrochemical in the workplace or elsewhere.[4] Certain illnesses, medications, recreational drugs, and psychosocial stress have also been associated with the onset of the syndrome.[5] In Table 1 are summarized inducing conditions that have been suggested. Commonly, detailed medical evaluation discloses no objective physical or laboratory abnormalities that would account for the reported symptoms.[6] Affected individuals experience varying degrees of morbidity, with some becoming totally disabled in terms of being able to carry on their normal activities in an urban society.[4]

The basis for the signs and symptoms of MCS syndrome is unclear. There is debate whether the syndrome is a single entity or a manifestation of one or more diseases that may present with similar findings. Some authors believe that the condition is a psychiatric disorder, which they conceptualize as post-traumatic stress disorder,[9] behavioral sensitization,[10,11] a result of having been inculcated into a "clinical ecology subculture,"[12] a consequence of sexual abuse during childhood,[13] an anxiety neurosis,[14] an obsessive-paranoid personality style,[15] depression, or a somatoform disorder.[13-19] Others have portrayed MCS syndrome as a somatic disorder characterized by such aberrations as altered irritability with a lowered threshold for irritant effects,[19] immunological hypersensitivity,[20-22] or neural damage associated with a lowered threshold for neurotoxic effects.[23] Objective literature relating to the syndrome consists primarily of case studies.

Although evidence in support of the existence of MCS syndrome is equivocal, some authors have suggested that the condition is prevalent.[1,2,4,24] Before meaningful studies can take place, a uniform case definition is needed. We report the results of a study conducted to delineate the clinical criteria that physicians, who are familiar with MCS syndrome, are using to characterize such patients.

Materials and methods

We selected 148 physicians to receive the questionnaire for this study. Our primary criterion for inclusion was demonstrated interest in, or familiarity with, MCS syndrome. Of the study population, 90% was assembled from the sources outlined in Appendix A, and 10% was assembled from physicians known to the authors to be interested in the condition. The majority of study subjects had published an article or position paper on the syndrome, or had served either on a task force or committee assembled expressly to review information about the condition or a related topic (e.g., clinical ecology), or were members of an editorial board, executive committee, or board of directors of a professional body concerned with the syndrome or a related topic.

The first mailing to each physician consisted of a cover letter in which the goals of our study were described and he or she was invited to participate, a questionnaire, and a self-addressed stamped envelope. Twice, at approximately 3-wk intervals, reminder letters were sent to the physicians and were accompanied by another questionnaire and a self-addressed stamped envelope. Hence, each invited participant had three opportunities to respond to the survey.

For purposes of evaluation, we assembled 15 diagnostic criteria that had been proposed by groups interested in MCS syndrome.[2,3] The diagnostic criteria, grouped according to thematic content, are presented in Appendix B. Subjects were asked to specify whether

Table 1.—Examples of Factors Associated with the Onset of MCS

Factor	Report to the Province of Ontario 1985[3]	Cone et al. 1987[7]	Terr 1989[8]
Solvents		Paint or lacquer thinner, printing ink/press cleaners, xylene, methylene chloride, paints, petroleum distillates, glycol ethers	Paint thinner, xylene, trichlorethane, kerosene, methylene chloride
Pesticides	Chlordane	Diazinon, guthion	"Pesticides"
Miscellaneous	Formaldehyde	Hydrogen sulfide	Formaldehyde, germicide, nitric acid, freon, toluene diisocyanate, argon
Environments	Workplace, home heating	Copy machines, new carpets and other new materials	Smoke, new carpets, office machines, new building, hair sprays, dry air, heat at work
Metals			Nickel, lead
Dusts			Wood, beet, sugar
Illness, injury, surgery, medical procedures	Root canal, physical injury, viral infection, food poisoning, childbirth, drug reaction		Scabies, herpes zoster, fall at work
Stress	Stress		Stress at work

they considered each criterion *major, minor,* or *irrelevant* for categorizing patients as having the syndrome. Demographic and professional information (i.e., primary discipline, number of individuals believed to be suffering from MCS syndrome personally evaluated, age, and sex) was also obtained.

Univariate descriptive analyses were used initially to examine the frequency distribution of the study variables. Bivariate analyses were performed on the outcome measures and potential covariates (i.e., age, sex, occupational affiliation, and number of patients evaluated). Nominal data were evaluated by chi-square analyses; statistically significant differences between cells were assessed by logistic regression[25] or by partitioning the degrees of freedom and computing a chi-square value for each pairwise comparison. In all statistical analyses, a probability level of $p \leq .05$ served as the criterion for statistical significance.

Results

Respondent characteristics. Of the 148 physicians to whom questionnaires were mailed, 89 (60.1%) returned scoreable questionnaires. An additional 14 physicians responded to disqualify themselves, yielding a total response rate of 70%. As shown in Table 2, allergists (n = 36) made up 40% of the sample who returned scoreable questionnaires; occupational physicians (n = 23), 26%; clinical ecologists (n = 20), 22%; and internal medicine and otolaryngology specialists (grouped together, n = 10), 11%. Those who disqualified themselves did so for various reasons (i.e., not being a clinician [n = 2], being confused about the issues [n = 2], disbelieving in the condition [n = 2], worrying about hurting patients' welfare or professional issues [n = 3], finding the questions confusing [n = 1], and feeling that their knowledge was inadequate [n = 4]). The respondents who returned scoreable questionnaires were predominantly men (90%). Their mean age was 49.7 ± 10.5 (mean ± standard deviation [*SD*]). The median number of patients whom they had evaluated was 50. The first quartile included practitioners who had evaluated 8 or fewer patients; the fourth quartile included practitioners who had evaluated 200 or more.

Differences between the physician specialist groups, based on the results of Bonferroni t tests[25] that were computed for pairwise comparisons, are presented in Table 2. Allergists, occupational physicians, and clinical ecologists did not differ significantly from one another with respect to the percentages who responded with scoreable questionnaires. However, the percentages of allergists and occupational physicians who responded with scoreable questionnaires did significantly exceed the percentages of other responding physicians, for internists in particular. The physician groups also differed significantly from one another with respect to age; both allergists and clinical ecologists were significantly older than occupational physicians. Groups also differed significantly in terms of the mean number of patients evaluated; clinical ecologists reported examining significantly more affected individuals than did either allergists or occupational physicians. Finally, the groups did not differ significantly from one another with respect to sex distribution.

Major criteria identified. Five criteria were identified by at least 50% of the physician respondents as major for categorizing patients as having MCS syndrome (Table 3). No criterion was identified as minor or irrelevant by more than 50% of the respondents, whether or not "don't knows" and skips were deleted from the sample. In subsequent analyses, "don't knows" and skips were considered as nonresponses for the criterion under consideration.

Major criteria versus number of patients evaluated. Subsequently, we examined the criteria reported as major by medical practitioners who had examined many patients (top quartile) or few patients (bottom quartile). In all cases, separate analyses were performed on the entire sample of practitioners and on the entire practitioner sample, excluding clinical ecologists (Table 4). Six diagnostic criteria were selected as major by at least 50% of all bottom quartile practitioner subjects (n = 21). These six criteria, in descending order, were: symptoms are reproducible with exposure; condition is chronic; responses occur at low exposure levels; symptoms resolve when incitants are removed; responses occur to multiple, unrelated substances; and no single accepted test correlates with symptoms. Excluding the single clinical ecologist in the bottom

Table 2.—Characteristics of Physician Respondents

	All (+CE) (n = 89)	All (−CE) (n = 69)	Allergists (n = 36)	Occupational physicians (n = 23)	CE (n = 20)	Others (n = 10)
Percentage of total sample	100	78	40	26	22	11
Percentage of invitees responding	60	64	69	72	50	40
Mean age	49.7	48.1	52.9	41.0	54.9	47.8
Percentage male	90	88	89	87	95	90
Median number of patients	50	22	22	20	450	62

Note: CE = clinical ecologists.

quartile (n = 20) did not alter the number of diagnostic criteria selected as major.

Eight diagnostic criteria were selected as major by at least 50% of the top quartile practitioners (n = 27); these included the six criteria judged as major by the bottom quartile subjects plus two additional criteria—adverse responses affect more than one bodily system and odor sensitivity is altered. The same eight diagnostic criteria plus two in addition—individual perceives the response as disturbing and neuropsychiatric symptoms are among primary complaints—were considered to be major by the top quartile subjects (n = 10) when clinical ecologists were excluded.

Major criteria versus specialization. Next, we examined the criteria identified as major by at least 50% of the physician groups of particular interest: allergists, occupational physicians, and clinical ecologists (Table 5). Four of the five diagnostic criteria identified as major by the entire practitioner sample were also identified as major by more than 50% of the allergists (n = 36), occupational physicians (n = 23), and clinical ecologists (n = 20). One diagnostic criterion—symptoms resolve when incitants are removed—was identified as major by 50% or more of only two of the three groups: allergists and clinical ecologists. In addition, three diagnostic criteria were considered major by at least 50% of only one group. One criterion—identifiable exposure preceded the onset of disorder—was designated as major by at least 50% of occupational physicians alone. Two criteria—symptoms affect more than one bodily system and symptoms are not confined to one or several environments—were only considered major by at least 50% of the clinical ecologists.

Evaluation of differences among allergists, occupational physicians, and clinical ecologists was achieved by examination of differences between the groups in the criteria identified as *important* or *unimportant*. For these analyses, criteria identified as major or minor were categorized as important, whereas criteria identified as irrelevant were categorized as unimportant. After "don't knows" and skips were excluded from the analyses, there were five statistically significant differences among the three specialist groups with respect to the importance placed on particular MCS syndrome criteria (Table 6).

Odds ratios for comparisons among physician groups are shown on Table 7. For "odor sensitivity is altered," clinical ecologists differentiated significantly from the other physician groups; they were 7.5 times more likely than allergists and 6.0 times more likely than occupational physicians to assign importance to this criterion. Allergists and occupational physicians did not differ significantly from one another on this criterion. For "individual perceives the response as disturbing," clinical ecologists were more than 9.0 times more likely than allergists to consider the diagnostic criterion important. There was a nonsignificant trend for clinical ecologists to be more likely than occupational physicians to con-

Table 3.—Criteria of MCS Syndrome, Identified by Physician Respondents

Criterion	Percentage responding (n = 89) "Major"	"Minor"	"Irrelevant"	"Don't know"/ no response
Symptoms reproducible	80	10	6	4
Condition chronic	65	19	11	4
Symptoms resolve when incitants removed	57	26	12	4
Reaction to multiple, unrelated substances	56	19	16	9
Responses at low exposure levels	53	17	12	18
No accepted test correlated	49	13	25	12
Identifiable exposure precedes onset	44	34	18	4
More than one system involved	44	33	20	6
Response disturbs patient	39	36	18	7
Neuropsychiatric symptoms	35	28	26	11
Exposures avoided	34	31	30	4
Patient believes s/he has disorder	25	21	45	9
Response in more than one setting	23	45	23	10
Odor sensitivity altered	21	31	31	16
Professional advice sought	18	25	52	6

Table 4.—Clinical Criteria Identified as "Major" by at Least 50% of Physician Practitioner Respondents Who Had Evaluated More Than 200 Affected Individuals (Upper Quartile) or Less Than 8 Affected Individuals (Lower Quartile)

Criterion	Percentage responding			
	Less than 8		More than 200	
	+CE (*n* = 21)	−CE (*n* = 20)	+CE (*n* = 27)	−CE (*n* = 10)
Symptoms reproducible	80	79	96	100
Condition chronic	67	65	73	78
Responses at low exposure levels	59	56	79	89
Symptoms resolve when incitants removed	53	56	50	53
Reaction to multiple unrelated substances	63	61	75	75
No accepted test correlated	63	60	67	86
More than one system involved	25	21	54	56
Response disturbs patient	33	29	48	70
Neuropsychiatric symptoms	31	27	40	50
Odor sensitivity altered	19	13	50	50

Notes: +CE includes respondents who identified themselves as clinical ecologists, and −CE excludes respondents who identified themselves as clinical ecologists.

Table 5.—Criteria Identified as "Major" by More Than 50% of Allergists, Occupational Physicians, or Clinical Ecologists

Criterion	Allergists (*n* = 36)	Occupational physicians (*n* = 23)	Clinical ecologists (*n* = 20)
Symptoms reproducible	82	77	89
Condition chronic	56	86	70
Responses at low exposure levels	52	75	72
Symptoms resolve when incitant removed	69	43	55
Reaction to multiple unrelated substances	64	50	68
No accepted test correlated	61	52	60
More than one system	41	41	50

Table 6.—Statistically Significant Differences between Allergists, Occupational Physicians, or Clinical Ecologists on Criteria Considered Important for Diagnosing Multiple Chemical Sensitivities Syndrome

Criterion	Percentage report "important"			
	Allergists (*n* = 36)	Occupational physicians (*n* = 23)	Clinical ecologists (*n* = 20)	*p* value
Response disturbs patient (*n* = 75)	66	82	100	.01
Odor sensitivity altered (*n* = 68)	53	59	89	.03
Professional advice sought (*n* = 75)	57	15	50	.01
Patient believes s/he has disorder (*n* = 72)	61	26	47	<.05
Condition chronic (*n* = 78)	90	100	78	.04

sider the "individual is disturbed by the disorder" criterion important, and for allergists to be less likely than occupational physicians to consider this criterion important. For "individual has sought professional advice," clinical ecologists and allergists placed similar weight on this criterion, and they were significantly more likely than occupational physicians to judge this criterion important. For "individual believes s/he as a disorder," the only difference was between allergists and occupational physicians, i.e., the allergists were more than 4.0 times as likely to identify this as an important criterion. Finally, for "condition is chronic," allergists were significantly less likely than occupational physicians to identify this criterion as important. Clinical ecologists were less likely than occupational physicians and more likely than allergists to do so, although neither trend reached statistical significance.

Acceptance of chemical sensitivity diagnosis. Eighty-two respondents replied to the question "Do you think chemical sensitivity should be accepted as a diagnostic category (with or without subsets)?" Sixty-seven percent responded affirmatively. When clinical ecologists were excluded from the sample, 59% had so responded. In every physician group, at least 50% indicated that the entity should be accepted as a diagnostic category. However, different proportions of the allergists (50%), occupational physicians (70%), and clinical ecologists (95%) accepted the condition. Clinical ecologists were 18.0 times more likely than allergists and 7.7 times more likely than occupational physicians to report that they believed the syndrome should be accepted as a diagnostic category. Occupational physicians were not significantly different from allergists in this regard.

Discussion

This study reveals some consensus among a sample of physicians with an interest in MCS syndrome regarding major criteria for the syndrome. There were five criteria that had considerable consensus. Two related to the nature of incitants presumed to provoke a response (i.e., responses occur at low exposure levels; responses occur to multiple, unrelated substances); two related to the response to exposure (i.e., symptoms are reproducible with exposure; symptoms resolve when incitants are removed); and the remaining criterion related to chronicity of the condition.

Agreements and disagreements among sampled physician groups with respect to the importance of the five criteria differed. Occupational physicians, for example, were less likely than allergists to consider two diagnostic criteria (i.e., individual has sought professional advice; individual believes he or she has a disorder) to be important. The basis for this difference is unclear. It may imply that allergists, as secondary medical practitioners, most commonly see patients on the referral of a primary contact physician, whereas occupational physicians are likely to see patients earlier. Of the three groups, the clinical ecologists were more likely to judge altered odor sensitivity as important; they were also more likely than allergists, but not occupational physicians, to emphasize the importance of individuals perceiving the response to be disturbing. The basis for these differences is also unclear.

No psychiatrists were included in our physician sample. Further refinements of the MCS case definition should use diagnostic criteria from this discipline to differentiate MCS syndrome from psychiatric conditions. Similarly, the basis for distinguishing MCS syndrome from other medical conditions (e.g., vasomotor rhinitis, sinusitis, asthma, multiple sclerosis, lupus erythematosus, chronic fatigue syndrome, and various intoxicants) will also bear further consideration.

The external validity of this investigation is open to question. A shortcoming of the study was the impossi-

Table 7.—Odds Ratio on Criteria Considered Important for Diagnosing MCS Syndrome

Criterion	Odds ratio	*p* value
Odor sensitivity altered		
Clinical ecologist vs. allergist	7.5	<.05
Clinical ecologist vs. occupational physician	6.0	<.05
Allergist vs. occupational physician	1.3	>.05
Response disturbs patient		
Clinical ecologist vs. allergist	9.4	<.01
Clinical ecologist vs. occupational physician	4.0	<.10
Allergist vs. occupational physician	0.4	<.10
Professional advice sought		
Clinical ecologist vs. allergist	0.8	>.05
Clinical ecologist vs. occupational physician	5.7	<.05
Allergist vs. occupational physician	7.6	<.05
Patients believe they have the disorder		
Clinical ecologist vs. allergist	0.6	>.05
Clinical ecologist vs. occupational physician	2.5	>.05
Allergist vs. occupational physician	4.4	<.05
Condition chronic		
Clinical ecologist vs. allergist	2.6	>.05
Clinical ecologist vs. occupational physician	0.4	>.05
Allergist vs. occupational physician	0.2	<.02

bility of evaluating how closely the nonrespondents resembled the respondents on characteristics other than specialist status, which was the only information available to us regarding the nonrespondents. More allergists and occupational physicians responded than internists. We suspect that our respondents may have also been particularly accepting of the condition, as evidenced by the fact that more than 50% of each specialist group indicated that the condition should be accepted as a diagnostic category.

This investigation did not allow us to evaluate the basis for our respondents' judgments about criteria. We had no evidence that participants based their judgments on patient observations; hence, the concordance observed in respondents may simply reflect reading or hearsay. Similarities on consensus judgments about major criteria between practitioner respondents who had evaluated few and many patients are consistent with the notion that some of the sampled experts were drawing on second-hand observations or inference for some impressions.

Consensus with respect to a preliminary case definition for MCS syndrome is needed. A working definition of the syndrome is required to initiate a rational dialogue and to investigate the problem in an objective manner. We, therefore, propose that the consensus criteria that have emerged from this survey be used to categorize patients as having MCS syndrome for the purpose of scientific inquiry into the nature of the disorder. The provisional criteria are as follows:

1. The symptoms are reproducible with exposure.
2. The condition is chronic.
3. Low levels of exposure result in manifestations of the syndrome.
4. The symptoms improve or resolve when the incitants are removed.
5. Responses occur to multiple, chemically unrelated substances.

* * * * * * * * * *

The authors are grateful to Judith Cuthie and Marie Skane for their assistance.

This study was supported, in part, by grant ES03819 from the National Institute for Environmental Health Sciences and by grant OH07090 from the National Institute of Occupational Safety and Health.

Submitted for publication January 21, 1992; revised; accepted for publication July 30, 1992.

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APPENDIX A

Major Sources of Experts for the Study of Diagnostic Criteria of MCS Syndrome

Contributors: *Workers with MCS* (1987).
NAS Workshop Participants: *On Health Risks from Exposure to Common Indoor Household Products in Allergic or Chronically Diseased Persons* (1987).
NAS Task Force: *Subcommittee on Immunotoxicology* (1989–90).
Review Board: *Maryland Chemical Hypersensitivity Syndrome Study* (1989).
American College of Physicians: *Clinical Efficacy Assessment Subcommittee and Health and Public Policy Committee* (1989).
Position paper authors: *Annals of Internal Medicine* (1989).
Advisory Panel on Environmental Hypersensitivity Disorders, Toronto (1986).
Ad-Hoc Committee on Environmental Hypersensitivity Disorders, Toronto (1985).
Consults for New Jersey Department of Health Report: *Chemical Sensitivity* (1989).
American Public Health Association MCS Task Force (1989–90).
Editorial board: *Clinical Ecology* (1989).
Board of Directors: American Academy of Environmental Medicine (1989).
Executive Committee: American Academy of Allergy and Immunology (1989).
Scientific Board Task Force on Clinical Ecology (California, 1986).
Board of Regents of American College of Allergy and Immunology (1989).
Board of Directors (physicians only): American Academy of Clinical Toxicology (1989).

APPENDIX B

Clinical Diagnostic Criteria of MCS Syndrome, Organized by Common Themes

Nature of incitants provoking a response

Responses to offending environmental toxicants occur at levels of exposure below the 2.5 percentile for response in general population.
Individuals respond to multiple substances that are unrelated chemically (i.e., causes lack specificity). The symptoms are not confined to one or several environments (e.g., only "sick" buildings).

Biological plausibility, identifiable exposure

Symptoms are reproducible with exposure with reasonable consistency.
Symptoms resolve after removal of incitant exposures.
An identifiable exposure preceded the onset of the problem.

Topology of responses

Adverse responses affect more than one bodily system.
Primary complaints include neuropsychological symptoms.
The individual exhibits altered sensitivity to odor.

Persisting nature of perceived changes

The disorder is chronic.

Differential diagnosis

No single, widely accepted test of physiological function correlates with the symptoms.

Subjective responses and ameliorative actions of affected individuals

The individual perceives the response as unpleasant or disturbing.
The individual has sought professional advice.
The individual believes he or she has a disorder.
The individual takes action to avoid exposures to symptom-inducing chemicals.

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