SICK BUILDING SYNDROME IN WATER DAMAGED BUILDINGS: GENERALIZATION OF THE CHRONIC BIOTOXIN-ASSOCIATED ILLNESS PARADIGM TO INDOOR TOXIGENIC FUNGI

Ritchie C. Shoemaker[1,a], Judith M. Rash[2], Elliott W. Simon[3]

[1]Center for Research on Biotoxin Associated Illnesses, Pocomoke City, MD
[2]Delmont Laboratories, Swarthmore, PA
[3]Elwyn, Inc, Elwyn, PA
[a]Contact author email: ritchieshoemaker@msn.com

INTRODUCTION

There is no academic consensus on whether or not health effects relating to exposure to indoor bioaerosols, sometimes called Sick Building Syndrome (SBS), is a distinct clinical entity (Redd, 2002, Council on Scientific Affairs, 2002). Despite repeated reports of acute and chronic, multi-symptom illnesses acquired by patients following exposure to buildings with both water intrusion and indoor amplification of toxigenic microorganisms (Croft *et al.* 1986; Johanning *et al.* 1996; Hodgson *et al.* 1998; Johanning *et al.* 1999; Sudakin *et al.* 1998; Andersson *et al.* 1997; Dales *et al.* 1999; Dearborn *et al.* 1999; Montana *et al.* 1997; Fung *et al.* 2003: 18; Trout *et al.* 2001), including fungi and bacteria, methodological deficiencies in published studies have precluded drawing definitive conclusions on causation. No studies have identified a robust, objective indicator of neurologic dysfunction to confirm reports of illness. The only medical interventions for SBS to date involved allergy and pulmonary medications or to suggest removal from exposure. The lack of any treatment that could correct the symptoms ascribed to exposure to bioaerosols from water damaged buildings (WDB) has further weakened the contention that SBS is a recognizable illness. Our initial report (43) and the current study addressed the methodological limitations present in the previous studies.

Based on pilot data from 103 cases from 43 WDB (Hudnell *et al.* 2002), the general hypothesis of our initial study (Shoemaker, 2003) was that SBS was a chronic, biotoxin-associated illness (CBAI, Shoemaker *et al.* 2001; Shoemaker *et al.* 2001) caused by exposure to water-damaged buildings (CBAI-WDB). The study design included screening of potential participants for confounding factors, a longitudinal, five time-point series of assessments, and the interventions of therapeutic treatment, removal from exposure, and re-exposure. Assessments included stan-

dardized recording of symptoms, measurements of visual contrast sensitivity (VCS) as an indicator of neurologic function, measurements of leptin and the hypothalamic hormone, alpha melanocyte stimulating hormone (MSH), as markers for illness, and cholestyramine therapy (CSM) to enhance toxin elimination rates. An effective therapeutic approach for enhancing toxin elimination rates allowed the demonstration of illness resolution with therapy, continued good health without re-exposure, relapse with re-exposure without prophylactic therapy, and re-recovery with re-treatment (Shoemaker *et al.* 2003). The results indicated that CBAI-WDB could be defined as a syndrome involving multiple-system symptoms, a neurologic functional deficit, and biochemical abnormalities.

VCS has been used for many years as a marker for neurotoxicity and has shown high sensitivity to effects caused by exposure to other biologically produced neurotoxins (biotoxins), including those produced by dinoflagellates (Shoemaker *et al.* 2001; Shoemaker *et al.* 2001), cyanobacteria (Shoemaker *et al.* 2000), spirochetes (Shoemaker *et al.* 2002), and apicomplexans (Shoemaker *et al.* 2002). VCS is a non-invasive, bedside measure of the contrast threshold at which the visual system can detect sinusoidal bar patterns of different sizes or spatial frequencies (i.e., cycles of dark and light bars per degree of visual arc). VCS deficits due to biotoxin exposure are greatest at 6-12 cycles per degree of visual arc, and resolved with CSM therapy (Shoemaker *et al.* 2001; Shoemaker *et al.* 2001; Shoemaker *et al.* 2000, Shoemaker *et al.* 2002; Shoemaker *et al.* 2002, Hudnell *et al.* 2002). CSM is a non-absorbable, anion-binding resin, used in doses FDA-approved for treatment of hypercholesterolemia, binds many biologically- and synthetically- produced toxins (Cohn *et al.* 1978; Mutter *et al.* 1988; Rateau *et al.* 1986; Brouillard *et al.* 1990; Creppy *et al.* 1995; Kerkadi *et al.* 1998; Underhill *et al.* 1995; Dahlem *et al.* 1989).

METHODS

We hypothesized that patients with chronic illness associated with exposure to water damaged buildings and the potential for formation of bioaerosols including, but not limited to mycotoxins, would present the same characteristics as those seen in patients with other CBAI. These characteristics include symptoms, VCS deficits, response to CSM therapy, lack of production of a protective immune response that would result in resolution of illness with removal from exposure, reacquisition of illness with re-exposure and presence of multiple biomarkers, including the genetic basis of susceptibility and markers for excessive release of pro-inflammatory cytokines.

156 consecutive symptomatic patients with exposure to 150 different indoor environments with water intrusion and musty smells, or visible mold growth or documented presence of toxigenic fungal species and without confounding biotoxin

exposures, coming to a specialty clinic 1/02-4/03 for treatment of chronic illness were enrolled in an open label treatment protocol. A control group of 111 patients, without exposure to WDB, was recruited as the first patient, matched for age and sex, coming to the clinic for a physical exam after a study patient was enrolled. Study patients served as their own controls for each of the 5-steps of the repetitive exposure trial and were compared to the clinic control group. Each patient was interviewed, with a complete medical history, symptoms recording, tobacco use, VCS testing, physical exam, pulmonary function testing (PFT), electrocardiogram and diagnostic lab studies, including HLA DR by PCR, MSH, leptin, MMP9, ACTH, cortisol, ADH, osmolality, testosterone, DHEA-S, androstenedione, MBP, tumor necrosis factor alpha (TNF), c-reactive protein (CRP), sedimentation rate (ESR), and aerobic culture of deep nasal space, were performed. Building exposures, VCS and symptoms review in control patients were recorded. All patients with an acute medical problem not related to exposure to water damaged buildings were excluded from the treatment and control groups. All patients with known occupational exposure to solvents, metal fumes and metal dust, hydrocarbons, ongoing neurologic disease, active Lyme disease, possible estuarine associated syndrome (PEAS), exposure to toxigenic cyanobacteria, and alcoholism with chronic liver disease were excluded. For those patients meeting the case definition of CBAI-WDB (Table 1), CSM was prescribed (Shoemaker *et al.* 2001; Shoemaker *et al.* 2001).

Table 1. Case definition of CBAI-WDB

SBS Case Definition

1. We propose that a definition of a case of SBS include each of the following elements:

- potential for exposure to buildings with documented presence of toxigenic fungi, evident fungal growth or a history of water intrusion with musty smells;
- presence of multiple symptoms in at least 4 of 8 system categories
- absence of confounders

2. The case definition continues with at least 3 of following 6 criteria

- VCS deficits
- MSH deficiency
- MMP9 elevation
- HLA genotype

- ADH/osmolality dysregulation, measured simultaneously
- ACTH/cortisol dysregulation, measured simultaneously

3. The final criteria for case management include 2 of 3 of the following

- Response to CSM, with abatement of symptoms and resolution of VCS deficit to control levels
- Reduction of leptin, if elevated, with treatment
- Reduction in MMP9, if elevated, with treatment

4. Clinical note needs to be made of

- Presence of MARCoNS in deep nasal spaces
- Elevated levels of myelin basic protein antibodies

Patients were divided into three groups by location of exposure: 1) Consult (n=40); patients with potential for exposure to bioaerosols, who would not be returning for follow-up, 2) Residential (n=62); patients with potential for residential exposure to bioaerosols, with follow-up 3) Occupational (n=54); patients with potential for occupational exposure to bioaerosols, with follow-up. Baseline symptoms and VCS were compared for each group. Patients were then re-grouped for comparison by specificity of exposure, independent of residential/occupational exposure: 1) definitive fungal identification (fungal) (n=88), 2) presence of visible mold growth (growth) (n=48), 3) presence of water intrusion and musty smells (water) (n=20). Symptoms and VCS are compared for each group. Patients returning for follow-up care were evaluated with symptoms and VCS in sequential steps.

For patients with ongoing exposure to buildings with the potential for bioaerosols contamination, a 5-step exposure protocol was employed. Patients were evaluated at baseline (BASE), then treated until resolution of VCS deficits and symptoms were both obtained (AC-1). Patients were then kept away from the putative source of bioaerosols exposure, off CSM for 7 days (HOC). With informed consent, patients were returned to the suspect building, with re-evaluation in 3-5 days (BOC). Following documentation of symptoms and VCS, patients were then re-treated with CSM (AC-2), with final recording of all parameters. A subset of exposed patients elected to continue exposure in the suspected building, with ongoing use of CSM in prophylactic doses of one scoop of CSM taken twice a day (Prophyl). Vision tests and statistical analyses were performed as previously (Shoemaker *et al.* 2001; Shoemaker *et al.* 2001). LabCorp and Esoterix performed laboratory testing, both CLIA approved, high complexity, national laboratories.

RESULTS

VCS scores and symptoms are each similar in all 6 groups at baseline and each is markedly different from non-exposed, control patients, $p < .001$ (Figure 1-5). Treatment results in resolution of VCS deficits and reduction of symptoms to levels of controls. There is no difference in biomarkers at baseline between the groups. Exposure to defined fungal species showed no difference in symptoms or VCS compared to exposures to visible mold growth, water intrusion and musty smells. Reduction of leptin with treatment was seen in 85%, and MMP9 reduction was seen in 90% of patients.

Figure 1. Controls vs. initial illness: Occupational exposure, residential exposure, consultation but no treatment

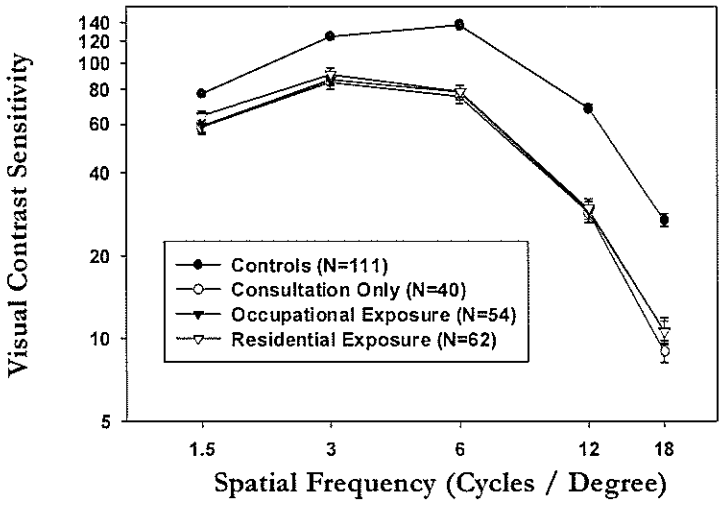


Figure 2. Controls vs. initial illness: Fungi genera identified, visible evidence of fungi only, water damage evidence only

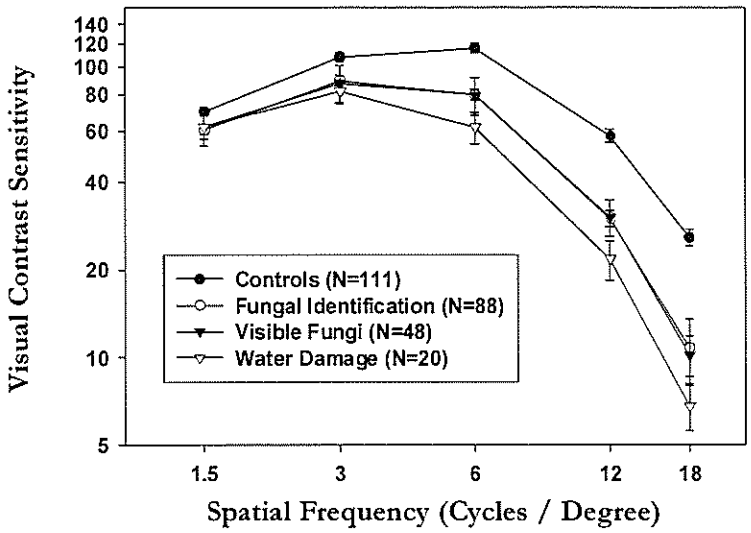


Figure 3. Occupational cohort: time series

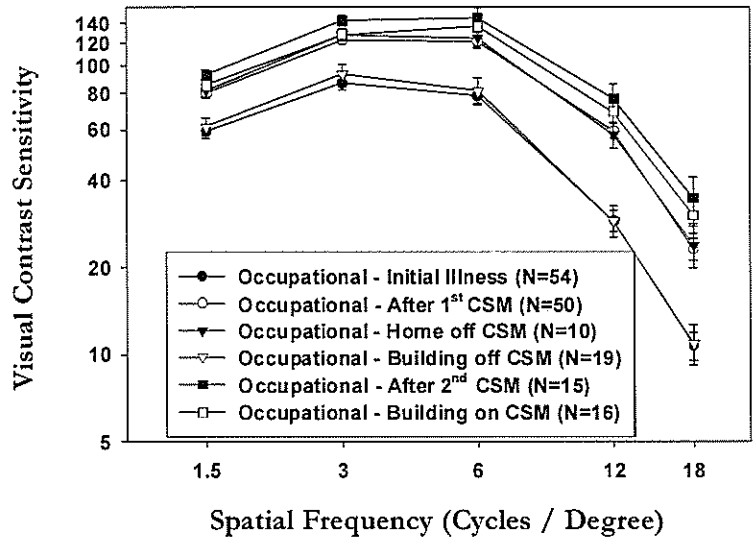


Figure 4. Residential cohort: time series

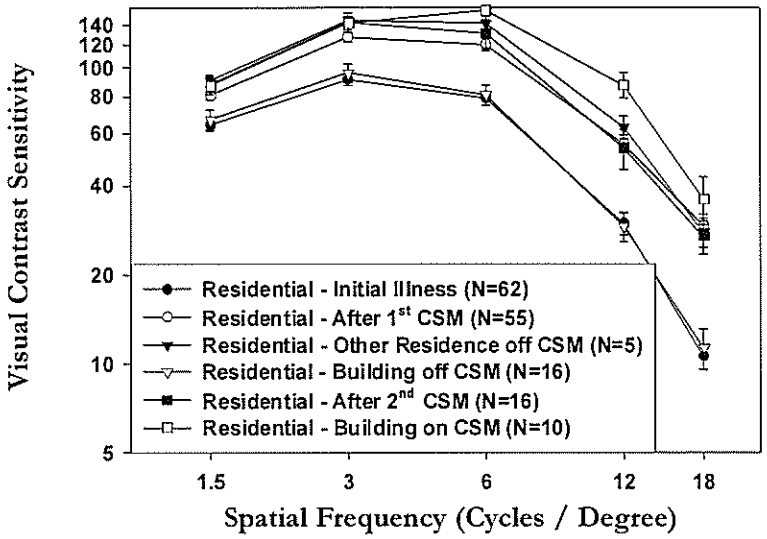
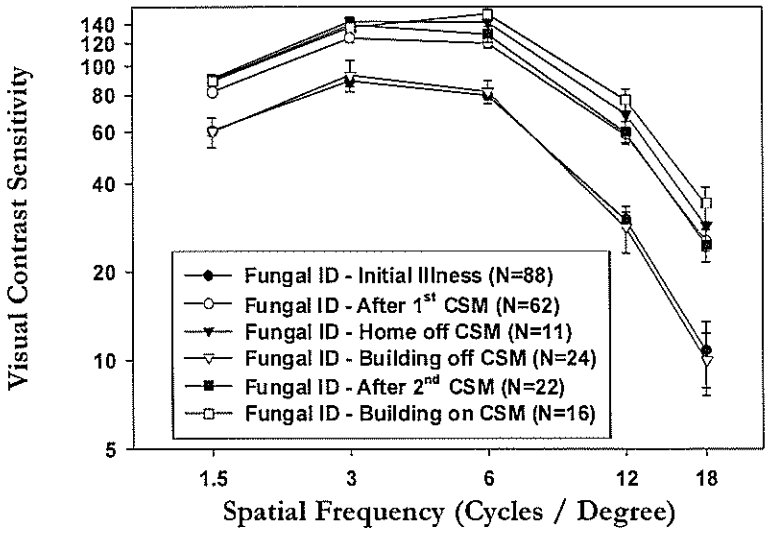


Figure 5. Fungal identification cohort: time series



Marked differences in symptoms and VCS scores were seen with the 5-step protocol. Base scores approximated BOC scores (figures 1, 2, 3, 4, 5). AC-1 and AC-2, as well as Prophyl were essentially identical and equal to controls in both symptoms and VCS. HOC approximated the AC-1 group. Figures 1, 2, 3 show no differences between Base for consult, residential or occupational groups. Figures 2, 3 show no differences between residential or occupational groups for each of the six time steps. Figure 4 shows no differences between before and after treatment for groups of patients exposed to defined fungal genera, visible mold growth or those exposed to water intrusion and musty smells.

HLA DR by PCR showed a strong relative risk (>2.0) for illness for a select group of genotypes (Table 2), specific, non-specific or protective. The rapid re-acquisition of illness, with VCS changes noted, in patients with high relative risk genotypes within 3-5 days of re-exposure to the same building, with no changes in water intrusion in the building, strongly argues against a linear, dose-response relationship as the operative factor in illness acquisition. HLA susceptibility was present in over 75% of cases.

MSH deficiency was present in over 92% of cases in all groups, correlating closely with symptoms and VCS deficits. Leptin elevation was found in 60% of affected patients; a better measure of the importance of leptin as a marker was change in leptin levels with treatment. ADH/osmolality, ACTH/cortisol and androgens showed marked dysregulation before treatment, markedly different from controls. MMP9 showed significant elevations at baseline, with return to normal in over 90% of affected patients following treatment.

Table 2. Susceptible genotypes

		RR
Fungal Only	7-2-53	4.6
	13-6-52A,B,C	3.4
	17-2-52A	3.5
Multiple	4-3-53	2.1
	11/12-3-52B	4.6
	14-5-52B	2.0
Post-Lyme	15-6-51	2.1
Dinoflagellate	4-8-53	2.6

VCS showed dynamic changes, in-step with treatment and re-exposure in other biotoxin illnesses (Cohn *et al.* 1978; Mutter *et al.* 1988). VCS had a low false negative rate (7%) and no false positives. VCS showed correction in 95% of treated patients. The role of second hand smoke as a confounder in diagnosis from water-damaged buildings is not supported by this study.

DISCUSSION

These data support the concept that the illness in patients exposed to bioaerosols in water-damaged buildings is readily identified as a CBAI. CBAI-WDB is a complex clinical condition that demonstrates inflammatory, hormonal and neurotoxicological biomarkers found in other chronic, biotoxin-associated illnesses. The treating physician can recognize the illness at the bedside, rule out confounding diagnoses, perform VCS and document the multiple biochemical abnormalities present in patients to satisfy the three tiered case definition (Table 2). The large treatment group in this study documents the utility of CSM as a therapeutic agent, as well as for prophylactic use. CBAI-WDB does not follow a dose-response relationship, but is associated with genetic susceptibility factors in HLA DR (Shoemaker *et al.* 2003; Shoemaker *et al.* 2002).

CONCLUSIONS

This study demonstrates the benefits of approaching chronic illness acquired by individuals with exposure to water damaged buildings as a CBAI. A registry of biomarkers, documentation of therapeutic benefit from CSM, a benign, FDA approved medication, and documentation of prevention of relapse in susceptible, exposed patients using CSM is consistent with other CBAI. VCS is a useful, inexpensive, non-invasive, portable, reproducibly reliable, bedside diagnostic test of significant utility in all 5 steps of the repetitive exposure times. MSH, leptin, MMP9, MBP, pituitary hormones, taken together with symptoms, HLA, and VCS, all contribute to the diagnostic basis of CBAI-WDB and provide the basis for follow-up of affected patients. The benefits of VCS and symptoms recording in screening large populations and building-wide prevalence studies will await completion of further studies, currently in progress. A double blinded, placebo controlled clinical trial that will add confirmation to these results is underway.

REFERENCES

- Andersson, M. A, Nikulin, M., Koljalg, U., Anderson, M. C., Rainey, F., Reijula, K., Hintikka, E. L., Salkinoja-Salonen, M. 1997, "Bacteria and toxins in water-damaged building materials", *App Environ Microb*; Vol. 63: 387-393.

- Brouillard, M. Y., Rateau, J. G. 1990, "La Cholestyramine fixe les toxines d'escherichia coli et de vibrio cholerae par une liaison ionique", *Ann Gastroenterolo Hepatol* 26:27-30 .
- Cohn, W. J., Boylan, J. J., Blanke, R. V., Fariss, M. W., Howell, Jr., Guzilian, P. S. 1978, "Treatment of chlordecone (kepone) toxicity with cholestyramine. Results of a controlled clinical trial", *New Eng J Med* 298:243-248.
- Council on Scientific Affairs, Texas Medical Association, "Black Mold and Human Illness", 1/1/02; http://www.texmed.org/has/CSA%20Black%20Mold.doc
- Creppy, E. E., Baudrimont, I., Betbeder, A.-M. 1995, "Prevention of nephrotoxicity of ochratoxin A, a food contaminant", *Toxicol Let* 82/83: 869-877.
- Croft, W. A., Jarvis, B. B., Yatawara, C. S. 1986, "Airborne outbreak of trichothecene toxicosis", *Atmos Environ*; 20: 549-552.
- Dahlem, A. M., Hassan, A. S., Swanson, S. P., Carmichael, W. W., Beasley, V. R. 1989, "A model system for studying the bioavailability of intestinally administered microcystin-LR, a hepatotoxic peptide from the cyanobacterium Microcystis aeruginosa", *Pharmacol & Toxicol* 64:177-181.
- Dales, R., Burnett, R., Zwanenburg, H. 1999, "Adverse health effects among adults exposed to home dampness and mold", *Am Rev Respir Dis;* 143: 505-509.
- Dearborn, D. G., Yike, I., Sorenson, W. G., Miller, M. J., Etzel, R. A. 1999, "Overview of investigations into pulmonary hemorrhage among infants in Cleveland, Ohio", EHP; 107 (3): 495-499.
- Fung, F., Hughson, W. G. 2003, "Health effects of indoor fungal bioaerosols exposure", *Applied Occupational and Environmental Hygiene*: 18; 535-544.
- Hodgson, M. G., Morey, P., Leung, W. Y. 1998, "Building-associated pulmonary disease from exposure to *Stachybotrys chartarum* and *Aspergillus versicolor*", *J Occup Environ Med*; 40: 241-249.
- Hudnell, H. K., Shoemaker, R. C. 2002, "Sick building Syndrome: possible association with exposure to mycotoxins from indoor air fungi", 8th International Symposium of Neurotoxicology, Neurobehavioral methods and effects in occupational and environmental health, Brescia, Italy, 6/26/02.
- Johanning, E., Biagini, R., Hull, D., Morey, P., Jarvis, B., Landsbergis, P. 1996, "Health and immunology study following exposure to toxigenic fungi (*Stachybotrys chartarum*) in a water-damaged office environment", *Int Arch Occup Environ Health*; 68: 207-218.
- Johanning, E., Landsbergis, P., Gareis, M., Yang, C. S., Olmsted, E. 1999, "Clinical experience and results of a sentinel health investigation related to indoor fungal exposure", EHP; 107(3): 489-494.
- Kerkadi, A., Barriault, C., Tuchweber, B., Frohlich, A. A., Marquardt, R. R., Bouchard, G., Yousef, M. 1998, "Dietary cholestyramine reduces ochratoxin A-induced nephrotoxicity in the rat by decreasing plasma levels and enhancing fecal excretion of the toxin", *J Toxicol Environ Health* 53:231-250.

- Montana, E., Etzel, R. A., Allan, T., Horgan, T. E., Dearborn, D. G. 1997, "Environmental risk factors associated with pediatric idiopathic pulmonary hemorrhage and hemosiderosis in a clinical community", *Pediatrics*; 99(1): 1-8.
- Mutter, L. C., Blanke, R. V., Jandacek, R. J., Guzelian, P. S. 1988, "Reduction in the body content of DDE in the Mongolian gerbil treated with sucrose polyester and caloric restriction", *Toxicol & Applied Pharmacol* 92:428-435.
- Rateau, J. G., Broillard, M., Morgant, G., Aymard, P. 1986, "Etude experimental chez le lapin de l'effet de la cholestyramine dans le traitement des diarrhees infectieuses d'origine cholerique", *Actualite Therapeut* 22:289-296.
- Redd, S. C. 2002, "State of the science on molds and human health; statement for the record; Committee on Oversight and Investigations and Housing and Community Opportunity, Committee and Financial Services", US House of Representatives, 7/18/02.
- Shoemaker, R., House, D. 2005, "A time-series study of Sick Building syndrome chronic, biotoxin associated illness from exposure to water damaged buildings", accepted for publication by *Neurotoxicology and Teratology* 7/30/04 (will appear in Jan. 2005)
- Shoemaker, R. 2002, "Differential Association of HLA DR genotypes with chronic, neurotoxin mediated illness: Possible genetic basis for susceptibility", *American Journal of Tropical Medicine and Hygiene*; 67(2): 160.
- Shoemaker, R. 2004, "Poster 85, Linkage disequilibrium of HLA DR genotypes, autoantibodies and wingspan/height ratios in patients with environmentally acquired toxigenic illness", American Society for Microbiology, Integrating Metabolism and Genomics, Montreal, Quebec, Canada, 4/30-5/3/04
- Shoemaker, R. C., House, D., van Kempen, A., Pakes, G. E. 2002, "Atovaquone (Mepron) plus cholestyramine (Questran) in patients who are co-infected with Babesia Microti and Borrelia burgdorferi and refractory to antibiotics and cholestyramine alone", American Society of Tropical Medicine 51st annual meeting, 11/11/02, Denver, Colo, (abst) *AJTMH*; 67(2): 30.
- Shoemaker, R. C., Hudnell, H. K. 2001, "Possible Estuary Associated Syndrome: symptoms, vision and treatment", *Environmental Health Perspectives* ; 109(5): 539-545.
- Shoemaker, R. C. 2002, "Poster 539-P. ADA funded research; Use of pioglitazone to prevent intensification of persistent symptoms following cholestyramine treatment of patients with the Post-Lyme Syndrome", (Abst.) *Diabetes*; 51 (S2): A133.
- Shoemaker, R. C. 2000, "Poster H05, Treatment of Possible Estuarine Associated syndrome: Neurotoxins, contrast sensitivity and cholestyramine", CDC National Conference on Pfiesteria: From Biology to Public Health 10/18-10/20/2000, Stone Mountain, Georgia.
- Shoemaker, R. C. 2001, "Residential and recreational acquisition of Possible Estuary Associated Syndrome: a new approach to successful diagnosis and treatment", *Environmental Health Perspectives*; 109(S5): 791-796.

- Sudakin, D. L. 1998, "Toxigenic fungi in a water-damaged building: an intervention study", *Am J Ind Med*; 34:183-190.
- Trout, D., Bernstein, J., Martinez, K., Biagini, R., Wallingford, K. 2001, "An attempt to measure exposure to mycotoxins, and comments on appropriate medical evaluation of persons with symptoms potentially related to bioaerosol exposure: bioaerosol lung damage in a worker with repeated exposure to fungi in a water-damaged building", EHP; 109 (6): 641-644.
- Underhill, K. L., Totter, B. A., Thompson, B. K., Prelusky, D. B., Trenholm, H. L. 1995, "Effectiveness of cholestyramine in the detoxification of zearalenone as determined in mice", *Bull Environ Contam Toxicol* 54:128-134.